PRE-EXISTING MENTAL ILLNESS AND BREAST CANCER AMONG ELDERLY PATIENTS IN THE US:

A SEER-MEDICARE DATABASE ANALYSIS

By

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ABSTRACT OF THE DISSERTATION

Pre-existing Mental Illness and Breast Cancer Among Elderly Patients in the US:
A Seer-Medicare Database Analysis

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The effect of pre-existing mental illness on diagnosis/treatment delays and survival in elderly patients with breast cancer is poorly defined in the literature. Because early detection and treatment are critical to long-term survival, it is important to identify the role of pre-existing mental illness in diagnosis and treatment delays of breast cancer. Therefore, this study sought to (1) describe the demographic, clinical, and tumor characteristics of elderly patients with pre-existing mental illness that were also diagnosed with breast cancer; (2) compare diagnosis and treatment delays of elderly breast cancer patients with and without pre-existing mental illness, and (3) compare rates of all cause and breast cancer-specific survival for elderly patients with and without mental illness. A retrospective cohort study of women aged 68+ at breast cancer diagnosis (stage I, II, or IIIa) was conducted using the SEER-Medicare database. Descriptive statistics, logistic regression, binomial regression, Cox proportional Hazards regression and competing risk models were utilized for the analysis. Compared to those without mental illness, those with mental illness were slightly more likely to be white, reside in neighborhoods with a lower income, use tobacco, and have more medical comorbidities. Breast cancer patients with pre-existing mental illness were also less likely to receive mammography and to be married. Compared to those without mental illness, a higher proportion of patients with mental illness

had poorly differentiated tumors and more positive lymph nodes. Breast-conserving surgery was more common than mastectomies overall, but patients with mental illness were less likely to receive adjuvant radiation following this procedure compared to those without mental illness. There were no significant differences in the risk of diagnosis, initial treatment, surgery, or adjuvant radiation treatment delays of ≥60 days or ≥90 days for those with versus without mental illness. However, breast cancer patients with pre-existing mental illness experienced a significant 13% higher risk of adjuvant chemotherapy delay of ≥90 days. When examining these associations by type of mental illness, patients with a diagnosis of both anxiety and depression were more likely to experience an increased risk of a diagnosis delay of ≥90 days. Breast cancer patients with major psychiatric illness (i.e., bipolar disorder, schizophrenia, or other psychotic disorders) were more likely to experience a prolonged initial treatment delay of ≥60 days. Patients with mental illness compared to those without faced a significant 43% increase in the rate of all-cause mortality and a non-significant 12% increase in the rate of breast cancer-specific mortality. The increased mortality from all causes remained for each category of mental illness, but the strongest impact was seen in those with major psychiatric illness (127% increased rate of all-cause death). Although the presence of mental illness overall did not significantly impact the rate of breast cancer death, a significant 40% increased rate was observed for patients with major psychiatric illness compared to those without mental illness. The findings of this dissertation provide evidence that breast cancer patients with major psychiatric illness experience significant treatment delays and face shorter survival. Breast cancer patients with major psychiatric illness would benefit from increased coordination of care among psychiatrists, primary care physicians, and other specialties. The reason for the increased breast cancer death rate in patients with pre-existing major psychiatric disorders deserves attention in order to understand the underlying mechanism(s).

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DEDICATION

This dissertation is dedicated to my wonderful husband Scott—who spent many days and nights cooking, cleaning, and taking care of our son while I was working behind closed doors. Thank you for being my rock, my comfort and my light at the end of the tunnel. I love you more than yesterday and less than tomorrow.

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BREAST CANCER

Epidemiology

Breast cancer is the most commonly diagnosed form of cancer among women in the United States—with the exception of non-melanomatous skin cancer—and a significant cause of morbidity and mortality. It is estimated that breast cancer accounted for almost 30% of newly diagnosed cancer cases in 2014. Specifically, 232,670 incident cases of invasive breast cancer and 62,570 incident cases of in situ breast cancer were diagnosed among women. Although death rates from breast cancer have been declining since the late 1980's—mostly due to advances in detection and treatment, as well as the decreased use of menopausal hormonal therapy—an estimated 40,000 deaths occurred in women in 2014 (Siegel, 2014; ACS, 2014).

Risk Factors for Breast Cancer

Many risk factors contribute to the development of breast cancer, but the two most important risk factors are female sex and increasing age (ACS, 2014). Ninety nine percent of newly diagnosed cancer cases occur in women, with the risk being largest after the age of 75. The median age at the time of breast cancer diagnosis is 61, with only approximately 20% of breast cancers in those younger than 50 (ACS, 2012). There are many additional risk factors that may contribute to the development of breast cancer, such as smoking, family history of breast cancer, genetic mutation, atypical hyperplasias, use of oral contraceptives, and previous breast cancer (Table 1). However, breast cancer is the result of a constellation of risk factors.

Table 1. Risk Factors for Breast Cancer

Modifiable Risk Factors	**Non-modifiable Risk Factors**	**Protective Factors**
Weight/Overweight/Obese	Age	Breastfeeding
Physical Inactivity	Female Sex	Having children
Alcohol Consumption	High breast tissue density	Having first child before the age of 30
Radiation exposure	Atypical hyperplasias or other high risk lesions	Prophylaxis with tamoxifen or raloxifene among women at high risk
Use of oral contraceptives	Menstrual periods that start early and/or end later in life	
Smoking	Family history of breast cancer	
Night shift work	Genetic mutations (i.e., BRCA1 and BRCA2 genes)	
Use of hormone replacement therapy	Previous breast cancer	

Diagnosis and Staging

Making a diagnosis of breast cancer can be complex, as breast cancer usually does not produce symptoms while the tumor is small. For this reason, routine screening is very important to ensure that breast cancer is detected while it is still at an early stage. When the tumor is larger, women may notice a mass in their breast, but often there is no pain accompanying the mass. Changes to the breast, such as swelling, thickening, distortion, skin irritation, scaliness, tenderness, redness, or nipple abnormalities can occur, but in the current day, this is no longer common (NCCN, 2015; ACS, 2014).

A screening evaluation generally consists of breast awareness, a physical exam, and mammography (or in some circumstances, additional magnetic resonance imaging [MRI] scan) (NCCN, 2015). Ultrasonography can be useful in women with dense breasts, but at this time, the National Comprehensive Cancer Network does not recommend ultrasound, scintigraphy, or ductal lavage as part of routine screening (NCCN, 2015; Bevers, 2008; Berg, 2008). For women 20 to 39 years of age with an average risk for breast cancer, the NCCN panel recommends a clinical breast exam every 1 to 3 years along with education on breast cancer. For women 40 years of age or older with an average risk for breast cancer, they recommend a clinical breast exam yearly, along with a mammogram and education on breast cancer. Clinical and family history need to be taken into account to determine the patient's risk and if the patient is deemed to be at high risk, the screening schedule should be adjusted accordingly (NCCN, 2015). Although routine mammography can still be considered controversial for younger patients (Gøtzsche, 2006; Smith, 2003; Buist, 2004; Fletcher, 2003; Armstrong, 2007; Moss, 2006; van Schoor, 2008), overall it has demonstrated a sensitivity of 75% (Carney, 2003) and has been shown to increase survival in several large-scale clinical trials with many years of follow-up (Nemec, 2007; Barton, 1999).

Once a positive diagnosis has been made, the cancer is staged based on the TNM Staging System, which was developed by the American Joint Committee on Cancer (AJCC). Staging determines the prognosis of breast cancer based on the size of the tumor, the involvement of lymph nodes, and spread to organs other than the breast (simplified version shown in Table 2). Staging has important prognostic significance and serves as a tool for determining a course of treatment (AJCC, 2010; Edge, 2010).

Table 2. The TNM Staging System

The T category describes the primary tumor.

TX	Primary tumor cannot be evaluated
T0	No evidence of primary tumor
Tis	Carcinoma in situ (early cancer that has not spread to neighboring tissue)
T1–T4	Size and/or extent of the primary tumor

The N category describes whether or not the cancer has reached nearby lymph nodes.

NX	Regional lymph nodes cannot be evaluated
N0	No regional lymph node involvement (no cancer found in the lymph nodes)
N1-N3	Involvement of regional lymph nodes (number and/or extent of spread)

The M category tells whether there are distant metastases (spread of cancer to other parts of the body).

M0	No distant metastasis (cancer has not spread to other parts of the body)
M1	Distant metastasis (cancer has spread to distant parts of the body)

Survival

From the early 1960s to present day, the overall 5-year relative survival rate for women with breast cancer has improved from 63% to 90% (Berry, 2005). This is due to a combination of early detection and advances in treatment. According to the National Cancer Institute, the 5-year survival rate for those over the age of 65 is almost identical to the rate for those under 65 (90.3% vs. 90.7%, respectively; NCI, 2014).

Treatment

The treatment strategy for breast cancer depends largely on the stage at diagnosis, the tumor characteristics, and the patient's age (ACS, 2014). Therapeutic options are many and vary widely based on these prognostic factors. Options include surgery (breast-conserving surgery [BCS] or mastectomy), chemotherapy, radiation, hormonal therapy, and targeted therapy (NCCN, 2015).

Breast-conserving Surgery and Mastectomy

For most of the early 20th century, radical mastectomy was considered the standard of care for all stages of breast cancer (Fisher, 2002). However, the recognition that breast cancer is a systemic disease resulted in a paradigm shift in treatment. Studies have since shown that radical mastectomy and even modified radical mastectomy may not be necessary for all patients and patients may benefit from systemic therapy. For example, in early-stage invasive breast cancers there has been a significant shift towards BCS followed by radiation therapy in lieu of mastectomy. Clinical trials have demonstrated that for the majority of women with early-stage breast cancer, no significant difference was observed between BCS followed by radiation therapy and modified radical mastectomy for time to distant metastases or overall survival (Litière, 2012; EBCTCG, 2011; EBCTCG, 2005). BCS is not recommended for women at high risk of local recurrence. Instead, a mastectomy is often recommended, but studies have shown that less extensive surgery (e.g., total mastectomy or modified radical mastectomy) can result in similar rates of disease-free survival, relapse-free survival, distant-disease–free survival, and overall survival compared to radical mastectomy (Fisher, 2002; Maughan, 2010).

Adjuvant Therapy

Often surgery alone is insufficient to prevent disease recurrence or death, even for the earliest stages of breast cancer. Many patients will also need adjuvant therapy with chemotherapy, radiotherapy, endocrine therapy, targeted therapy, or a combination of these treatments (NCCN, 2015). Chemotherapy is commonly used in patients with node-positive breast cancer, and in patients with hormone receptor-negative tumors. It is the only option available to patients with ER/PR/Her2 negative disease, but there are subsets of patients with ER positive and/or HER2 positive tumors that would benefit from chemotherapy as well. Radiotherapy is often recommended after breast conserving surgery, and may be recommended following mastectomy, in order to remove any remaining cancer cells post-surgery. Endocrine therapies comprise treatment classes such as selective estrogen receptor modulators, aromatase inhibitors, and gonadotropin-releasing hormone agonists. These treatments are only effective in patients with hormone receptor positive tumors and act by either preventing hormone production or blocking their action. Targeted therapy includes agents such as monoclonal antibodies that target pathways associated with the mutation or overexpression of oncogenes or the loss of tumor suppressor genes (Maughan, 2010).

Breast Cancer Treatment and the Elderly Population

The treatment of breast cancer in elderly patients remains controversial. Clinical trials often include fewer elderly patients and also may not include those patients with multiple comorbidities. Thus, there is a lack of evidence-based guidelines on the optimal approach to management of these patients. Current evidence suggests that elderly patients are often undertreated when compared to younger patients (Wanebo, 1997; DeMichele, 2003; Gaidos, 2001; Malik, 2013, Rocco, 2013). A study by Malik et al showed that 51% of patients over the

age of 71 were undertreated for their breast cancer (Malik, 2013). Specifically, adjuvant therapy with radiation and chemotherapy was significantly less frequent in the elderly compared to younger patients. Conversely, the use of hormonal therapy was more frequent in elderly patients. A separate study by Rocco and colleagues demonstrated a similar trend, with 46% of patients over 65 years of age being undertreated. Additionally, elderly patients had less axillary surgery and adjuvant radiation therapy, but more frequent use of hormonal therapy compared to younger counterparts (Rocco, 2013).

MENTAL ILLNESS AND BREAST CANCER

Mental Illness Epidemiology

Mental disorders are extremely common in the US, with approximately one in four people facing a diagnosis in a given year and one in two facing a diagnosis in their lifetime (Kessler, 2005; Kessler, 2008; NIH, 2013). Specifically, the projected lifetime risk at age 75 years for any anxiety disorder, mood disorder, or impulse-control disorder is 31.5%, 28%, and 25.4%, respectively (Kessler, 2005). The vast majority of mental disorders have an early age of onset, often starting in childhood or adolescence, and most cases that occur later in life can be attributed to psychiatric comorbid disorders (Kessler, 2008).

The elderly population, specifically, is faced with a litany of psychosocial stressors as they age. A decrease in cognitive skills, sensory abilities, and social relationships, as well as an increase in comorbidities, are just a few factors influencing their mental health status (Harris, 2003). It has been reported that 20% of adults over the age of 65 suffer from one or more mental disorders

in the US and this number is only expected to rise. By 2030, it is estimated that 15 million elderly people will have a mental disorder (Jeste, 1999).

Delayed Diagnosis and Treatment

Although the majority of women in the US obtain a medical consultation within 2 weeks of finding a lump in their breast, as many as 34% delay medical consultation for over 3 months (Facione, 2002). Previous research has suggested that patients with mental illness experience an even longer delay in time to diagnosis and treatment of their cancers compared to the general population (O'Rourke, 2008; Farasatpour, 2013; Hwang, 2012). In patients with esophageal cancer, O'Rourke and colleagues demonstrated a median time from symptom to diagnosis of 90 days in those with mental illness compared to just 35 days in those without a diagnosis (P=0.002). Additionally, patients with mental illness were less likely to receive necessary surgery. Further, Hwang et al. reported that among patients with pre-existing schizophrenia, 38% overlooked breast cancer symptoms such as a mass or ulceration for six months to nine years and 29% of patients with biopsy-proven breast cancer delayed treatment for more than 3 months.

Many factors could contribute to this delay, one of which is delayed screening. Several studies have evaluated cancer screening in patients with mental illness, but their results were mixed. A number of studies have demonstrated decreased screening rates in those with mental disorders compared to the general population (Lindamer, 2003; Lindamer, 2006; Carney, 2006; Martens, 2009; Howard, 2010; Druss, 2002), while other studies have found no difference (Howard, 2010; Lasser, 2003; Dickerson, 2003; Owen, 2002; Steiner, 1998). A study by Weneke et al showed that psychiatric patients overall were as likely as those without mental illness to utilize screening services. It is important to note, however, that this study was conducted in the UK, where

universal insurance exists, and these results might not directly translate to the US population. Also, when Weneke and colleagues examined a subgroup of patients with severe mental illness, screening services were utilized less frequently (Werneke, 2006). A more recent study by Koroukian et al. determined that more women with mental illness had at least one screening mammography during the study period than those without mental illness; however, after adjusting for potential confounders, this relationship was reversed. Women with mental illness were 32% less likely to receive at least one screening mammography compared to those without mental illness. Further, in the subgroup of patients who received at least one screening mammography, less women with mental illness than without mental illness received their mammography annually (Koroukian, 2012).

Another potential factor contributing to delayed diagnosis and treatment is access to care. Some insurance carriers have limited access to care for comorbid conditions in those with mental illness, creating a financial burden to the patient (Howard, 2010). Additionally, patients often face a phenomenon known as “diagnostic overshadowing”, where their physical symptoms are mistakenly viewed as manifestations of their mental illness. This represents a barrier for patients with mental illness, who frequently feel as though they encounter discrimination from medical staff (Thornicroft, 2007). Jeste et al. revealed that patients and the healthcare staff underestimate the presence of comorbid conditions when more severe symptoms of mental illness are present (Jeste, 1996).

A patient’s specific mental illness diagnosis could also lead to differences in time to diagnosis. A patient with phobia, for example, might be more likely to seek early treatment, compared to a patient who has depression. This was demonstrated in a study by Desai et al., where patients with a positive history of major depression had 9.81 times the risk of late-stage diagnosis of

breast cancer compared to those without major depression (Desai, 1999). Additionally, a patient with schizophrenia could suffer from psychoses and/or cognitive impairment, which would lead to treatment delay and potentially to non-adherence as well. In severe cases, a patient with a mental disorder might not be able to understand the magnitude of their diagnosis, and therefore, also not realize why they would need treatment or need to remain on treatment (Inagaki, 2006; Kunkel, 1997; Kelly, 2000; Jeste, 1996; Greer, 2008). In contrast, having a positive history of phobic disorders decreased the risk of late-stage diagnosis by 99% compared to those without a phobic disorder (Desai, 1999).

Treatment Delay and Survival

A large systematic literature review of 87 studies assessing the influence of treatment delay on survival in patients with breast cancer found that patients with treatment delays of 3 months or more have a 12% lower 5-year survival rate than patients with delays less than 3 months. Breast cancer can progress quickly and delays can lead to advanced disease stage and poorer prognosis (Richards, 1999). A study by Goodwin et al. (2004) estimated that after controlling for age, ethnicity, comorbidity, AJCC stage, and SEER site, women with depression had a 42% greater rate of death from breast cancer during 3-year follow-up than those patients without depression.

Many factors affect breast cancer prognosis, but presence of comorbid conditions contributes significantly to determining a patient's survival (Hjerl, 2003; Louwman, 2005). Patients with severe mental illness are more likely than those without to have comorbid conditions including cardiovascular disease, respiratory disease, diabetes, and obesity (Bresee, 2011; Filik, 2006; Compton, 2006), and are also 70% more likely to smoke (CDC, 2014). Numerous publications have cited a statistically significant association between the presence of comorbid conditions

and overall survival or all-cause mortality in breast cancer patients (Nagel, 2004; Houterman, 2004; Louwman, 2005; Janssen-Heijnen, 2007; Cronin-Fenton, 2007; Yancik, 2001). A recent publication by Patnaik et al further supports this relationship by examining the individual associations between 13 comorbidities and overall survival and all-cause mortality in a cohort of breast cancer patients. Each comorbid condition examined was associated with decreased overall survival and increased mortality (Patnaik, 2011). Smoking is a large risk factor in and of itself, not only for breast cancer, but for comorbidities as well. Thirty-six percent of patients with mental illness smoke cigarettes, compared to only 21% of those without mental illness (CDC, 2014). It is also interesting to note that in addition to increased risk for comorbidities and smoking, patients with mental illness often lack certain protective factors associated with breast cancer, such as history of breastfeeding or being married (Usher, 2005; Wu, 2012). Wu and colleagues (2012) showed that patients with mental illness who never married required significantly longer durations of treatment for their mental illness than their counterparts who were married or previously married. This is likely a result of increased social support in those who were married. Further, Aizer et al. (2013) found that being married significantly decreased the risk of having metastatic cancer at the time of diagnosis and conferred a decreased likelihood of death compared with those who were single, separated, divorced, or widowed.

There are also complications associated with the co-administration of anti-neoplastic therapy and psychotropic drugs. Co-administration of these therapies puts the patient at risk for drug-drug interactions that can result in adverse events or decreased efficacy, making treatment in this population complex (Yap, 2011). Riechelmann et al reported that 27% of cancer patients experience at least one drug-drug interaction, with 86% classified as severe or moderate (Riechelmann, 2007). As an example, psychotropic drugs such as carbamazepine increase the metabolism of chemotherapy drugs, resulting in lower plasma concentrations and reduced

efficacy of docetaxel, paclitaxel, progesterone, and cyclophosphamide (Howard, 2010). However, the effects of other psychiatric medications may differ and many have not been evaluated. In contrast to tamoxifen effects, certain antipsychotics, including chlorpromazine, risperidone, quetiapine, paliperidone and clozapine, have been shown to be inhibitors of breast cancer resistance protein (BCRP). BCRP is involved in the absorption, excretion and distribution of substrate drugs and has been implicated in multidrug resistance of cancer cells (Wang, 2008). The human cytochrome P450 2D6 (CYP2D6) gene is also involved in drug metabolism. Currently, there is some evidence that co-administration of certain anti-depressant medication (i.e., paroxetine, fluoxetine, and bupropion) are likely to inhibit CYP2D6 and interfere with tamoxifen treatment. The use of paroxetine and tamoxifen together was associated with an increased risk of death from breast cancer (Kelly, 2010; Desmarais, 2009). This is likely due to a decrease in the plasma concentration of tamoxifen as a result of the inhibition of CYP2D6 enzyme activity from paroxetine. Many antipsychotic medications are also metabolized by CYP2D6, so therapeutic drug monitoring has been strongly recommended for patients treated by any of these agents in conjunction with tamoxifen (Zhou, 2009). Despite this recommendation, a more recent study that examined the effects of co-administration of risperidone (an antipsychotic medication) and tamoxifen found that risperidone (although metabolized by CYP2D6) did not inhibit CYP2D6 and concluded that the medication could be useful in relieving tamoxifen-induced side effects without interfering with tamoxifen's anticancer effect (Yeh, 2014). Other potential adverse events related to combination therapy with psychotropics and anti-neoplastic therapies include drug-induced prolongation of the QTc interval, neutropenic sepsis, and agranulocytosis (Howard, 2010).

Organization of the dissertation

This dissertation is presented in three chapters, each focusing on a specific research question. The specific aims of the three chapters are as follows:

Chapter 1:

- To compare the descriptive characteristics (i.e., demographic, clinical, and tumor characteristics) of elderly breast cancer patients with and without pre-existing mental illness

Chapter 2:

- To compare diagnosis and treatment delays of elderly breast cancer patients with and without pre-existing mental illness

Chapter 3:

- To compare rates of all-cause and breast cancer specific death rates for those with and without pre-existing mental illness

CHAPTER 1

CHARACTERISTICS OF ELDERLY BREAST CANCER PATIENTS WITH PRE-EXISTING MENTAL ILLNESS

Abstract

Aim: To describe the demographic, clinical, and tumor characteristics of elderly breast cancer patients diagnosed with breast cancer with and without pre-existing mental illness.

Methods: Subjects 68 years of age or older diagnosed with stage I, II, or IIIa incident breast cancer between January 1, 2005 and December 31, 2007 were identified in the SEER-Medicare dataset. The index date was defined as the date of breast cancer diagnosis. Subjects were required to have continuous enrollment in Medicare fee-for-service parts A and B three years before (baseline) and two years after (follow-up) breast cancer diagnosis. Patients were excluded if they had another cancer, breast cancer diagnosed on death certificate/autopsy, diagnosis month not available in the dataset, or diagnosed with dementia or personality disorders in the baseline period. International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes were utilized at baseline to identify patients with anxiety, depression, or major psychiatric illness (i.e., bipolar disorder, schizophrenia, or other psychotic disorders). Demographic and clinical characteristics for subjects with and without mental illness were summarized. Odds ratios and 95% confidence intervals for the association between mental illness and demographic and clinical characteristics were estimated.

Results: A total of 16,636 subjects were selected for inclusion in this analysis, with 23.8% having a diagnosis of mental illness in the 3-year baseline period. Compared to those without mental illness, those with mental illness were slightly more likely to be white (91.6% vs. 88.9%), reside in a neighborhood with a lower income ($49,577 vs. $53,031), use tobacco (5.9% vs. 3.6%), and have more medical comorbidities (≥3 medical comorbidities: 28.2% vs. 17.8%). Mentally ill breast cancer patients were also less likely to be married (39.6% vs. 46.0%). Compared to those without mental illness, a slightly higher proportion of patients with mental illness had poorly

differentiated tumors (24.0% vs. 23.0%) and more positive lymph nodes (≥10 positive lymph nodes: 12.3% vs. 10.9%). Breast-conserving surgery was more common than mastectomies overall, but patients with mental illness were less likely to receive adjuvant radiation following this procedure compared to those without mental illness (83.9% vs. 86.5%). In the logistic regression model, patients with mental illness were more likely to be younger, white, divorced and have multiple comorbidities.

Conclusion: The findings of this study provide evidence that mentally ill breast cancer patients were more likely to suffer from medical comorbidities and have more positive lymph nodes. They are also less likely to receive adjuvant radiation therapy following breast conserving surgery. Increased attention and care coordination would benefit mentally ill breast cancer patients.

Introduction

Breast cancer is the most commonly diagnosed cancer among women in the United States—with the exception of non-melanomatous skin cancer—and a significant cause of morbidity and mortality. In 2014 alone, it is estimated that breast cancer accounted for almost 30% of newly diagnosed cancer cases. Specifically, 232,670 incident cases of invasive breast cancer were diagnosed among women. Although death rates from breast cancer have been declining since the late 1980's, an estimated 40,000 deaths occurred in women in 2014 (Siegel, 2014). Many risk factors contribute to the occurrence of breast cancer, but the two most important risk factors are female sex and increasing age (ACS, 2014). Ninety nine percent of newly diagnosed cancer cases occur in women, with the risk being largest in the elderly (Siegel, 2014; ACS, 2014; Berry, 2005).

Along with an increased risk for breast cancer, the elderly population is faced with a barrage of psychosocial stressors. A decrease in cognitive skills, sensory abilities, and social relationships, as well as an increase in comorbidities, are just a few factors influencing their mental health status (Harris, 2003). It has been reported that 20% of adults over the age of 65 suffer from one or more mental disorders in the US and this number is only expected to rise. By 2030, it is estimated that 15 million elderly persons will have a mental disorder (Jeste, 1999).

Because mental disorders are very common in the general population, one can estimate that the prevalence of mental illness at the time of breast cancer diagnosis is similar to or higher than that of the general population. However, the relationship between pre-existing mental illness and breast cancer is poorly understood in the literature. The purpose of this study is to describe the demographic, clinical, and tumor characteristics of mentally ill elderly breast cancer patients.

Materials and Methods

Data Source

This retrospective cohort study was conducted using the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database. The linked SEER-Medicare dataset is a collaborative project of the National Cancer Institute, the SEER cancer registries, and the Centers for Medicare and Medicaid Services. The dataset links SEER registry data with Medicare claims for covered health care services, including hospital, physician, outpatient, home health, and hospice care. The SEER dataset is made up of population-based tumor registries that collect information on incident cancer cases occurring in SEER geographic locations. The information collected is extensive and covers a patient's demographic characteristics, date of diagnosis, tumor histology, tumor stage, tumor grade, type of initial surgical treatment or radiation therapy (recommended or provided within 4 months of diagnosis), follow-up of vital status, and cause of death. The SEER data are the best available for assessing cancer incidence and capture neoplasms occurring in approximately 28% of the US population. Although a very useful database, the SEER data alone do not contain information on screening, comorbidities, or treatment provided more than 4 months after diagnosis (Warren, 2002). By linking to Medicare claims, the dataset becomes much more comprehensive, allowing for a thorough evaluation of patient characteristics and treatment. Medicare is the primary insurer for those over 65 years of age in the US; therefore, Medicare has wide coverage, encompassing 97% of the elderly. The linkage of the SEER data with the Medicare data was based on an algorithm that uses a patient's social security number, name, sex, and date of birth. When examined for completeness, 93% of patients in the SEER database who were 65 years or older were found in the Medicare enrollment file. Data for

the analysis were extracted from the SEER-Medicare dataset from January 1, 2002 through December 31, 2009.

Patient Selection

In this retrospective cohort study, subjects 68 years of age or older diagnosed with stage I, II, or IIIa incident breast cancer between January 1, 2005 and December 31, 2007 were identified in the SEER-Medicare dataset (Figure 1). The index date was defined as the date of breast cancer diagnosis. Subjects were required to have continuous enrollment in Medicare parts A and B for the three years before and two years following breast cancer diagnosis. Patients were excluded if (1) they were enrolled in an HMO in the three years before or two years after breast cancer diagnosis, (2) they had another cancer in addition to breast cancer, (3) were diagnosed with breast cancer on death certificate or autopsy, (4) if diagnosis month was not available in the dataset, or (5) if they were diagnosed with dementia or personality disorders in the three years prior to breast cancer diagnosis. Patients were classified as having mental illness if an International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) code for anxiety, depression, or major psychiatric illness (i.e., bipolar disorder, schizophrenia or other psychotic disorder) was present in the Medicare claims data during the 3-year pre-diagnosis (baseline) period (Table 1). Medical comorbidities were also determined for the baseline period based on ICD-9-CM codes from the Medicare claims files and these were used to calculate the Deyo-Charlson Comorbidity Index. This index was validated in cohort studies using administrative claims data. The calculation of this index excluded all cancer-related and dementia diagnoses.

Variables of Interest

Variables of interest included patient demographics, clinical and tumor characteristics, and type of breast cancer treatment provided in the first two years after breast cancer diagnosis. Patient and tumor characteristics were extracted from the SEER data. Information on surgery, chemotherapy, and radiotherapy for the 2-year follow-up period was extracted from Medicare claims data, using ICD-9-CM, Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes (see Appendix).

Statistical Analysis

Demographic, clinical and tumor characteristics, as well as treatment received, for subjects with and without mental illness were summarized using descriptive statistics. Logistic regression was used to estimate the odds ratios and 95% confidence intervals for the association between mental illness and clinic-demographic characteristics, including treatment received. Analyses were also repeated by mental illness type using multinomial logistic regression. For analyses conducted by type of mental illness, patients were categorized into the following mutually exclusive groups: anxiety only, depression only, both anxiety and depression, or major psychiatric illness. If a patient had depression and/or anxiety in addition to major psychiatric illness, the major psychiatric illness was considered primary and they were analyzed in that group.

Results

A total of 16,636 subjects were selected for inclusion in this analysis. Of those, 3,961 (23.8%) had a diagnosis of mental illness in the 3-year baseline period. The most common form of

mental illness in this population was depression (8.3%), followed by anxiety (7.6%), anxiety and depression (5.1%%), and major psychiatric illness (2.9%).

Demographic and Clinical Characteristics

A detailed description of all demographic and clinical characteristics for those with and without mental illness is presented in Table 2. Compared to those without mental illness, those with mental illness were slightly more likely to be white (91.6% vs. 88.9%), to reside in a neighborhood with a lower income ($49,577 vs. $53,031), have more tobacco use (5.9% vs. 3.6%), and have more medical comorbidities (≥3 comorbidities: 28.2% vs. 17.8%). A larger proportion of those with mental illness had also never been married (39.6% vs. 46.0%) or had been divorced (8.0% vs. 6.2%). Additionally, of all the types of mental illness, those with major psychiatric illness were least likely to have been married, most likely to have been divorced, had the largest medical comorbidity burden, and were the most likely to use tobacco. Patients with major psychiatric illness also had a larger proportion of patients over the age of 85 years compared to those without mental illness (17.3% vs. 12.1%). In the multivariable logistic regression model (Figure 2), patients with mental illness were more likely to have multiple comorbidities, to be divorced, and to use tobacco, while they were less likely to be African American or Asian/Pacific islander. When examining these relationships by type of mental illness (Table 5), those with depression or comorbid depression and anxiety were less likely to be older. Patients with any type of mental illness were more likely to have multiple comorbidities, but the magnitude of the association increased with increasing severity of mental illness (anxiety, depression, anxiety and depression, and major psychiatric illness). Those with depression or comorbid depression and anxiety were less likely to be African American, while patients with all types of mental illness were less likely to be Asian/Pacific Islander, except for anxiety. Patients

with anxiety were also more likely to be Hispanic, while those with major psychiatric illness were less likely to be Hispanic. The only group to be significantly less likely to be married was those patients with major psychiatric disorders, while only those with depression were more likely to be divorced. Patients with anxiety and major psychiatric disorders were also significantly more likely to use tobacco. For receipt of mammogram, those with anxiety and depression were significantly more likely to have received a mammogram in the 3 years prior to breast cancer diagnosis, while those with major psychiatric disorder were significantly less likely to have received this procedure.

Tumor Characteristics

Table 3 presents data on the tumor characteristics at the time of breast cancer diagnosis. When evaluating the presence of any form of mental illness compared to those without mental illness, a slightly higher percentage of those with mental illness had poorly differentiated tumors (24% vs. 23%, respectively) and ten or more positive lymph nodes (12.3% vs. 10.9%, respectively). However, it is important to note that tumor characteristics varied by type of mental illness. For example, patients with anxiety had a slightly smaller proportion of poorly differentiated tumors and slightly larger proportion of larger tumors compared to those without mental illness. A smaller proportion of patients with depression as compared to those without mental illness had stage IIIa cancer, but a larger proportion had ER/PR negative tumors, poorly differentiated tumors and more than 10 positive lymph nodes. In patients with comorbid anxiety and depression, a larger proportion of patients had ER/PR negative tumors, larger tumors, and more positive lymph nodes compared to those without mental illness. A larger proportion of patients with major psychiatric illness had stage II or IIIa cancer, larger tumors, and more positive lymph nodes compared to those without mental illness. These patients also had the highest proportion

of stage II or IIIa cancers, large tumors and more positive lymph nodes among those with mental illness. In the logistic regression model, no significant differences were demonstrated between patients with and without mental illness with regard to aggressive tumor characteristics. The same was true in the multinomial logistic regression model that examined this relationship by types of mental illness (Table 5), with the exception of those with major psychiatric illness. Patients with major psychiatric illness were significantly more likely to have more positive lymph nodes than those without mental illness.

Treatment Received

When examining treatment received during the 2-year follow-up period (Table 4), mastectomies were much less common than BCS overall; however, when we compared those with and without mental illness, a higher proportion of patients with mental illness had a mastectomy, while the reverse was seen for BCS. Although the relationship between mental illness and surgery type was not significant in the logistic regression models (Figure 2, Table 5), a tendency was seen, especially for those with anxiety or major psychiatric illness. Consistent with standard of care, receipt of adjuvant radiation or chemotherapy treatment varied by type of surgery received. For all patients, adjuvant treatment with radiation was more commonly administered with BCS than mastectomies, while the opposite was true for adjuvant chemotherapy. Overall, the proportion of patients receiving adjuvant radiation with BCS was smaller for those with mental illness compared to those without this diagnosis. In those with major psychiatric illness, the proportion of patients receiving radiation after BCS was even smaller. When examining adjuvant treatment associated with mastectomies, a larger proportion of patients with mental illness received chemotherapy or radiation (with the exception of those patients with anxiety only). A larger proportion of patients with major psychiatric illness than those without mental illness received

no surgery. When surgery was not received, patients with major psychiatric illness were more likely to receive radiation than chemotherapy, but compared to those with mental illness, they had higher rates of chemotherapy and lower rates of radiation. Patients with major psychiatric illness were also slightly more likely to have no recorded treatment with surgery, chemotherapy, or radiation.

Discussion

In the present study, 23.8% of elderly early stage breast cancer patients had pre-existing mental illness at the time of breast cancer diagnosis. Compared to those without mental illness, those with mental illness were slightly more likely to be white, reside in a neighborhood with a lower income, to use tobacco use and to suffer from more medical comorbidities. A larger proportion of those with mental illness had also never been married or had been divorced. These results are consistent with previous literature suggesting that 20% of adults over the age of 65 suffer from mental illness in the US (Jeste, 1999). Kessler et al (2005) reported that non-Hispanic blacks or Hispanics have a significantly lower risk of anxiety and mood disorders compared with whites (Kessler, 2005). Sareen and colleagues (2011) examined the impact of household income on mental illness and found that not only is lower household income associated with mental disorders, but with suicide attempts as well. Additionally, when income levels decrease, there is an increased risk for incident mental disorders (Sareen, 2011). However, reverse causality cannot be ruled out, as it is unclear whether decreased income contributes to mental illness or the presence of mental illness contributes to a decrease in income. Tobacco use is known to be high in those with mental illness. The CDC reports that 36% of those with mental illness smoke compared to 21% of those without mental illness, representing a 71% increased risk (CDC,

2014). Although tobacco use in the current study is assessed based on ICD-9-CM codes, which we acknowledge led to underreporting, the magnitude of difference in those with and without mental illness is still consistent with reported rates of smoking. In our study, the increased risk for those with mental illness (5.9%) versus those without mental illness (3.6%) is approximately 64%.

The medical comorbidity burden among patients with mental illness was demonstrated to be much higher than that of their counterparts without mental illness in this study. Previous research has shown that those with mental illness are more likely to have chronic conditions such as cardiovascular disease, respiratory disease, diabetes, and obesity (Bresee, 2011; Filik, 2006; Compton, 2006; Goodwin, 2004). This finding is important to understanding the burden of mental illness on breast cancer prognosis, as numerous publications have cited a statistically significant association between the presence of comorbid conditions and overall survival or all-cause mortality in breast cancer patients. Although there are many factors affecting breast cancer prognosis, the presence of medical comorbidities plays a role in determining a patient's overall survival (Nagel, 2004; Houterman, 2004; Piccirillo, 2004; Louwman, 2005; Janssen-Heijnen, 2007; Cronin-Fenton, 2007; Yancik, 2001). A study by Piccirillo and colleagues found that the rate of overall mortality in breast cancer patients with moderate and severe comorbidity levels increased by 83% and 98%, respectively, compared to those without any medical comorbidities. An additional study by Louwman et al. (2005) found that women with breast cancer without medical comorbidity had a 5-year survival rate of 87%, but this rate dropped to 59% in those with 2 or more medical comorbidities.

In addition to having multiple medical comorbidities, patients with mental illness in our study lacked certain protective factors associated with breast cancer, such as being married. A study

by Wu and colleagues (2012) showed that patients with mental illness who never married required significantly longer durations of treatment for their mental illness than their counterparts who were married or previously married. Further, a more recent study by Aizer et al. (2013) found that being married significantly decreased the risk of having metastatic cancer at the time of diagnosis and conferred a decreased likelihood of death compared with those who were single, separated, divorced, or widowed. Not only was the survival benefit associated with marriage large, but it was larger than the benefit of chemotherapy for patients with breast cancer. A large proportion of the benefit derived from marriage is likely due to increased social support. Research has consistently demonstrated that social support confers significant benefits in cancer patients' quality of life, quality of care, and survival.

Another protective factor that is typically present to a smaller degree in patients with mental illness than without is receipt of appropriate screening services. Although a similar proportion of patients with and without mental illness received a mammogram in the 3 year period prior to breast cancer diagnosis, those with major psychiatric illness showed a much lower rate. Several studies have evaluated cancer screening in patients with mental illness, but their results are mixed. A number of studies have demonstrated decreased screening rates in those with mental disorders compared to the general population (Lindamer, 2003; Lindamer, 2006; Carney, 2006; Martens, 2009; Howard, 2010; Druss, 2002; Chochinov, 2009), while other studies have found no difference (Howard, 2010; Lasser, 2003; Dickerson, 2003; Owen, 2002; Steiner, 1998). A more recent study by Koroukian et al (2012) determined that women with mental illness were 32% less likely to receive at least one screening mammography compared to those without mental illness. Further, in the subgroup of patients who received at least one screening mammography, less women with mental illness than without mental illness received their mammography annually (Koroukian, 2012). In a study by Chochinov and colleagues (2009), women with

schizophrenia were 36% less likely to have received one screening mammogram within the past 2 years compared to those without this diagnosis.

When examining tumor characteristics between groups, a slightly higher proportion of patients with mental illness had poorly differentiated tumors and more positive lymph nodes than those without mental illness. Patients with major psychiatric illness were also more likely to be later stage and have larger tumors. A possible explanation for these more advanced tumor characteristics at diagnosis could be delayed diagnosis. Available research suggests that patients with mental illness face a delay in time to diagnosis of their cancers compared with that of the general population, resulting in worse prognosis at the time of diagnosis (O'Rourke, 2008; Farasatpour, 2013; Hwang, 2012).

In the current study, different treatment patterns were shown for those with and without pre-existing mental illness. Although BCS was more common than mastectomy overall, for those with mental illness compared to those without mental illness, a higher proportion received mastectomies and a lower proportion received BCS. For BCS, radiation was more commonly received than chemotherapy in both groups; however, the rate of chemotherapy was higher in those with mental illness versus those without and the rate of adjuvant radiation was lower, especially in those with major psychiatric illness. In patients who underwent a mastectomy, adjuvant chemotherapy was more commonly provided than radiation in those with and without mental illness, but the rate of each was slightly higher in those with mental illness, especially major psychiatric illness. Because patients with mental illness, especially those with major psychiatric illness, have more positive lymph nodes than those without mental illness, radiation and systemic treatment with chemotherapy are appropriate. Additionally, those with anxiety or comorbid anxiety and depression were more likely to have ER/PR negative tumors than those

without mental illness, so they would also be more likely to benefit from adjuvant chemotherapy. Regarding the lower rate of treatment with radiation in the BCS group, another possibility is that the administration might pose a challenge for those with severe mental illness and physicians might opt to perform chemotherapy even in the absence of radiation therapy. Due to the risk of ionizing radiation, the patient must be able to be left alone in the treatment room and be able to follow instructions from the technician. For those with mental illness, especially schizophrenia or other paranoid disorders, this could cause severe distress for the patient and might not be possible to perform. Additionally, if the patient is institutionalized, it could be challenging to transport the patient daily for several weeks at a time to receive their full course of treatment (Howard, 2010). However, recent advances in radiotherapy leading to shortened courses may ameliorate this issue.

The design of this study does have several limitations. First, there is no information available for the claims of HMO enrollees, healthcare provided in other settings, such as the Veterans Administration. Additionally, since we are requiring 3 years of continuous Medicare enrollment prior to diagnosis, this study is limited to patients 68 years of age or older with Medicare coverage and without HMO insurance. As such, the results might not be generalizable to the population of women with breast cancer that are younger than 68 years or to those with commercial insurance. We also require 2 years of continuous enrollment following diagnosis in order to capture complete information on initial treatment decisions. This criterion, however, might make our patients healthier than the general population of breast cancer patients. Furthermore, all reports of mental illness were based on ICD-9-CM codes. Considering that certain forms of mental illness, such as depression, are often underdiagnosed, this could lead to under-reporting and misclassification of these patients as not having a mental illness (Davidson,

1999). Further, some patients with mental illness may have never received a diagnosis, yet could still be treated as such. Additionally, mental health benefits have historically been limited for Medicare patients. Because of this, patients may not have sought medical care for their illness due to lack of coverage and therefore, would not have a diagnosis of mental illness in the database. Any of these misclassification scenarios would bias the effect to the null, thus diluting the differences seen between groups. It is important to keep in mind that diagnoses of mental illness made prior to enrollment in Medicare are not included and severity and duration of mental illness cannot be captured in this database. Patients with mental illness have up to a 25 year reduced life expectancy compared to those without mental illness. Because our study is conducted in older patients, we could be missing the most seriously mentally ill, who might have already died from a competing cause. By missing these patients, the result seen is likely not as pronounced as if these patients would have been included. Also, substance abuse was severely underreported based on claims data and could not be taken into account. Further, Part D prescription data was not available for all patients during the course of the study, so hormonal therapy was not able to be assessed. Lastly, as is the case with any observational database study, unobserved confounders that are not available in the data could affect the study results.

In conclusion, the findings of this study provide evidence that mentally ill breast cancer patients were more likely to suffer from medical comorbidities and have more positive lymph nodes. They are also less likely to receive adjuvant radiation therapy following breast conserving surgery. Increased attention and care coordination would benefit mentally ill breast cancer patients.

Figures and Tables

Figure 1. Study Design

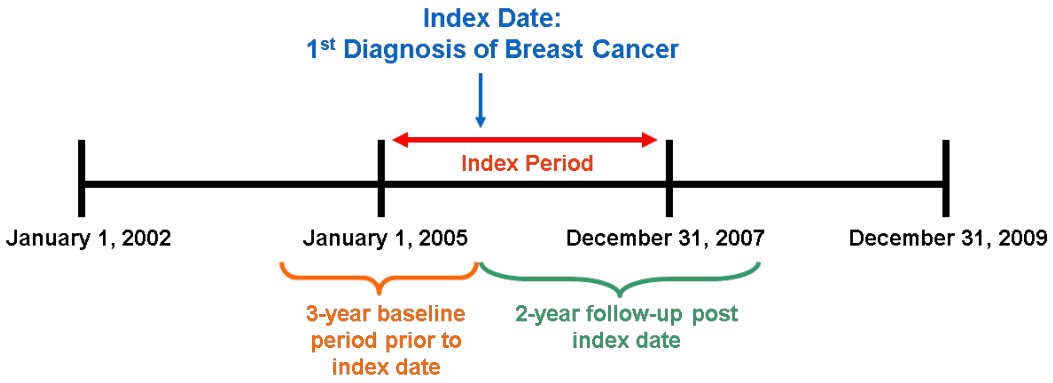


Table 1. ICD-9-CM Codes Used for the Determination of Mental Illness Status

Diagnosis	**ICD-9-CM codes**
Anxiety Disorder	308, 293.84, 300.0, 300.1, 300.2, 300.89
Depressive Disorder	296.2, 296.3, 300.4, 311, V79.0
Major Psychiatric Illness (i.e., bipolar disorder, schizophrenia or other psychotic disorder)	295, 297, 298, 293.81, 293.82, 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8, 296.9

Table 2. Demographic and clinical characteristics of early stage breast cancer patients by mental illness status

	Any Form of Mental Illness n=3961 (23.8%)	**Anxiety only n=1256 (7.6%)**	**Depression only n=1373 (8.3%)**	**Anxiety and depression n=847 (5.1%)**	**Major psychiatric illness n=485 (2.9%)**	**No Mental Illness n=12,675 (76.2%)**
Age at Diagnosis, Mean±SD	76.7±6.1	76.7±6.0	76.5±6.1	76.3±6.0	77.6±6.5	76.6±6.2
Age Group at Diagnosis, %						
68-74 years	41.7%	39.8%	44.0%	44.0%	35.9%	42.3%
75-84 years	46.7%	49.4%	44.7%	45.6%	46.8%	45.6%
85+ years	11.7%	10.8%	11.3%	10.4%	17.3%	12.1%
SEER State, %						
Connecticut	6.6%	6.4%	6.5%	6.9%	7.0%	6.4%
Michigan	4.8%	4.5%	4.5%	4.6%	7.0%	6.6%
Hawaii	0.8%	1.1%	0.5%	0.8%	0.4%	1.4%
Iowa	7.8%	7.3%	7.6%	8.5%	8.7%	6.2%
New Mexico	1.9%	1.5%	2.3%	2.1%	1.4%	2.0%
Washington	5.7%	4.9%	7.1%	4.6%	5.4%	5.6%
Utah	3.3%	2.6%	4.0%	3.7%	2.1%	2.0%
Georgia	12.3%	11.2%	13.0%	13.2%	12.0%	11.3%
California	29.3%	29.7%	29.1%	29.1%	29.5%	31.3%
Kentucky	8.8%	8.5%	8.7%	8.6%	10.3%	6.4%
Louisiana	6.3%	7.6%	5.5%	5.2%	7.4%	5.8%
New Jersey	12.4%	14.8%	11.3%	12.6%	8.9%	15.1%
Race, %						
White	91.6%	89.7%	92.9%	93.7%	89.0%	88.9%
African American	5.6%	6.4%	4.6%	3.9%	9.1%	6.2%
Asian or Pacific Islander	2.2%	3.7%	1.5%	1.8%	1.2%	4.2%
American Indian/Alaska Native Islander	0.3%	0.1%	0.5%	0.2%	0%	0.2%

	Any Form of Mental Illness n=3961 (23.8%)	Anxiety only n=1256 (7.6%)	Depression only n=1373 (8.3%)	Anxiety and depression n=847 (5.1%)	Major psychiatric illness n=485 (2.9%)	No Mental Illness n=12,675 (76.2%)
Other	0.2%	0.2%	0.1%	0.1%	0.4%	0.1%
Unknown	0.3%	0.1%	0.4%	0.2%	0.2%	0.4%
Ethnicity, %						
Hispanic	5.0%	5.8%	4.8%	5.7%	2.9%	4.3%
Non-Hispanic	95%	94.2%	95.2%	94.3%	98.1%	95.7%
Marital Status, %						
Single (never married)	6.4%	6.4%	5.4%	6.7%	8.7%	6.3%
Married (including common law)	39.6%	42.4%	39.4%	38.3%	35.5%	46.0%
Separated	0.4%	0.6%	0.4%	0.4%	0.2%	0.4%
Divorced	8.0%	7.5%	8.1%	7.7%	9.7%	6.2%
Widowed	42.1%	39.5%	43.1%	44.0%	42.5%	37.2%
Unknown	3.5%	3.7%	3.6%	3.0%	3.5%	3.9%
Census-based median income level, Mean±SD	49,577±22,967	49,745±23,350	50,647±23,708	48,029±20,744	48,807±23,409	53,031±24,857
Comorbid Conditions, %						
Myocardial Infarction	8.2%	7.6%	6.6%	9.1%	12.4%	5.2%
Congestive Heart Failure	20.8%	17.8%	19.5%	22.8%	28.9%	13.5%
Peripheral Vascular Disease	15.2%	13.5%	14.9%	16.7%	18.4%	10.7%
Cerebrovascular Disease	29.7%	25.8%	28.4%	30.6%	42.3%	20.1%
Chronic Pulmonary Disease	39.2%	37.8%	39.5%	41.2%	38.4%	27.6%
Rheumatologic Disease	9.1%	7.6%	8.9%	12.8%	6.8%	7.2%
Peptic Ulcer Disease	5.7%	4.4%	5.1%	8.2%	6.4%	3.3%

	Any Form of Mental Illness n=3961 (23.8%)	Anxiety only n=1256 (7.6%)	Depression only n=1373 (8.3%)	Anxiety and depression n=847 (5.1%)	Major psychiatric illness n=485 (2.9%)	No Mental Illness n=12,675 (76.2%)
Mild Liver Disease	1.0%	0.8%	0.8%	1.5%	0.8%	0.8%
Moderate or Severe Liver Disease	0.8%	0.8%	0.4%	1.1%	1.2%	0.4%
Diabetes	34.1%	31.1%	34.7%	34.4%	39.6%	30.9%
Diabetes with Chronic Complications	7.6%	6.3%	7.8%	7.0%	11.3%	4.9%
Hemiplegia or Paraplegia	1.8%	0.9%	1.8%	2.0%	3.7%	0.8%
Renal Disease	7.8%	6.8%	7.4%	8.0%	11.1%	4.9%
AIDS	0.6%	0.4%	0.5%	0.9%	0.6%	0.4%
Number of Medical Comorbidities, %						
0	23.4%	27.5%	23.3%	20.8%	17.5%	35.3%
1-2	48.4%	49.4%	48.8%	47.9%	45.6%	46.9%
≥3	28.2%	23.1%	27.9%	31.3%	36.9%	17.8%
Charlson Comorbidity Index, Mean±SD	2.0±2.0	1.8±1.9	2.0±1.9	2.2±2.2	2.5±2.3	1.4±1.7
Mammogram Performed, %	77.5%	76.7%	79.2%	80.6%	69.5%	77.9%
Tobacco Use, %	5.9%	5.3%	5.2%	6.7%	8.0%	3.6%

Table 3. Tumor characteristics of patients with early-stage breast cancer by mental illness status

	Any Form of Mental Illness n=3961 (23.8%)	Anxiety only n=1256 (7.6%)	Depression only n=1373 (8.3%)	Anxiety and depression n=847 (5.1%)	Major psychiatric illness n=485 (2.9%)	No Mental Illness n=12,675 (76.2%)
AJCC Stage at Diagnosis, %						
I	59.9%	59.4%	62.6%	58.0%	57.1%	61.5%
IIa	25.7%	25.0%	24.0%	28.6%	27.0%	24.5%
IIb	9.6%	10.0%	9.7%	8.4%	10.1%	9.0%
IIIa	4.8%	5.6%	3.6%	5.1%	5.8%	5.0%
ER/PR Status, %						
ER+/PR+	65.2%	66.6%	65.6%	63.2%	64.1%	66.6%
ER+/PR-	12.7%	13.1%	12.0%	13.6%	12.2%	12.9%
ER-/PR+	0.6%	0.6%	0.8%	0.4%	0.6%	0.7%
ER-/PR-	13.5%	12.7%	14.1%	14.4%	12.8%	12.5%
Other/Unknown	7.9%	7.0%	7.6%	8.5%	10.3%	7.3%
Histologic Grade, %						
Well differentiated	26.5%	27.3%	25.6%	26.3%	27.0%	26.4%
Moderately differentiated	42.4%	43.3%	42.8%	42.0%	39.4%	43.8%
Poorly differentiated	24.0%	22.0%	24.8%	24.2%	26.2%	23.0%
Undefined	0.9%	1.0%	1.0%	1.0%	0.8%	0.9%
Unknown	6.2%	6.5%	5.8%	6.5%	6.6%	5.9%
Tumor size, %						
≤10 mm	29.5%	29.1%	30.8%	29.2%	27.6%	29.9%
>10 to ≤20 mm	39.0%	38.9%	40.2%	38.3%	37.1%	39.4%

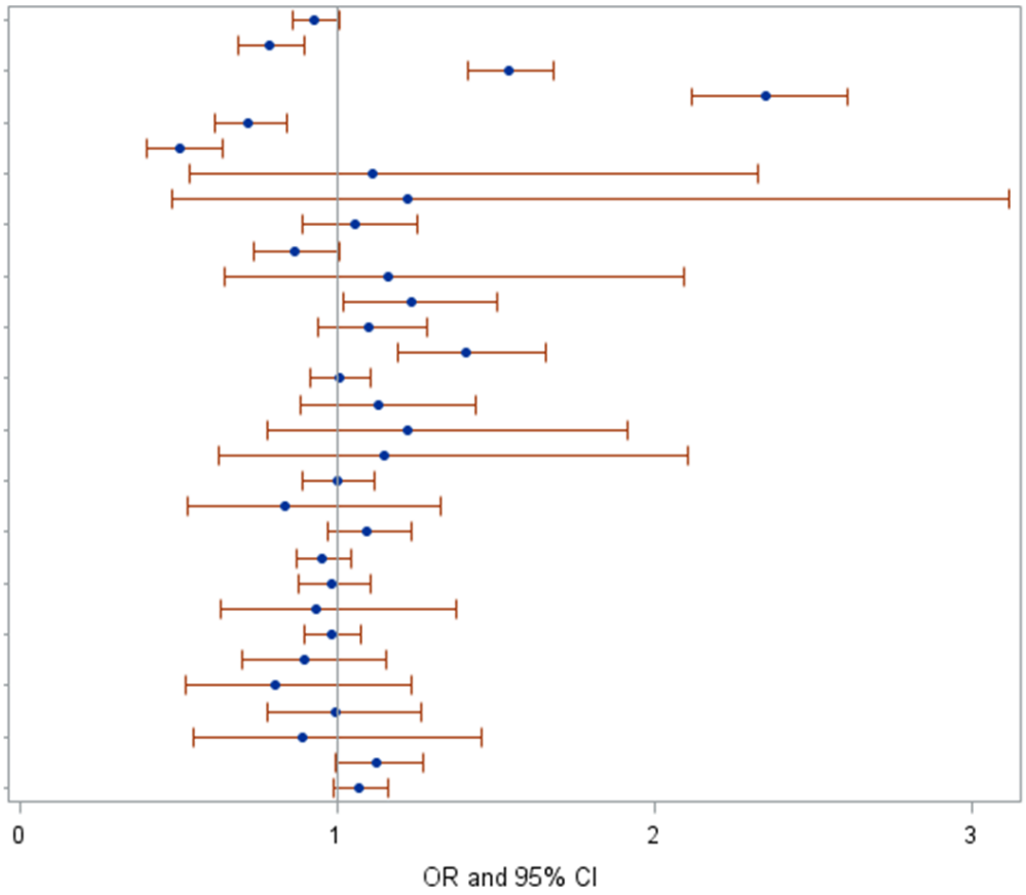
	Any Form of Mental Illness n=3961 (23.8%)	Anxiety only n=1256 (7.6%)	Depression only n=1373 (8.3%)	Anxiety and depression n=847 (5.1%)	Major psychiatric illness n=485 (2.9%)	No Mental Illness n=12,675 (76.2%)
>20 to ≤50 mm	26.4%	26.8%	24.5%	27.3%	29.1%	25.4%
>50 mm	2.9%	3.0%	2.0%	3.0%	4.7%	3.2%
Unknown	2.2%	2.2%	2.4%	2.4%	1.4%	2.1%
Number of Positive Lymph Nodes, %						
0	66.1%	67.0%	67.7%	66.1%	59.0%	68.7%
1-3	17.4%	17.8%	17.4%	16.9%	17.3%	16.2%
4-9	4.0%	4.7%	3.0%	4.6%	3.9%	4.1%
≥10	12.3%	10.3%	11.7%	12.3%	19.8%	10.9%
Unknown	0.2%	0.2%	0.2%	0.1%	0%	0.1%

Table 4. Treatment received in the 2 years following breast cancer diagnosis, by mental illness status

	Any Form of Mental Illness n=3961	**Anxiety only n=1256**	**Depression only n=1373**	**Anxiety and depression n=847**	**Major psychiatric illness n=485**	**No Mental Illness n=12,675**
Breast-conserving surgery, n (%)	2204 (55.6%)	677 (53.9%)	804 (58.6%)	481 (56.8%)	242 (49.9%)	7283 (57.5%)
Adjuvant Chemotherapy	924 (41.9%)	264 (39.0%)	347 (43.2%)	203 (42.2%)	110 (45.5%)	2679 (36.8%)
Adjuvant Radiation	1850 (83.9%)	573 (84.6%)	686 (85.3%)	410 (85.2%)	181 (74.8%)	6300 (86.5%)
Mastectomy, n (%)	1461 (36.9%)	480 (38.2%)	480 (35.0%)	309 (36.5%)	192 (39.6%)	4399 (34.7%)
Adjuvant Chemotherapy	744 (50.9%)	237 (49.4%)	238 (49.6%)	163 (52.8%)	106 (55.2%)	2133 (48.5%)
Adjuvant Radiation	569 (39.0%)	179 (37.3%)	187 (39.0%)	125 (40.5%)	78 (40.6%)	1653 (37.6%)
No surgery, n (%)	296 (7.5%)	99 (7.9%)	89 (6.5%)	57 (6.7%)	51 (10.5%)	993 (7.8%)
Chemotherapy	138 (46.6%)	41 (41.4%)	44 (49.4%)	31 (54.4%)	22 (43.1%)	353 (35.6%)
Radiation	168 (56.8%)	59 (59.6%)	52 (58.4%)	33 (57.9%)	24 (47.1%)	582 (58.6%)
No recorded treatment with surgery, chemotherapy or radiation	78 (2.0%)	29 (2.3%)	20 (1.5%)	12 (1.4%)	17 (3.5%)	291 (2.3%)

Figure 2. Adjusted odds ratios and 95% confidence intervals for the association between mental illness and patient/tumor characteristics

Effect	Odds Ratio	95% Confidence Interval	
75-84 yrs vs. 68-74	0.93	0.86	1.01
85+ yrs vs. 68-74*	0.78	0.69	0.90
1-2 comorbidities vs. 0*	1.54	1.41	1.68
3+ comorbidities vs. 0*	2.35	2.12	2.61
African American vs. white*	0.72	0.61	0.84
Asian/PI vs. white*	0.51	0.40	0.64
Amer. Indian vs. white	1.11	0.53	2.33
Other vs. white	1.22	0.48	3.12
Hispanic vs. non-Hispanic	1.06	0.89	1.25
Married vs. single	0.86	0.74	1.01
Separated vs. single	1.16	0.65	2.09
Divorced vs. single*	1.24	1.02	1.50
Widowed vs. single	1.10	0.94	1.28
Tobacco use vs. none*	1.41	1.19	1.66
Mammography vs. none	1.01	0.92	1.11
Stage IIa vs. I	1.13	0.88	1.44
Stage IIb vs. I	1.22	0.78	1.91
Stage IIIa vs. I	1.15	0.63	2.11
ER+/PR- vs. ER+/PR+	1.00	0.89	1.12
ER-/PR+ vs. ER+/PR+	0.84	0.53	1.33
ER-/PR- vs. ER+/PR+	1.09	0.97	1.23
Grade II vs. I	0.95	0.87	1.05
Grade III vs. I	0.98	0.88	1.10
Grade IV vs. I	0.93	0.63	1.37
Size 10-20 mm vs. ≤10	0.98	0.90	1.08
Size 20 to 50 vs. ≤10	0.90	0.70	1.16
Size >50 vs. ≤10	0.80	0.52	1.24
1-3 Positive nodes vs. 0	1.00	0.78	1.27
4-9 Positive nodes vs. 0	0.89	0.55	1.45
10+ Positive nodes vs. 0	1.12	0.99	1.27
Mastectomy vs. BCS	1.07	0.99	1.16



*P<0.05.

Table 5. Odds ratios and 95% confidence intervals for the association between specific types of mental illness (vs. no mental illness) and patient/tumor characteristics

	Anxiety only vs. no mental illness	**Depression only vs. no mental illness**	**Anxiety and depression vs. no mental illness**	**Major psychiatric illness vs. no mental illness**
Age (vs. 68-74 yrs)				
75-84 yrs	1.11 (0.98, 1.26)	**0.83 (0.73, 0.94)***	**0.82 (0.70, 0.96)***	1.02 (0.82, 1.26)
85+ yrs	0.88 (0.71, 1.10)	**0.71 (0.58, 0.87)***	**0.62 (0.47, 0.80)***	1.09 (0.80, 1.47)
Comorbidities (vs. 0 comorbidities)				
1-2 comorbidities	**1.33 (1.16, 1.53)***	**1.58 (1.37, 1.81)***	**1.74 (1.45, 2.09)***	**1.86 (1.44, 2.41)***
3+ comorbidities	**1.61 (1.36, 1.91)***	**2.42 (2.06, 2.84)***	**3.06 (2.50, 3.75)***	**3.69 (2.82, 4.84)***
Race (vs. white)				
African American	0.93 (0.73, 1.19)	**0.59 (0.45, 0.77)***	**0.46 (0.32, 0.66)***	1.03 (0.74, 1.43)
Asian/Pacific Islander	0.87 (0.64, 1.18)	**0.33 (0.21, 0.52)***	**0.40 (0.24, 0.68)***	**0.29 (0.13, 0.65)***
American Indian/Alaskan	0.37 (0.05, 2.72)	2.28 (0.98, 5.31)	1.01 (0.24, 4.29)	NA
Other	1.22 (0.28, 5.30)	0.58 (0.08, 4.35)	0.93 (0.12, 7.03)	**4.46 (1.01, 19.78)***
Ethnicity (vs. non-Hispanic)				
Hispanic	**1.33 (1.03, 1.72)***	1.00 (0.77, 1.30)	1.16 (0.85, 1.58)	**0.38 (0.19, 0.74)***
Marital Status (vs. single)				

	Anxiety only vs. no mental illness	**Depression only vs. no mental illness**	**Anxiety and depression vs. no mental illness**	**Major psychiatric illness vs. no mental illness**
Married	0.94 (0.73, 1.21)	0.97 (0.75, 1.25)	0.77 (0.57, 1.04)	**0.66 (0.46, 0.94)***
Separated	1.76 (0.80, 3.88)	1.12 (0.43, 2.94)	0.88 (0.26, 2.95)	0.45 (0.06, 3.41)
Divorced	1.20 (0.88, 1.65)	**1.43 (1.04, 1.95)***	1.10 (0.76, 1.60)	1.17 (0.76, 1.80)
Widowed	1.05 (0.81, 1.34)	**1.34 (1.04, 1.73)***	1.12 (0.83, 1.50)	0.76 (0.54, 1.08)
Tobacco use (vs. no tobacco use)				
Tobacco user	**1.37 (1.05, 1.79)***	1.20 (0.93, 1.56)	1.20 (0.93, 1.56)	**1.84 (1.29, 2.60)***
Baseline Mammography (vs. no mammography)				
Mammography	0.95 (0.82, 1.11)	1.05 (0.91, 1.22)	**1.25 (1.04, 1.51)***	**0.76 (0.62, 0.95)***
AJCC Stage (vs. stage I)				
Stage IIa	1.09 (0.74, 1.59)	1.29 (0.87, 1.89)	1.29 (0.81, 2.05)	0.78 (0.41, 1.48)
Stage IIb	1.23 (0.61, 2.49)	1.93 (0.94, 3.97)	1.07 (0.45, 2.53)	0.56 (0.17, 1.80)
Stage IIIa	1.26 (0.49, 3.24)	1.68 (0.63, 4.48)	0.80 (0.25, 2.51)	0.66 (0.14, 3.16)
ER/PR Status (vs. ER+/PR+)				
ER+/PR-	1.01 (0.85, 1.21)	0.95 (0.80, 1.13)	1.10 (0.89, 1.36)	0.93 (0.70, 1.24)
ER-/PR+	0.80 (0.37, 1.75)	1.08 (0.57, 2.06)	0.50 (0.16, 1.58)	0.79 (0.25, 2.54)
ER-/PR-	1.04 (0.86, 1.27)	1.11 (0.93, 1.33)	1.20 (0.96, 1.51)	1.01 (0.74, 1.36)

	Anxiety only vs. no mental illness	Depression only vs. no mental illness	Anxiety and depression vs. no mental illness	Major psychiatric illness vs. no mental illness
Histologic Grade (vs. grade I)				
Grade II	0.94 (0.81, 1.08)	1.01 (0.88, 1.17)	0.95 (0.79, 1.13)	0.85 (0.68, 1.08)
Grade III	0.87 (0.72, 1.04)	1.10 (0.92, 1.31)	0.98 (0.78, 1.22)	1.02 (0.77, 1.34)
Grade IV	0.96 (0.52, 1.78)	1.01 (0.56, 1.83)	0.86 (0.41, 1.81)	0.79 (0.28, 2.21)
Tumor size (vs. ≤10 mm)				
Size 10-20 mm	0.99 (0.86, 1.15)	0.98 (0.85, 1.13)	0.98 (0.82, 1.18)	0.95 (0.74, 1.20)
Size 20 to 50 vs. ≤10	0.93 (0.63, 1.38)	0.69 (0.46, 1.02)	0.98 (0.60, 1.58)	1.31 (0.67, 2.57)
Size >50 vs. ≤10	0.78 (0.40, 1.52)	0.42 (0.20, 0.87)	1.10 (0.49, 2.47)	1.95 (0.65, 5.87)
Positive Lymph Nodes (vs. 0 positive nodes)				
1-3 Positive nodes	1.00 (0.68, 1.46)	0.82 (0.56, 1.21)	0.99 (0.62, 1.58)	1.46 (0.78, 2.73)
4-9 Positive nodes	0.94 (0.44, 2.02)	0.55 (0.24, 1.28)	1.45 (0.58, 3.59)	1.03 (0.32, 3.30)
10+ Positive nodes	0.94 (0.76, 1.16)	1.07 (0.88, 1.30)	1.17 (0.93, 1.49)	**1.67 (1.28, 2.18)***
Surgery (vs. BCS)				
Mastectomy	1.14 (0.997, 1.30)	1.00 (0.88, 1.13)	1.03 (0.87, 1.20)	1.22 (0.99, 1.51)

*P<0.05.

CHAPTER 2

DIAGNOSIS AND TREATMENT DELAYS OF ELDERLY BREAST CANCER PATIENTS WITH PRE-EXISTING MENTAL ILLNESS

Abstract

Aim: To compare diagnosis and treatment delays for elderly breast cancer patients with and without pre-existing mental illness.

Methods: Patients 68 years of age or older diagnosed with incident breast cancer (stage I, II, or IIIa) during the period between January 1, 2005 and December 31, 2007 were identified in the SEER-Medicare database. The index date was defined as the date of breast cancer diagnosis. Subjects had continuous enrollment in Medicare fee-for-service parts A and B for three years before (baseline) and two years after (follow-up) breast cancer diagnosis. Patients were excluded if they had another cancer, diagnosed on death certificate/autopsy, diagnosis month was not available, or diagnosed with dementia or personality disorder in the baseline period. Mental illness was defined using ICD-9-CM codes for anxiety, depression, and major psychiatric disorders in the baseline period. End-points were time to diagnosis, initial treatment, surgery, adjuvant chemotherapy, and adjuvant radiation. Mean and median time to diagnosis and time to start of therapy was assessed. Adjusted relative risks and 95% confidence intervals were estimated to assess the association between mental illness and diagnosis/treatment delays of ≥60 and ≥90 days.

Results: Of the 16,636 subjects included in this analysis, 3961 (23.8%) had a diagnosis of mental illness in the baseline period. There were no significant differences in the risk of diagnosis, initial treatment, surgery, or adjuvant radiation delays of ≥60 days or ≥90 days between those with and without mental illness. Mentally ill breast cancer patients were more likely than those without mental illness to experience adjuvant chemotherapy delay of ≥90 days (RR=1.13 [95% CI 1.01, 1.26]). When examining these associations by type of mental illness, there were no significant differences in diagnosis and treatment delays seen for those with depression or

anxiety only. However, patients with comorbid anxiety and depression had an increased risk for diagnosis delay of ≥90 days (RR=1.11 [95% CI 1.003, 1.23]) and those with major psychiatric illness had an increased risk of initial treatment delay of ≥60 days (RR=1.36 [95% CI 1.06, 1.74]).

Conclusion: Patients with mental illness had an increased risk of delay to adjuvant chemotherapy. When examining specific types of mental illness, patients with comorbid depression and anxiety experienced an increased risk for diagnosis delays, while those with major psychiatric illness were at a high risk for initial treatment delays. Patients should be closely managed by a cross-functional care team, including a psychiatrist and oncologist, to ensure adequate care is received within an appropriate timeframe.

Introduction

Mental disorders are common in the US, with approximately one in two people facing a diagnosis in their lifetime (Kessler, 2005; Kessler, 2008; NIH, 2013). Specifically, the projected lifetime risk at age 75 years for any anxiety or mood disorder is 31.5% and 28%, respectively (Kessler, 2005).

Current literature suggests that patients with mental disorders may be less likely to follow cancer screening recommendations or pursue appropriate medical care when needed. Although the majority of women in the US obtain a medical consultation within 2 weeks of finding a lump in their breast, as many as 34% delay medical consult for over 3 months (Facione, 2002). Patients with mental illness may face an even longer delay in time to diagnosis and treatment of their cancers compared to the general population, which could result in poorer outcomes for these patients (O'Rourke, 2008; Farasatpour, 2013; Hwang, 2012). Previous research has suggested that diagnosis and treatment delays of 2 to 3 months are linked to worse tumor characteristics—such as later stage, larger tumors, more positive lymph nodes, and metastatic disease—as well as decreased survival in breast cancer patients (McLaughlin, 2012; Richards, 1999; Smith, 2013; Ermiah, 2012; Duijm, 2009; Gullatte, 2010).

Many factors could contribute to diagnosis or treatment delays in patients with mental illness, including decreased screening rates, limited access to care, misinterpretation of symptoms by the physician as psychological manifestations, and impact of the mental disorder on the patient's willingness to seek care (Mitchell, 2014; Martens, 2009; Lindamer, 2006; Carney, 2006; Lindamer, 2003; Druss, 2002; Howard, 2010; Thornicroft, 2007; Jeste, 1996; O'Rourke, 2008; Farasatpour, 2013; Hwang, 2012; Desai, 1999). The purpose of the current study was to

investigate diagnosis and treatment delays in elderly early-stage breast cancer patients with and without pre-existing mental illness.

Materials and Methods

Data Source

A retrospective cohort study using the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database was conducted to examine diagnosis and treatment delays. The SEER-Medicare dataset links SEER registry data with Medicare claims for covered hospital, physician, outpatient, home health, and hospice care services. SEER provides information on demographic characteristics, date of diagnosis, tumor histology, tumor stage, tumor grade, initial surgical treatment or radiation therapy, follow-up of vital status, and cause of death, while Medicare provides information on all paid services (Warren, 2002). As the primary insurer for those ≥65 years of age in the US, Medicare has a wide coverage of about 97% of the elderly. The SEER and Medicare data are linked based on a unique algorithm using social security number, name, sex, and date of birth. Data for the current analysis were extracted from the SEER-Medicare dataset from January 1, 2002 through December 31, 2010.

Patient Selection

Newly diagnosed, early stage (I, II, or IIIa) breast cancer patients aged 68 years or older were identified in the SEER-Medicare dataset. Patients had to be diagnosed between January 1, 2005 and December 31, 2007 (Figure 1). In order to be included in the study, subjects were required to have continuous enrollment in Medicare parts A and B for the three years before and two years following breast cancer diagnosis. Patients were excluded from the study cohort if they

met any of the following criteria: (1) had HMO insurance in the three years before or two years after breast cancer diagnosis, (2) had another cancer in addition to breast cancer, (3) were diagnosed with breast cancer on death certificate or autopsy, (4) the diagnosis month was not available in the SEER-Medicare dataset, or (5) diagnosed with dementia or personality disorder in the 3 years prior to breast cancer diagnosis. The index date was defined as the date of breast cancer diagnosis.

Main Explanatory Variable and Other Covariates

In order to be classified as having mental illness, an International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) code for anxiety (308, 293.84, 300.0, 300.1, 300.2, 300.89), depression (296.2, 296.3, 300.4, 311, V79.0), or major psychiatric illness (296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8, 296.9, 295, 297, 298, 293.81, 293.82) had to be present in the Medicare claims data during the 3-year period prior to breast cancer diagnosis. Patients were classified as having anxiety only, depression only, comorbid anxiety and depression, or major psychiatric illness. If a patient was diagnosed with a major psychiatric illness and also had anxiety or depression, the diagnosis of major psychiatric illness was considered primary and they were included that group. Patient and tumor characteristics were extracted from the SEER data. Comorbidities were assessed during the 3-year period prior to breast cancer diagnosis using ICD-9 codes from the Medicare claims files. These codes were used to calculate the Deyo-Charlson Comorbidity Index (calculation excluded all cancer-related and dementia diagnoses). The Charlson Comorbidity Index was created for use in longitudinal studies in order to classify comorbidity and estimate the risk of death from comorbid disease. Deyo and colleagues adapted this index for use in administrative datasets.

Outcome Assessment

The outcomes of interest were diagnosis and treatment delays for patients with and without mental illness (Figure 2). Treatment was defined as surgery (breast-conserving surgery or mastectomy), chemotherapy, or radiation provided in the first 2 years after breast cancer diagnosis. Treatment information was extracted from the Medicare claims data, using ICD-9-CM, Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes (see Appendix). Diagnosis delay is the time interval in days from the date of symptom recognition to the date of breast cancer diagnosis. Because the exact date of symptom recognition cannot be determined from the database, an algorithm was created as a proxy for this date. The first claim for breast symptoms (611.7x or 611.9), a breast mass (611.72), breast cancer (174.xx) or a mammogram (76090 or 76091) with a corresponding code for an abnormal result (793.8) in the baseline period was used. The initial treatment delay was defined as the number of days between diagnosis and the beginning of the first treatment (surgery, radiation, or chemotherapy). Surgical treatment delay was defined as days from diagnosis to first operation (BCS or mastectomy). Subjects who received neo-adjuvant chemotherapy were excluded from this analysis. Delay to adjuvant radiation therapy was defined as either days from last breast surgery or from last dose of chemotherapy, to the start date of radiation treatment. Only subjects receiving surgery with BCS were included in this subset analysis and subjects who received radiation before adjuvant chemotherapy or who received neo-adjuvant chemotherapy were excluded. Delay to adjuvant chemotherapy was defined as days from last operation (either the first operation or, when appropriate, the last re-operation) to date of administration of the first dose of adjuvant chemotherapy. Subjects who did not receive surgery, who received radiation before adjuvant chemotherapy or who received neo-adjuvant chemotherapy were excluded from the analysis.

Statistical Analysis

Demographic, clinical and tumor characteristics, as well as treatment received, for subjects with and without mental illness were summarized using descriptive statistics. Mean and median time to diagnosis and time to start of therapy were assessed. Adjusted relative risks (RR) and 95% confidence intervals (CI) were estimated to assess the association between mental illness and diagnosis/treatment delays of ≥60 and ≥90 days. Multivariable binomial regression with robust variance estimate (i.e., sandwich estimator) was conducted to obtain RRs. Diagnosis delay models were adjusted for age, income, comorbidities, race, ethnicity, SEER state, and marital status. Treatment delay models were adjusted for age, income, comorbidities, race, ethnicity, SEER state, and AJCC stage. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Of the 16,636 subjects selected for inclusion in this analysis, 3961 (23.8%) had a diagnosis of mental illness in the 3-year period prior to breast cancer diagnosis. Depression (8.3%) was the most common diagnosis, followed by anxiety (7.6%), comorbid anxiety and depression (5.1%), and major psychiatric illness (2.9%). Patients with mental illness were more likely to reside in neighborhoods with a lower income, have more medical comorbidities, and were less likely to have been married. Table 1 describes the baseline characteristics for those with and without mental illness. When examining tumor characteristics at breast cancer diagnosis, patients with mental illness were more likely to have poorly differentiated tumors, slightly larger tumors, and more positive lymph nodes (Table 2). During follow-up, patients in both groups were more likely to receive BCS than mastectomy. Those patients who received BCS were more likely to receive

adjuvant radiation and those who received mastectomy were more likely to receive chemotherapy. When comparing those with and without mental illness, those with mental illness were slightly less likely to receive BCS and slightly more likely to receive mastectomy than those without mental illness. For those who received BCS, rates of adjuvant radiation were lower for those with mental illness than those without mental illness, while adjuvant chemotherapy was higher. For mastectomy, rates of adjuvant chemotherapy and adjuvant radiation were higher for those with mental illness compared to those without. The proportion of patients who did not receive surgery was similar between the two groups (Table 3).

Diagnosis Delays

Mean and median time from symptom recognition to diagnosis was relatively similar between those with and without mental illness (Mean: 215 vs. 212 days, Median: 25 vs. 26 days, respectively; Table 4). The majority of patients (approximately 65% in both groups) were diagnosed within 60 days of symptom recognition, but about one third of patients still experienced delays of more than 90 days. There were no significant differences between those with and without mental illness by various delay categories (<60, 60-90, and ≥90 days; P=0.93; Figure 3a). In the adjusted binomial regression model, there were also no differences demonstrated for those with and without mental illness for the risk of diagnosis delay ≥60 days (RR=1.01 [0.96, 1.07]) and ≥90 days (RR=1.02 [0.96, 1.08]; Table 5a). When examining this relationship by type of mental illness, no association was demonstrated for risk of diagnosis delay ≥60 days or ≥90 days in those with anxiety only, depression only, or major psychiatric illness compared to those without mental illness (Table 5b). However, for those with comorbid anxiety and depression there was an 11% increased risk of a diagnosis delay of 90 days or more compared to those without mental illness.

Initial Treatment Delays

Mean and median time to initial treatment was similar between those with and without mental illness (Mean: 34 vs. 33 days, Median: 22 vs. 23 days, respectively; Table 4). Over 90% of patients were treated within 60 days of diagnosis, with no significant differences between those with and without mental illness by different categories of initial treatment delay (<60, 60-90, and ≥90 days; P=0.22; Figure 3b). When examining the adjusted regression model, no difference in risk for initial treatment delay was demonstrated for those with versus without mental illness (≥60 days: RR=0.98 [0.87, 1.10]; ≥90 days: RR=1.08 [0.90, 1.29]). When evaluating specific types of mental illness, an association was demonstrated for those with major psychiatric illness compared to those without mental illness for a delay of ≥60 days (RR=1.36 [1.06, 1.74]), but this was not significant for ≥90 days (RR=1.39 [0.95, 2.04]). No association was seen for the other forms of mental illness.

Surgery Delays

Time to BCS or mastectomy was similar in those with and without mental illness (Mean: 27 vs. 28 days; Median: 21 vs. 22 days, respectively; Table 4). Approximately 93% of patients in each group received surgery within 60 days of diagnosis, while just over 2% had delays greater than 90 days. There were no significant differences between those with and without mental illness by various cut-offs of surgery delay (<60, 60-90, and ≥90 days; P=0.43; Figure 3c). In the adjusted binomial regression model, there was no difference in the risk of surgery delay of ≥60 days or ≥90 days for those with and without mental illness (≥60 days: RR=0.93 (0.81, 1.07); ≥90 days: RR=0.98 (0.77, 1.25); Table 5a). When examining this association by type of mental illness, no significant differences in the risk of surgery delay was shown compared to those without mental illness (Table 5b).

Adjuvant Chemotherapy Delays

Mean time to adjuvant chemotherapy was longer in those with than without mental illness, although the median time was similar (Mean: 129 vs. 112 days; Median: 43 vs. 42 days, respectively; Table 4). There was a significant difference for those with and without mental illness by length of adjuvant chemotherapy delay. Patients with mental illness were much more likely to have delays of ≥90 days and less likely to have delays of 60 to 90 days or less than 90 days (P=0.003; Figure 3d). However, in both groups, a substantial proportion of patients faced delays of more than 60 and more than 90 days. In the binomial regression models, the risk of adjuvant chemotherapy delay of ≥60 days was not significantly different between those with and without mental illness, or by any specific type of mental illness (Table 5a and 5b); however, there was a tendency for this association, as the majority of the confidence interval was greater than one. Those with mental illness had a 13% increased risk of a delay of ≥90 days compared to those without mental illness. This was not statistically significant when examined by types of mental illness, but again, the majority of the confidence intervals for anxiety, comorbid anxiety and depression, and major psychiatric illness were greater than one, suggesting a potential effect in these groups.

Adjuvant Radiation Delays

Mean time to adjuvant radiation was slightly longer in those with than without mental illness (49 vs. 46 days, respectively), but the median time was similar (29 vs. 30 days, respectively; Table 4). Approximately 86% of patients in each group received adjuvant radiation therapy within 60 days of breast conserving surgery, while about 14% and 7% faced delays of greater than 60 and 90 days, respectively. There were no significant differences between those with and without mental illness by categories of adjuvant radiation delay (<60, 60-90, and ≥90 days;

P=0.72; Figure 3d). This lack of association remained in the multivariable models for overall mental illness and by all types of mental illness.

Discussion

In the present study, after adjusting for potential confounders, no significant differences were demonstrated in the risk of diagnosis, initial treatment, surgery, or adjuvant radiation delays for those with versus without mental illness. Patients with mental illness had an increased risk of adjuvant chemotherapy delays ≥90 days compared to those without mental illness, with all individual types of mental illness, except depression, showing a non-significant trend for this association with delay. When examining the other delay outcomes by type of mental illness, patients with comorbid anxiety and depression had a significantly increased risk for a diagnosis delay of ≥90 days and patients with major psychiatric illness had a significantly increased risk of initial treatment delays of ≥60 days. For those with major psychiatric illness, a tendency was also seen for initial treatment delays of ≥90 days, but this was not significant.

The relationship between mental illness and care-seeking behavior is multifaceted and can present in many different ways depending on the diagnosis, and can even differ within a single diagnosis. For example, a moderate level of anxiety might motivate a woman to call her physician regarding a newly discovered symptom, while a very high anxiety level might be debilitating and render a person unable to take action (Mohamed, 2005). Patients with depression often lose interest in usual activities and have difficulty finding motivation to conduct the tasks of daily life; however, the level of disability varies greatly from person to person. Anxiety and depression can occur as comorbid mental illness and amplify the symptoms present in each individual diagnosis. For instance, depression and anxiety are both associated with a perceived low level of self-efficacy (Bandura, 1997), which has been shown to decrease

the likelihood of advocating for one's own health, prioritizing self-care, participating in breast cancer screening, and being adherent to cancer treatment (Lev, 1997; Mystakidou, 2010, Maciejewski, 2000; Chang, 2014). As a result, this could contribute to the increased risk of diagnosis delay seen for patients with both anxiety and depression in our study. Interestingly, this result was not seen for patients with anxiety alone or depression alone, suggesting that it is the synergistic impact of the two diagnoses together that is leading to the delay. Consistent with our results, Burgess et al (2000) interviewed 158 patients with breast cancer and demonstrated that the presence of depression or anxiety alone did not delay presentation to their physician after breast cancer symptom discovery. However, to our knowledge, no data are available assessing dual diagnosis with anxiety and depression and the impact on diagnosis delays.

In our study, patients with major psychiatric illness faced a significant risk of delay in time to initial treatment. Patients with major psychiatric illness often have difficulty communicating medical concerns to their physicians (Goldman, 1999; Howard, 2010), which makes treatment of their cancers more challenging. Inagaki and colleagues (2006) examined cancer treatment in patients with schizophrenia and found that patients with severe symptoms of their disorder had difficulty understanding and adhering to the cancer treatment plans prescribed by their physician. Further, Farastapour and colleagues (2013) found that 48% of patients delayed seeking medical attention after diagnosis of breast cancer and those patients who delayed seeking treatment were more likely to have postoperative complications. A disorganized thought process was associated with treatment delays, suggesting that cognitive difficulty and lack of understanding contribute to this delay. Additionally, Hwang et al. (2012) reported that among patients with pre-existing schizophrenia, 29% with biopsy-proven breast cancer delayed treatment for more than 3 months. Farastapour and Hwang both demonstrated diagnosis delays

in patients with schizophrenia, but this result was not seen in our broader category of major psychiatric illness.

Our study also demonstrated that patients with mental illness faced an increased risk of adjuvant chemotherapy delay compared to those without mental illness. Although not significant, a trend for this relationship was seen for every form of mental illness examined, with the exception of depression. Hwang and colleagues (2012) found that among patients with pre-existing schizophrenia and breast cancer, only 85% of patients eligible for adjuvant chemotherapy were offered this treatment. Of those patients, 31% refused or were non-compliant. A study by Greer et al (2008) conducted in patients with advanced non-small cell lung cancer showed that patients with higher levels of anxiety were significantly more likely to experience dose delays or dose reductions in their chemotherapy regimens. Past research has shown that in patients with anxiety, the physical side effects of chemotherapy can be perceived as so debilitating that patients decide to delay or discontinue treatment (Thuné-Boyle, 2006). Although no significant impact on adjuvant chemotherapy delay was seen in our study with depression alone, depression and anxiety together did show a similar trend to those patients with anxiety.

No significant differences were seen between those with and without mental illness with regards to delays in time to surgery or adjuvant radiation. In patients with major psychiatric illness, there was a non-significant increased risk for surgery delay of ≥60 days, where the majority of the confidence interval was greater than 1. Given that the initial treatment in this population was significantly delayed, it is possible that there is a tendency for delay in surgery as well. It is interesting to note that there was no delay in adjuvant radiation compared to those without mental illness, despite the delay to chemotherapy. Women with breast cancer generally

have higher levels of anxiety when beginning treatment with chemotherapy than they do for treatment with radiation (Schreier, 2004; Lim, 2011), which could lead to a delay in receipt of treatment while they weigh the risks and benefits. This impact could be more pronounced in patients with mental illness, especially in those patients with paranoid disorders or anxiety (Baillargeon, 2011). It is important to note that both groups of patients faced delays in adjuvant chemotherapy, so although the risk is higher for those with mental illness, the length of delay is still suboptimal for those without mental illness.

A large systematic literature review assessing the influence of treatment delay on survival in patients with breast cancer found that across 87 studies, patients with treatment delays of 3 months or more have a 12% lower 5-year survival rate than patients with delays less than 3 months. Breast cancer can progress quickly, and as such, delays lead to advanced disease stage and poorer prognosis (Richards, 1999).

It is important to keep in mind several limitations of the current study. Information for the claims of HMO enrollees is not available in the dataset, so these patients were excluded. Healthcare provided in other settings and any out of pocket expenditures are also not captured. The study is limited to patients 68 years of age or older with Medicare coverage and without HMO insurance and might not be generalizable to other populations. In order to capture complete information on initial treatment decisions, patients need to have 2 years of continuous enrollment following breast cancer diagnosis. It is possible that this makes the patients included in our study healthier than the general population of breast cancer patients. All reports of mental illness were based on ICD-9-CM codes, so there could be underreporting and misclassification. Because mental health benefits have historically been limited for Medicare patients, patients may not have sought care due to lack of coverage. Therefore, they

would not have a diagnosis of mental illness in the database. Also, severity and duration of mental illness cannot be captured and any diagnoses of mental illness made prior to enrollment in Medicare are not included. Due to the debilitating nature of mental illness, and the associated reduction in life expectancy, it is possible that because our study is conducted in older patients, we could be missing the most seriously mentally ill patients who already died from a competing cause. Further, part D prescription information was not available for all patients during the study and, therefore, hormonal therapy could not be taken into account. Additionally, the diagnosis delay algorithm was created as a proxy for the time from symptom recognition to breast cancer diagnosis. The true time of symptom recognition by the patient could not be determined. In the database, substance abuse was severely underreported based on claims data (2.3% in those with mental illness and 0.6% in those without mental illness) and, therefore, could not be examined. Finally, unobserved confounders that are not available in the data could impact the study results.

In conclusion, our study showed that patients with comorbid depression and anxiety faced an increased risk of diagnosis delays, while those with major psychiatric illness were at an especially high risk of initial treatment delays. Patients with mental illness overall face a higher risk of delay to adjuvant chemotherapy. These patients need to be closely managed by a cross-functional care team, including an oncologist and psychiatrist, or a psychiatrist with a specialization in cancer patient care, to ensure adequate care is received within a reasonable timeframe. Also, increased communication between the oncologist and patient regarding seriousness of their condition is warranted. Given challenges with cognition in the major psychiatric illness group and issues surrounding self-efficacy in those with anxiety and depression, patients may ultimately need assistance with their coordination of care.

Figures and Tables

Figure 1. Study Design

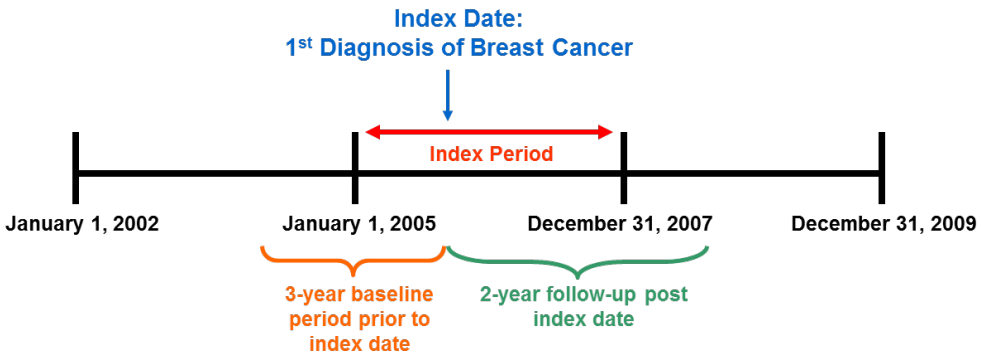
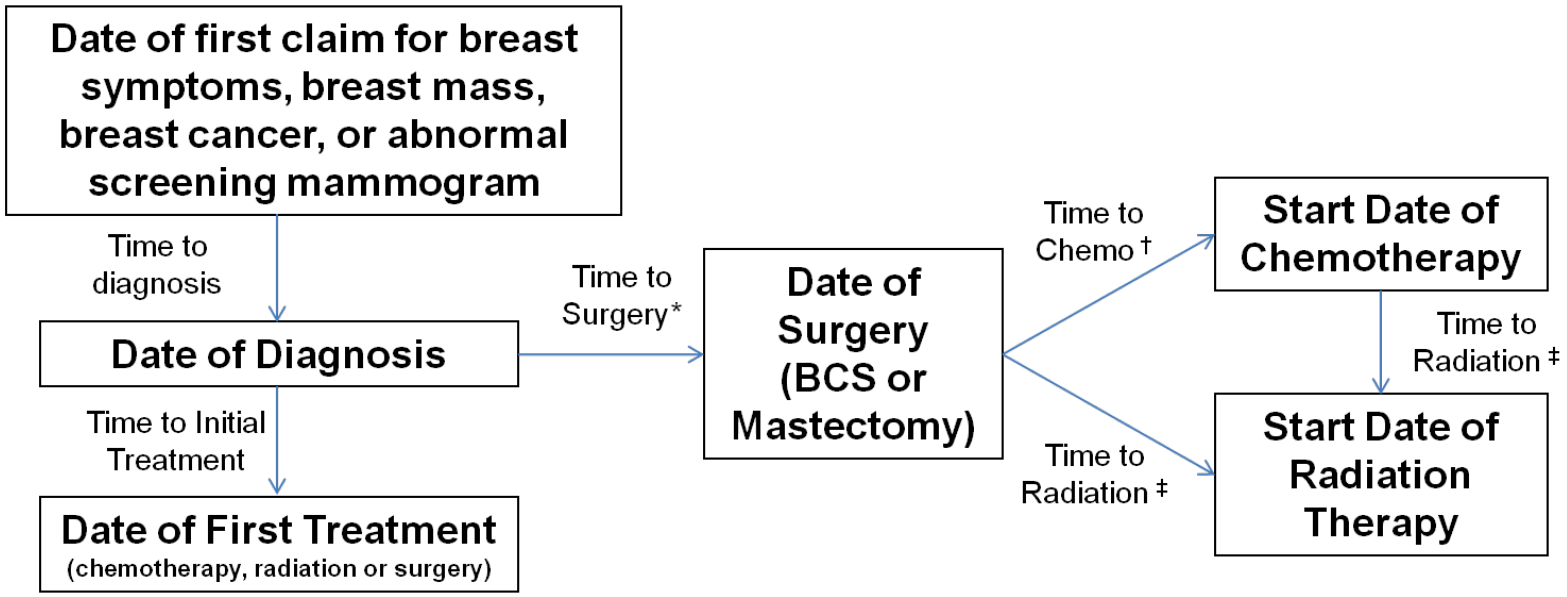


Figure 2. Delay schema outlining the definitions for diagnosis delay, initial treatment delay, surgery delay, adjuvant chemotherapy delay and adjuvant radiation delay



*Subjects who received neo-adjuvant chemotherapy were excluded from this analysis; †Subjects who received radiation before adjuvant chemotherapy or received neo-adjuvant chemotherapy were excluded from this analysis; ‡Subjects who received BCS were included in this analysis. Subjects who received radiation before adjuvant chemotherapy or received neo-adjuvant chemotherapy were excluded from this analysis.

Table 1. Demographic and clinical characteristics of early stage breast cancer patients by mental illness status

	Mental Illness n=3961 (23.8%)	No Mental Illness n=12,675 (76.2%)
Age at Diagnosis, Mean±SD	76.7±6.1	76.6±6.2
Age Group at Diagnosis, %		
68-74 years	41.7%	42.3%
75-84 years	46.7%	45.6%
85+ years	11.7%	12.1%
SEER State, %		
Connecticut	6.6%	6.4%
Michigan	4.8%	6.6%
Hawaii	0.8%	1.4%
Iowa	7.8%	6.2%
New Mexico	1.9%	2.0%
Washington	5.7%	5.6%
Utah	3.3%	2.0%
Georgia	12.3%	11.3%
California	29.3%	31.3%
Kentucky	8.8%	6.4%
Louisiana	6.3%	5.8%
New Jersey	12.4%	15.1%
Race, %		
White	91.6%	88.9%
African American	5.6%	6.2%
Asian or Pacific Islander	2.2%	4.2%
Other/Unknown	0.8%	0.7%
Ethnicity, %		
Hispanic	5.0%	4.3%
Non-Hispanic	95%	95.7%
Marital Status, %		
Single (never married)	6.4%	6.3%
Married (including common law)	39.6%	46.0%
Separated	0.4%	0.4%
Divorced	8.0%	6.2%
Widowed	42.1%	37.2%
Unknown	3.5%	3.9%

	Mental Illness n=3961 (23.8%)	No Mental Illness n=12,675 (76.2%)
Census-based median income level, Mean±SD	49,577±22,967	53,031±24,857
Comorbid Conditions, %		
Myocardial Infarction	8.2%	5.2%
Congestive Heart Failure	20.8%	13.5%
Peripheral Vascular Disease	15.2%	10.7%
Cerebrovascular Disease	29.7%	20.1%
Chronic Pulmonary Disease	39.2%	27.6%
Rheumatologic Disease	9.1%	7.2%
Peptic Ulcer Disease	5.7%	3.3%
Mild Liver Disease	1.0%	0.8%
Moderate or Severe Liver Disease	0.8%	0.4%
Diabetes	34.1%	30.9%
Diabetes with Chronic Complications	7.6%	4.9%
Hemiplegia or Paraplegia	1.8%	0.8%
Renal Disease	7.8%	4.9%
AIDS	0.6%	0.4%
Number of Medical Comorbidities, %		
0	23.4%	35.3%
1-2	48.4%	46.9%
≥3	28.2%	17.8%
Charlson Comorbidity Index, Mean±SD	2.0±2.0	1.4±1.7
Mammogram Performed, %	77.5%	77.9%
Tobacco Use, %	5.9%	3.6%

Table 2. Tumor characteristics of patients with early-stage breast cancer by mental illness status

	Mental Illness n=3961 (23.8%)	No Mental Illness n=12,675 (76.2%)
AJCC Stage at Diagnosis, %		
I	59.9%	61.5%
IIa	25.7%	24.5%
IIb	9.6%	9.0%
IIIa	4.8%	5.0%
ER/PR Status, %		
ER+/PR+	65.2%	66.6%
ER+/PR-	12.7%	12.9%
ER-/PR+	0.6%	0.7%
ER-/PR-	13.5%	12.5%
Other/Unknown	7.9%	7.3%
Histologic Grade, %		
Well differentiated	26.5%	26.4%
Moderately differentiated	42.4%	43.8%
Poorly differentiated	24.0%	23.0%
Undefined	0.9%	0.9%
Unknown	6.2%	5.9%
Tumor size, %		
≤10 mm	29.5%	29.9%
>10 to ≤20 mm	39.0%	39.4%
>20 to ≤50 mm	26.4%	25.4%
>50 mm	2.9%	3.2%
Unknown	2.2%	2.1%
Number of Positive Lymph Nodes, %		
0	66.1%	68.7%
1-3	17.4%	16.2%
4-9	4.0%	4.1%
≥10	12.3%	10.9%
Unknown	0.2%	0.1%

Table 3. Treatment received in the 2 years following breast cancer diagnosis by mental illness status

	Mental Illness n=3961	No Mental Illness n=12,675
Breast-conserving surgery	2204 (55.6%)	7283 (57.5%)
Adjuvant Chemotherapy	924 (41.9%)	2679 (36.8%)
Adjuvant Radiation	1850 (83.9%)	6300 (86.5%)
Mastectomy	1461 (36.9%)	4399 (34.7%)
Adjuvant Chemotherapy	744 (50.9%)	2133 (48.5%)
Adjuvant Radiation	569 (39.0%)	1653 (37.6%)
No surgery	296 (7.5%)	993 (7.8%)
Chemotherapy	138 (46.6%)	353 (35.6%)
Radiation	168 (56.8%)	582 (58.6%)
No recorded treatment with surgery, chemotherapy or radiation	78 (2.0%)	291 (2.3%)

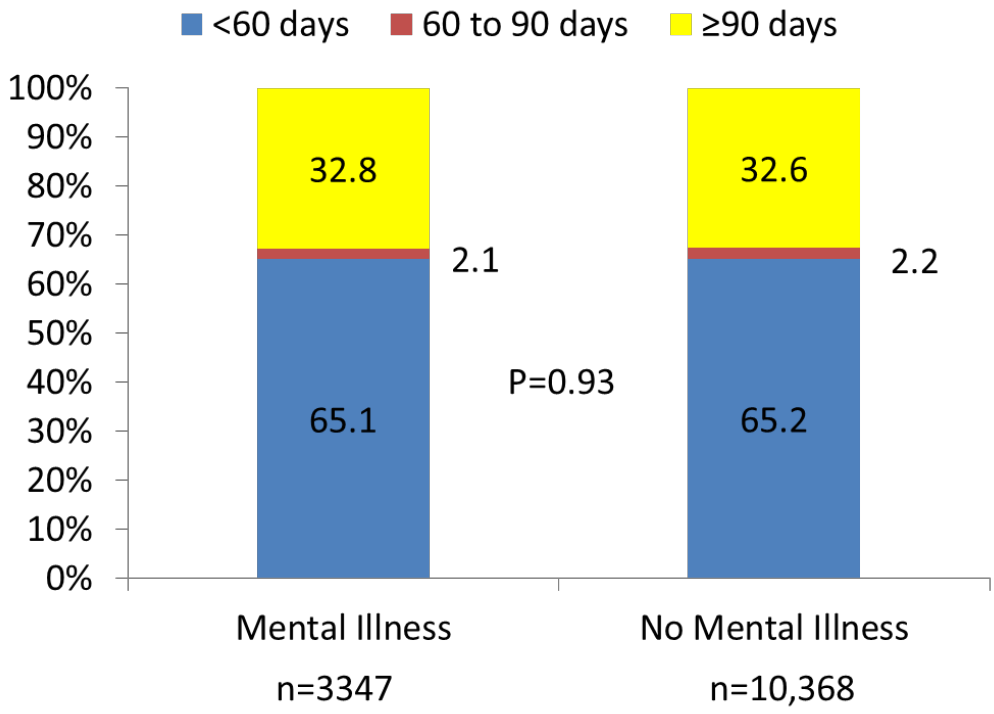
Table 4. Mean and median time to event for early stage breast cancer patients with and without mental illness

	Mental Illness n=3961		No Mental Illness n=12,675	
Time to diagnosis (days)				
Mean± SD	n=3347	215±327	n=10,368	212±324
Median (Q1, Q3)		25 (9, 383)		26 (10, 379)
Time to initial treatment (days)				
Mean±SD	n=3883	34±65	n=12,384	33±55
Median (Q1, Q3)		22 (11, 35)		23 (11, 37)
Time to first surgery (days)*				
Mean±SD	n=3511	27±33	n=11,290	28±34
Median (Q1, Q3)		21 (11, 34)		22 (11, 36)
Time to adjuvant chemotherapy (days)†				
Mean±SD	n=986	129±175	n=2953	112±166
Median (Q1, Q3)		43 (25, 166)		42 (24, 90)
Time to adjuvant radiation (days)‡				
Mean±SD	n=1308	49±89	n=4740	46±77
Median (Q1, Q3)		29 (17, 46)		30 (18, 45)

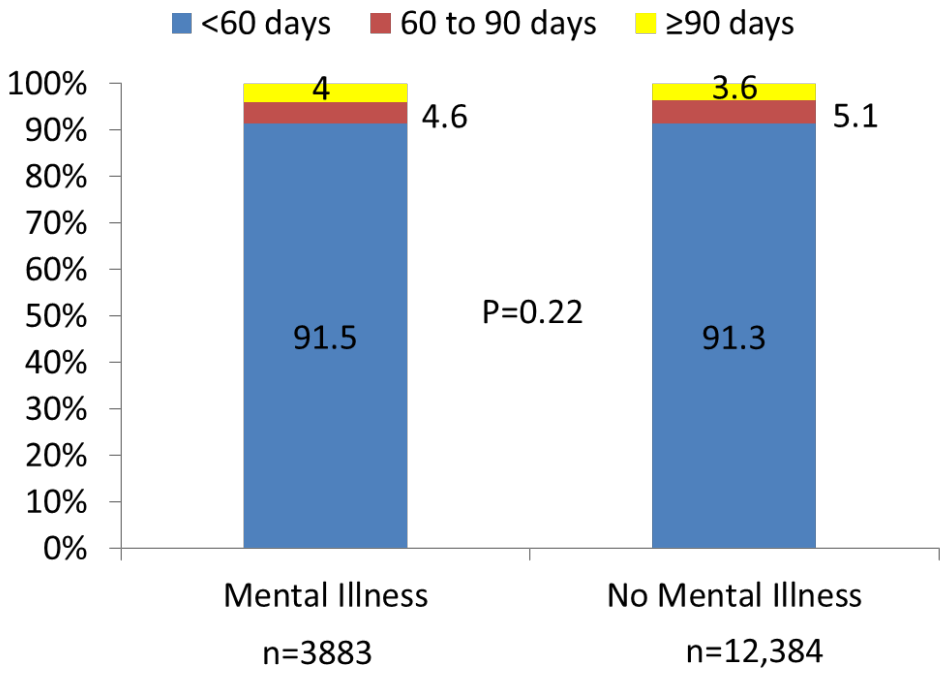
*Excludes patients who received neo-adjuvant chemotherapy; †Excludes patients who received neo-adjuvant chemotherapy or received radiation before chemotherapy; ‡Only includes patients who received BCS. Excludes patients who received neo-adjuvant chemotherapy or received radiation before chemotherapy.

Figure 3. Percentage of patients with and without mental illness by delay categories (<60, 60-90, and ≥90 days)

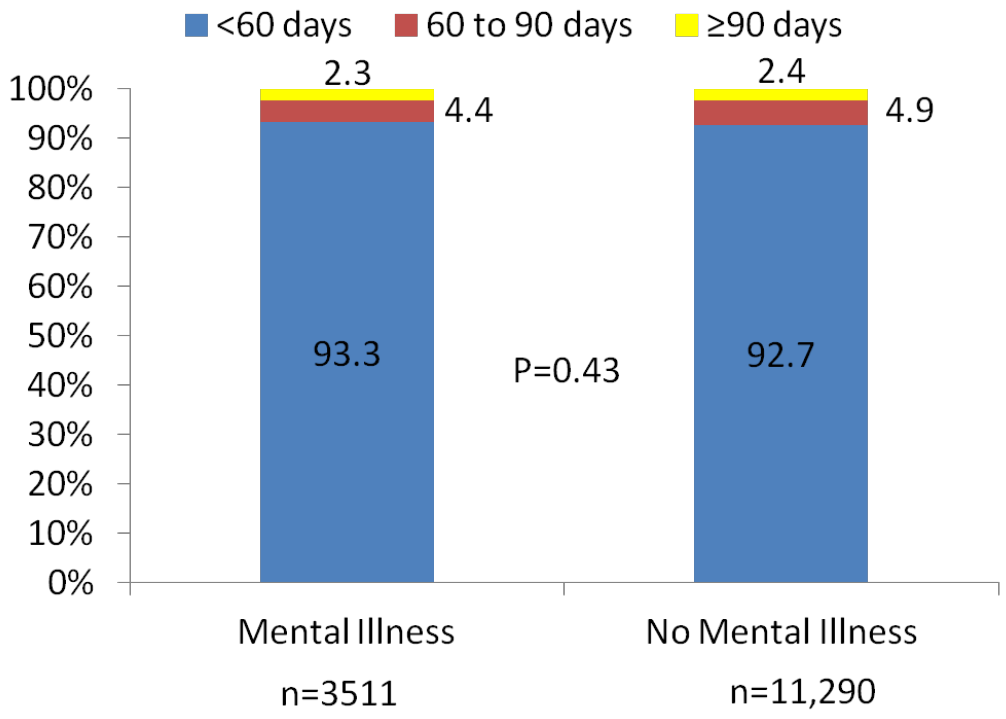
a. Diagnosis Delay



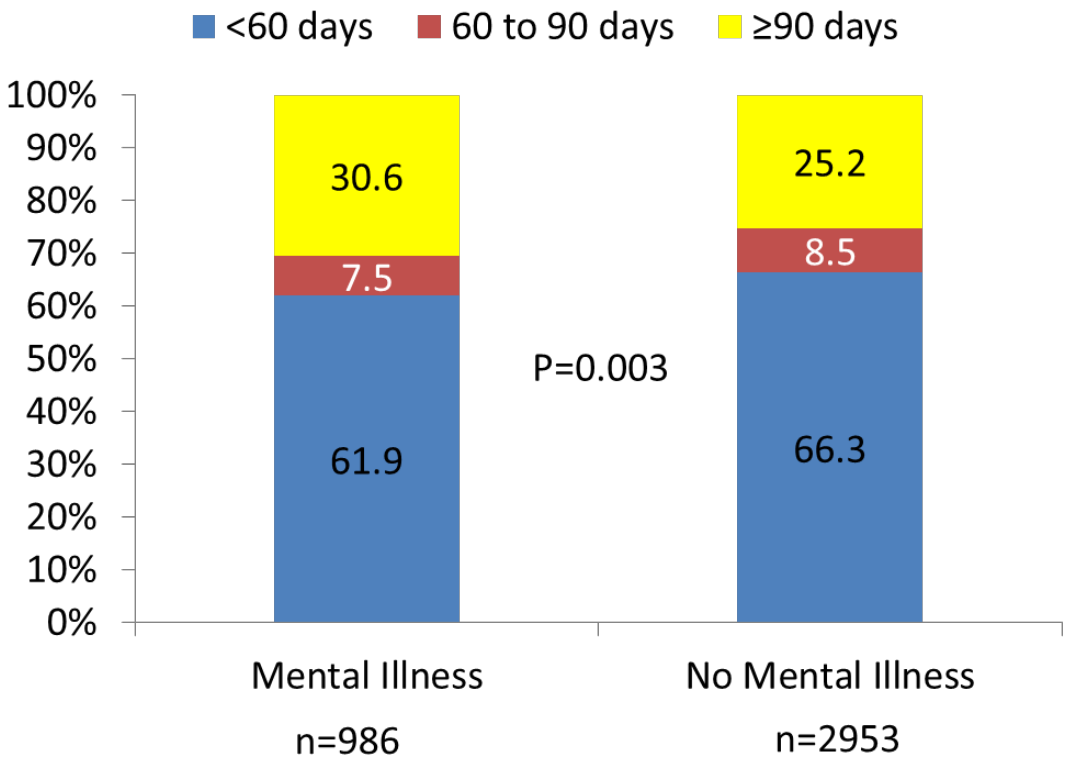
b. Initial Treatment Delay



c. Surgery Delay



d. Adjuvant Chemotherapy Delay



e. Adjuvant Radiation Delay

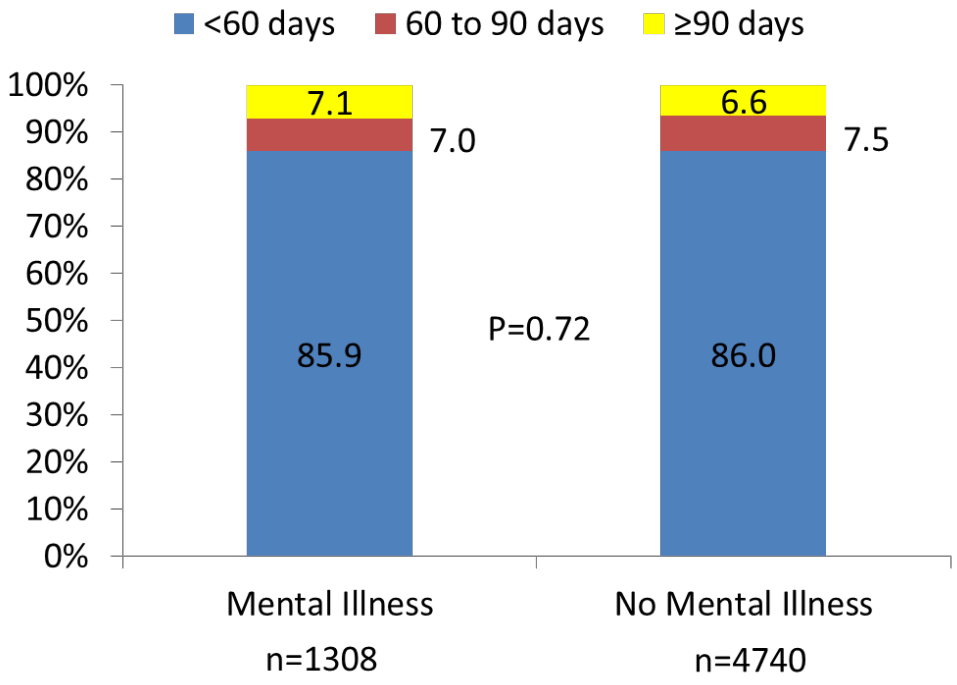


Table 5. Relative risks and 95% confidence intervals comparing those with and without mental illness for diagnosis and treatment delays.

a. Overall population

	Diagnosis Delay*	**Initial Treatment Delay****	**Surgery Delay****	**Adjuvant Chemotherapy Delay****	**Adjuvant Radiation Delay****
≥60 days **Mental illness vs. no mental illness**	1.01 (0.96, 1.07)	0.98 (0.87, 1.10)	0.93 (0.81, 1.07)	1.08 (0.99, 1.18)	1.00 (0.86, 1.17)
≥90 days **Mental illness vs. no mental illness**	1.02 (0.96, 1.08)	1.08 (0.90, 1.29)	0.98 (0.77, 1.25)	**1.13** **(1.01, 1.26)**	1.04 (0.83, 1.30)

b. By Type of Mental Illness

	Diagnosis Delay*	**Initial Treatment Delay****	**Surgery Delay****	**Adjuvant Chemotherapy Delay****	**Adjuvant Radiation Delay****
≥60 days					
Anxiety only vs. no mental illness	0.98 (0.90, 1.07)	0.92 (0.76, 1.12)	0.92 (0.73, 1.15)	1.12 (0.97, 1.28)	1.00 (0.78, 1.27)
Depression only vs. no mental illness	0.98 (0.90, 1.08)	0.96 (0.79, 1.15)	0.89 (0.71, 1.12)	0.99 (0.85, 1.15)	0.98 (0.77, 1.24)
Anxiety and depression vs. no mental illness	1.08 (0.97, 1.19)	0.89 (0.70, 1.13)	0.85 (0.64, 1.13)	1.10 (0.92, 1.31)	1.12 (0.86, 1.46)
Major psychiatric illness vs. no	1.05 (0.92, 1.20)	**1.36** **(1.06, 1.74)**	1.25 (0.92, 1.69)	1.20 (0.99, 1.44)	0.81 (0.48, 1.35)

	Diagnosis Delay*	**Initial Treatment Delay****	**Surgery Delay****	**Adjuvant Chemotherapy Delay****	**Adjuvant Radiation Delay****
mental illness					
≥90 days					
Anxiety only vs. no mental illness	0.96 (0.88, 1.06)	0.94 (0.70, 1.28)	0.97 (0.65, 1.44)	1.16 (0.99, 1.37)	1.10 (0.77, 1.58)
Depression only vs. no mental illness	1.01 (0.93, 1.10)	1.08 (0.82, 1.42)	0.96 (0.65, 1.43)	1.04 (0.87, 1.24)	0.88 (0.61, 1.28)
Anxiety and depression vs. no mental illness	**1.11 (1.003, 1.23)**	1.07 (0.76, 1.52)	0.94 (0.58, 1.53)	1.14 (0.93, 1.40)	1.20 (0.83, 1.72)
Major psychiatric illness vs. no mental illness	1.02 (0.88, 1.18)	1.39 (0.95, 2.04)	1.13 (0.63, 2.00)	1.24 (0.98, 1.56)	1.04 (0.55, 1.99)

*Adjusted for age, income, comorbidities, race, ethnicity, SEER state, and marital status.

** Adjusted for age, income, comorbidities, race, ethnicity, SEER state, marital status, and AJCC stage.

CHAPTER 3

The Impact of Pre-existing Mental Illness on All-Cause and Breast cancer-Specific Death Rates in Elderly Early-stage Breast Cancer Patients

Abstract

Aim: To compare rates of all-cause and breast cancer-specific death rates for elderly patients with and without mental illness.

Methods: Subjects 68 years of age or older diagnosed with stage I, II, or IIIa incident breast cancer between January 1, 2005 and December 31, 2007 were identified in the SEER-Medicare dataset. Subjects were required to have continuous enrollment in Medicare fee-for-service parts A and B for the three years prior to breast cancer diagnosis (baseline period). The date of breast cancer diagnosis was defined as the index date. Patients were excluded from the study if they had another cancer, diagnosis on death certificate/autopsy, baseline diagnosis of dementia or personality disorder, or month of diagnosis not available. Patients were classified as having a mental illness if an ICD-9-CM code for anxiety, depression, or major psychiatric illness (i.e., bipolar, schizophrenia, or other psychotic disorders) was present in the baseline period. Patients were followed for up to 5 years to determine the cumulative incidence of all cause and breast cancer specific death rates for those with and without mental illness. Regression models were constructed to determine the adjusted hazard ratio and 95% confidence intervals for the association between mental illness and the rate of all-cause and breast cancer-specific mortality.

Results: A total of 19,028 subjects met the inclusion criteria and 4651 (24.4%) had a diagnosis of mental illness in the baseline period. Mentally ill breast cancer patients as compared to those without mental illness have a slightly higher cumulative incidence of all cause (26.2% vs. 18.6%, P<0.0001) and breast cancer-specific mortality (6.6% vs. 6.2%, P=0.04). There was a significant 43% increase in the rate of all-cause mortality and a non-significant 12% increase in the rate of breast cancer-specific mortality in those with mental illness compared to those without. The association between mental illness and all-cause mortality remained for each category of mental

illness, but the strongest impact was seen in those with major psychiatric illness (HR=2.27 [95% CI 1.94, 2.65]). Although, presence of mental illness overall did not significantly impact the rate of breast cancer death, a significantly increased rate of breast cancer-specific death was observed for patients with major psychiatric illness (HR=1.40 [95% CI 1.02, 1.92]).

Conclusion: Patients with mental illness experience increased rates of all-cause survival compared to those without mental illness. Rates of breast cancer-specific death were significantly higher in those with major psychiatric illness compared to those without mental illness. Mentally ill elderly breast cancer patients may benefit from coordination of their care to address the management of their mental illness, breast cancer and other comorbid diseases.

Introduction

Breast cancer is a significant cause of morbidity and mortality, accounting for approximately 30% of newly diagnosed cancer cases. From the early 1960s to present day, the overall 5-year relative survival rate for women with breast cancer has improved from 63% to 90%, but an estimated 40,000 deaths still occurred in women in 2014 (Berry, 2005; Siegel, 2014).

Compared to the general population, patients with mental illness face a much higher rate of overall mortality, with a recent study estimating a life expectancy reduction of up to 24 years in those with severe mental disorders (Laursen, 2011; Vinogradova, 2010; Brown, 2010; Denollet, 2009; Falagas, 2007; Tran, 2009; Chesney, 2014). Moreover, this inequality in mortality has been increasing in the past few decades (Saha, 2007). Chronic diseases like cardiovascular disease and cancer account for the majority of deaths in those with mental illness (Joukamaa, 2001).

Although the incidence of breast cancer has been shown to be slightly lower in those with mental illness compared to those without, the mortality rate is higher (Kisely, 2013; Tran, 2009; Denollet, 2009; Falagas, 2007). Many factors could impact the association between mental illness and survival, with screening, diagnosis and treatment delays, and access to care often being cited as key considerations.

Few studies have been conducted examining the impact of pre-existing mental illness (overall and by specific diagnosis) on survival in patients with early-stage breast cancer. We, therefore, sought to undertake a study that examined the impact mental illness, overall and by type of mental illness, on survival.

Materials and Methods

Data Source

A retrospective cohort study was conducted using the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database. SEER registries are population-based and collect information on incident cancer cases that occur in SEER locations. Patient's demographic characteristics, date of diagnosis, tumor histology, tumor stage, tumor grade, initial surgical treatment or radiation therapy, follow-up of vital status, and cause of death are captured in the database (Warren, 2002). Medicare provides insurance coverage to more than 97% of Americans who are 65 years of age or older. The claims from Medicare are linked to SEER data based on an algorithm using social security number, name, sex, and date of birth. Ninety-three percent of patients in the SEER database over the age of 65 years were found in the Medicare enrollment file, demonstrating the completeness of these records. Data for this analysis were extracted from the SEER-Medicare dataset from January 1, 2002 through December 31, 2010.

Patient Selection

Subjects 68 years of age or older diagnosed with stage I, II, or IIIa incident breast cancer between January 1, 2005 and December 31, 2007 were identified in the SEER-Medicare dataset (Figure 1). Subjects were required to have continuous enrollment in Medicare parts A and B for the three years before breast cancer diagnosis. The date of breast cancer diagnosis was defined as the index date. Patients were excluded from the study if they had any of the following: HMO enrollment in the three years before breast cancer diagnosis, another cancer in addition to breast cancer, a diagnosis of breast cancer on death certificate or autopsy, or a diagnosis of dementia or personality disorders in the three years prior to breast cancer diagnosis. Patients

were also excluded if their month of diagnosis was not available in the dataset. International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to determine the presence of mental illness. Patients were classified as having a mental illness if a code for anxiety, depression, or major psychiatric illness (Table 1) was present in the Medicare claims data during the 3-years before the diagnosis of breast cancer. Patients were categorized as having anxiety only, depression only, comorbid anxiety and depression, or major psychiatric illness. If a patient had anxiety and/or depression along with a major psychiatric diagnosis, the major psychiatric illness was considered primary and they were included in that group. Medicare claims files were used to determine comorbidities in the 3 years prior to diagnosis based on ICD-9-CM codes. These codes were used to calculate the Deyo-Charlson Comorbidity Index (excluding all cancer and dementia-related diagnoses). The Charlson Comorbidity Index is a validated method for classifying comorbidity and estimating the risk of death from comorbid disease in longitudinal studies. The Deyo method is an adaptation of this index for use in administrative datasets. Patient and tumor characteristics were determined based on the SEER data. Data on surgery, chemotherapy, and radiotherapy for 2 years following breast cancer diagnosis were extracted from the Medicare data files using ICD-9-CM, Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes (see Appendix).

Statistical Analysis

Demographic, clinical and tumor characteristics, as well as treatment received during follow-up, for subjects with and without mental illness were summarized using descriptive statistics. Patients were followed for up to 5 years to determine whether death had occurred from any

cause, as well as from breast cancer specifically. Information on cause of death and survival time from the date of diagnosis was provided in the SEER data.

All-cause mortality

When examining all-cause mortality, patients were classified as dying from any cause or as alive/lost to follow-up. Mean and median time to all-cause mortality was examined for those patients who died during the follow-up period. The cumulative incidence function (i.e. the mortality event probability function) of all-cause mortality was determined using Kaplan-Meier estimation and compared for those with and without mental illness using the log rank test. Cox proportional hazards regression was performed to determine the association between mental illness and all-cause mortality. These analyses were conducted overall, by mental illness type, and by subgroups of age (68-74, 75-84, 85+). The covariates in the models included age, income, race, ethnicity, SEER location, and marital status.

Breast cancer-specific death

When examining breast cancer-specific death, observations were categorized as breast cancer deaths, other deaths (competing risks), or censored observations (alive or lost to follow-up). Breast cancer-specific death was defined when breast cancer was listed as the cause of death in SEER (ICD-9-CM 174). SEER cancer registries utilize a very detailed algorithm to determine a single, underlying cause of death from the death certificate. Mean and median time to breast cancer-specific death was examined for those patients who died of breast cancer during the follow-up period. The cumulative incidence of breast cancer-specific death was determined and compared for those with and without mental illness using the Gray method (Gray, 1988). Regression on cumulative incidence functions was performed using the Fine and Gray method

(Fine, 1999) to assess the association between mental illness and the rate of breast cancer death. This method is based on the proportional hazards model for the subdistribution of a competing risk and directly models the effect of covariates on the cumulative incidence function. Analyses were conducted overall, by mental illness type, and by subgroups of age (68-74, 75-84, 85+). The covariates in the models include age, income, race, ethnicity, SEER location, and marital status. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 19,028 subjects met the study inclusion criteria. Of those, 4,651 (24.4%) had a diagnosis of mental illness in the 3-year baseline period. Depression only (8.5%) was the most common form of mental illness in our study, followed by anxiety only (7.5%), comorbid depression and anxiety (5.1%), and major psychiatric illness (3.3%). Patients with mental illness were slightly more likely to be white, resided in neighborhoods with a lower income, used tobacco, and had more medical comorbidities compared to their counterparts without mental illness. They were also less likely to have been married. Table 2 provides a detailed description of the baseline characteristics by mental illness status.

The tumor characteristics at the time of breast cancer diagnosis are presented in Table 3. Compared to patients without mental illness, a smaller proportion of patients with mental illness had AJCC stage I cancer at diagnosis (57.3% vs. 59.8%) and a larger proportion had AJCC Stage II cancer at diagnosis (36.9% vs. 34.7%). Also, a slightly smaller proportion of patients with mental illness were ER/PR positive, while a slightly larger proportion were ER/PR negative. Additionally, there was a somewhat larger proportion of patients with poorly differentiated

tumors in the group with mental illness than in those without this diagnosis (25.0% vs. 24.0%). Further, tumor size and number of positive lymph nodes were higher in those with a diagnosis of mental illness.

Table 4 presents the treatment received in the 2 years following breast cancer diagnosis by mental illness status. Patients in both groups were more likely to receive breast-conserving surgery (BCS) than mastectomy. After surgery with BCS, a smaller proportion of patients with mental illness received adjuvant radiation per standard of care than those without mental illness, but a higher proportion received chemotherapy. After mastectomy, patients with mental illness more frequently received chemotherapy than those without mental illness, and the same was seen for radiation. Similar rates of no surgery and no treatment with surgery, chemotherapy or radiation were observed.

During the course of the study, mean time to death from any cause was 23.3 months for those with mental illness compared to 24.2 months for those without, while median time to death was similar in those with and without mental illness (23 vs. 23.5 months, respectively; Table 5). Of those patients who died of breast cancer, mean time to death was 21.6 months for those with mental illness compared to 23.7 months for those without mental illness. The median time to death was 2 months less in those with than without mental illness (21 vs. 23 months, respectively; Table 5). The unadjusted cumulative incidence curves for all-cause mortality and breast cancer-specific mortality are shown in Figures 2a and 2b. The cumulative incidence (95% confidence interval [CI]) for all-cause mortality in those with mental illness was 26.2% (23.6%, 29.1%) compared to 18.6% (17.4%, 20.0%) in those without mental illness ($P<0.0001$). The five most common causes of death in both groups were breast cancer, heart disease, acute myocardial infarction, stroke, and chronic obstructive pulmonary disease. The cumulative

incidence of breast cancer-specific death was 6.6% (5.7%, 7.5%) in those with mental illness versus 6.2% (5.6%, 6.7%) in those without mental illness (P=0.04). The relationship between breast cancer-specific mortality and mental illness is stratified by age group in Figure 2c, demonstrating that the relationship is maintained with increasing age. Additionally, breast cancer-specific death rates in both groups increased with increasing age.

A 43% increased rate of all-cause death for those with mental illness compared to those without mental illness was demonstrated in the regression model (HR=1.43 [95% CI 1.32, 1.56]; Table 6a). For each category of mental illness, this relationship remained. The strongest impact was seen in those with major psychiatric illness, who faced 127% greater rate of all-cause death than those without mental illness. When examining subgroups of age, patients with mental illness faced an increased rate of death for every subgroup of age, although the relationship decreased as age increased.

Although there was an increased rate of breast cancer-specific death for those with versus without mental illness, this did not achieve statistical significance (HR=1.12 [95% CI 0.96, 1.30]; Table 6b). However, when examining this relationship by type of mental illness, a significantly increased rate of breast cancer-specific death was observed for patients with major psychiatric illness (HR=1.40 [95% CI 1.02, 1.92]. An increased rate was also seen for those with depression, but this did not reach statistical significance (HR=1.21 [95% CI 0.96, 1.51). The presence of anxiety disorders or comorbid anxiety and depression did not significantly impact the rate of breast cancer death. When subgroup analyses were performed by age groups, the relationship between mental illness and an increased rate of breast cancer-specific death is no longer seen; however, for the 68-74 year age group, the majority of the 95% confidence interval lies over 1, suggesting that a relationship likely remains, but more power is needed to detect a significant

difference. When examining tumor biology, an increased rate of breast cancer-specific death was noted for those with versus without mental illness for stage IIIa cancer. None of the other strata examined showed a significant impact of mental illness on breast cancer death.

In order to evaluate potential reasons for the impact of major psychiatric illness on breast cancer-specific death, Table 7 presents the tumor and treatment characteristics of this subgroup. These patients are more likely to be later stage, have poorly differentiated tumors, have much larger tumors, and have more positive lymph nodes, all of which confer a poorer prognosis. They were much less likely to receive adjuvant radiation following breast conserving surgery than those without mental illness, but were more likely to receive adjuvant chemotherapy than those without mental illness. After mastectomy, they were more likely to receive adjuvant chemotherapy than those without mental illness and the same trend was seen for adjuvant radiation. More patients with major psychiatric illness did not receive surgery or did not receive any treatment with surgery, chemotherapy or radiation compared to those without mental illness.

Discussion

In the present study, the cumulative incidence of all-cause and breast cancer-specific mortality for those with mental illness was 26.2% and 6.6%, respectively, compared to 18.6% and 6.2% for those without mental illness. Patients with mental illness overall faced a 43% increased rate of all-cause mortality, with the relationship remaining for each category of mental illness and each subgroup of age. This relationship was especially pronounced for those with major psychiatric illness, who faced a 127% increased rate of death compared to those without mental illness. Patients with mental illness demonstrated an increased rate of breast cancer-specific death, but

this failed to achieve statistical significance (HR=1.12 [95% CI 0.96, 1.30]). After examining this relationship by types of mental illness, a significant association was seen, with major psychiatric illness conferring a 40% increased rate of breast cancer deaths.

Many studies have shown that overall survival is decreased in patients with mental illness (Chesney, 2014; Laursen, 2011; Vinogradova, 2010; Brown, 2010; Denollet, 2009; Falagas, 2007; Tran, 2009). Most recently, Chesney and colleagues performed a systematic literature review assessing all-cause mortality in patients with mental illness. All forms of mental illness demonstrated an increased risk of all-cause mortality compared to those without mental illness. Specifically, those with major psychiatric disorders had increased risks ranging from 120% to 150%, while those with depression only or comorbid anxiety and depression had increased risks of 60% and 40%, respectively. This is consistent with the current study, where major psychiatric illness carried that largest increased rate of death, followed by depression alone, comorbid anxiety and depression, and anxiety alone.

Unfortunately, very few studies are available assessing the impact of pre-existing mental illness on breast cancer specific survival. A study by Goodwin et al (2004) estimated that women with depression had a significant 42% higher rate of death from breast cancer during 3-year follow-up compared to those without depression. Although this relationship between depression and breast cancer death was not statistically significant in our study, we did see a tendency for this association (HR=1.21 [95% CI 0.96, 1.51]). It is possible that because Goodwin and colleagues did not perform a competing risk analysis, they overestimated the rate of breast cancer deaths. An additional study by Kisely et al (2009) found that during up to 20 years of follow-up, patients with mental illness were 27% more likely to die of their breast cancer than the general

population without mental illness. Consistent with our results, Denollet and colleagues found that the presence of anxiety was not related to breast cancer survival.

There are many pathways through which the presence of mental illness can impact rates of survival. In the current study, the most significant pathway through which mental illness impacts all-cause survival is likely comorbidity burden. In our study, 31% of patients with mental illness had 3 or more medical comorbidities compared to just 18.9% of those without mental illness. The association between medical comorbidity and all-cause mortality in breast cancer patients has been demonstrated in several studies (Nagel, 2004; Houterman, 2004; Piccirillo, 2004; Louwman, 2005; Janssen-Heijnen, 2007; Cronin-Fenton, 2007; Yancik, 2001). Louwman et al. (2005) showed that 5-year survival in patients with breast cancer decreased from 87% to 57% when 2 or more comorbidities were present. Piccirillo and colleagues used the Adult Comorbidity Evaluation-27 (ACE-27) to determine the severity of comorbidities found in a population of cancer patients. In patients with breast cancer, having comorbidity levels categorized as moderate or severe conferred an 83% and 98% increased rate of death, respectively, compared to having no comorbidities. Further, Patnaik et al. (2011) examined the individual associations between 13 comorbidities and overall survival and all-cause mortality in a cohort of breast cancer patients. Each comorbidity was associated with decreased overall survival and increased mortality. Additionally, the authors found that patients aged 66 to 74 years with stage I breast cancer and one comorbid condition had similar or poorer overall survival compared to patients of the same age who had no comorbid conditions and stage II breast cancer.

Tobacco use is a behavioral risk factor that is present to a much higher degree in those with than without mental illness. Although tobacco use is underestimated in this study—mostly due

to the availability of ICD-9-CM codes alone to define use—the magnitude of difference between those with and without mental illness is still very large (6.4% vs. 3.6%). Based on these results, patients with mental illness in our study had a 78% increased risk of tobacco use compared to those without mental illness. Research has shown that cigarette smoking increases the risk of death from any cause. Additionally, in cancer patients, it increases the risk of dying from their cancer, as well as their risk of dying from other comorbid diseases (US Department of Health and Human Services, 2014). This might offer some explanation as to why those patients in our study with major psychiatric illness had such a significantly increased rate of death. This subgroup had the largest comorbidity burden and highest tobacco use compared to the other forms of mental illness (data not shown).

Many studies have also evaluated the rates of screening in those with mental disorders, as a decrease in this type of preventative care-seeking behavior could lead to diagnosis and treatment delays. Although there are some studies demonstrating no difference in screening between those with mental illness and the general population (Lasser, 2003; Dickerson, 2003; Owen, 2002; Steiner, 1998), more recent evidence suggests that rates of screening are significantly lower for those with mental illness (Mitchell, 2014; Martens, 2009; Lindamer, 2006; Carney, 2006; Lindamer, 2003; Druss, 2002). Previous research has also shown that patients with mental illness face a longer delay in time to diagnosis of their cancers compared to the general population (O'Rourke, 2008; Farasatpour, 2013; Hwang, 2012; Desai, 1999). As evidenced in our study, patients with mental illness presented with later stage cancer at diagnosis compared to those without mental illness, demonstrating that there was a delay in diagnosis. Again, this difference was especially pronounced in those with major psychiatric illness. When examining the relationship between mental illness and breast cancer-specific death stratified by AJCC stage, the impact of mental illness on breast cancer death was only

demonstrated in patients with later stage (stage IIIa) cancers. Patients with stage IIIa breast cancer and mental illness had a significant 40% increased rate of breast cancer-specific death compared to those with the same stage cancer, but no mental illness. This suggests that there are factors beyond the delay itself that impact survival.

In prior studies, treatment decisions by the physician have been shown to influence survival. Patients with mental illness have a reduced likelihood of surgery, and receive significantly less radiotherapy and fewer chemotherapy sessions compared to those without mental illness (Kisely, 2013). In elderly patients, however, it is important to note that treatment is very complex and the risk/benefit assessments are not necessarily straightforward. For example, if a physician feels as though a patient's life expectancy is fairly low, it might not benefit the patient to subject them to chemotherapy or radiation. In the current study, patients with mental illness were less likely than those without mental illness to receive adjuvant radiation following BCS. This was especially pronounced in patients with major psychiatric illness, who also encounter a significantly increased rate of breast cancer-specific death. A factor to consider regarding receipt of treatment is that a larger proportion of patients with mental illness than without mental illness also had rheumatologic disease and chronic pulmonary disease, both of which could potentially decrease the likelihood of receiving radiation. Therefore, although there are differences in treatment, comorbidity could be driving some of these treatment choices.

Treatments used for mental illness may also play a role in the outcomes seen. For example, antipsychotics are drugs that can be used to treat major psychiatric illnesses such as schizophrenia or bipolar disorders. Evidence suggests that hyperprolactinemia is a common side effect of treatment, particularly with typical antipsychotic agents and the atypical antipsychotic agent risperidone. Hyperprolactinemia has been implicated in an increased risk of breast cancer

in post-menopausal women. Additionally, administration of prolactin in mice has been shown to increase the rate of mammary tumors (Halbreich, 2003). Although studies are ongoing and the impact on human breast tumors is yet to be fully elucidated, the potential exists for this mechanism to contribute to the development of breast cancer and a poorer prognosis in breast cancer patients receiving these medications. Lithium chloride is another medication approved for the treatment of bipolar disorder, but its role in breast cancer outcomes is yet to be determined. A study by Rouhani et al (2014) suggested that administration of lithium could make tumor cells more sensitive to radiation therapy, which has the potential improve outcomes, especially when used in radio-resistant cell lines. Additionally, Higgins and colleagues (2011) noted that combination therapy with lithium may prevent resistance of tumors to hormonal therapy, chemotherapy, and HER2-directed therapy, thereby increasing the efficacy of these medications. However, Suganthi et al. (2012a, 2012b) demonstrated that lithium also has the ability to promote mammary tumors at low doses and stated that careful consideration should be taken when prescribing mood-stabilizing drugs due to this effect.

An additional factor that could contribute to decreased survival in those with mental illness is access to care. Some insurance carriers have limited access to care for comorbid conditions in those with mental illness, creating a financial burden to the patient (Howard, 2010). Although all patients in our study were receiving Medicare without HMO insurance, Medicare has historically had limited coverage for mental illness. This could make patients with mental illness hesitant to seek out care for other medical issues. Additionally, even when patients with mental illness are able to access care, they often face a phenomenon known as “diagnostic overshadowing”—a process by which a patient’s physical symptoms are mistakenly viewed as manifestations of their mental illness. This poses a large barrier for patients with mental illness, who often feel that they encounter discrimination from medical staff (Thornicroft, 2007). A study by Jeste et al

revealed that both the patient and the healthcare staff underestimate the presence of comorbid conditions when severe symptoms of mental illness are present (Jeste, 1996). Additionally, it is important to note that a patient with major psychiatric illness could suffer from psychoses and/or cognitive dysfunction. In these cases, a patient might not be able to understand their symptoms, their diagnosis, why they would need treatment, or why they would need to remain on treatment (Inagaki, 2006; Kunkel, 1997; Kelly, 2000; Jeste, 1996; Greer, 2008).

Several limitations need to be considered in the context of this analysis. Information is not available for the claims of HMO enrollees, out of pocket costs, or healthcare provided in other settings. This study is limited to patients 68 years of age or older with Medicare coverage and without HMO insurance. Therefore, the results might not be generalizable to those outside of this population. It is important to keep in mind that all reports of mental illness were based on ICD-9-CM codes. This could lead to under-reporting and misclassification of these patients as not having a mental illness (Davidson, 1999). Additionally, some patients may have never received a diagnosis of mental illness, but are being treated for a disorder. Medicare coverage for mental health benefits is limited, so it is possible that patients may not have sought care. Any diagnoses of mental illness prior to enrollment in Medicare are not included, and duration of mental illness could not be captured. Because our study is conducted in older patients, and mental illness can substantially decrease survival, it is possible that the most seriously mentally ill are not included in our study. Substance abuse was significantly underreported based on claims data and could not be taken into account. Additionally, because Part D Medicare files were not available for all patients during follow-up, use of hormonal therapy could not be assessed. Lastly, unobserved confounders that were not available in the SEER-Medicare data could impact the study results.

Conclusion

Patients with mental illness face increased rates of all-cause survival compared to those without mental illness. This relationship remained for all forms of mental illness and was especially pronounced in those with major psychiatric illness. Rates of breast cancer-specific death were significantly higher in those with major psychiatric illness compared to those without mental illness. It is important for oncologists, psychiatrists, and primary care physicians to collaborate on care for these patients. In order to confront this survival disparity, patients may ultimately need assistance with coordination of their care to address the management of their mental illness, breast cancer and other comorbid diseases.

Figures and Tables

Figure 1. Study Design

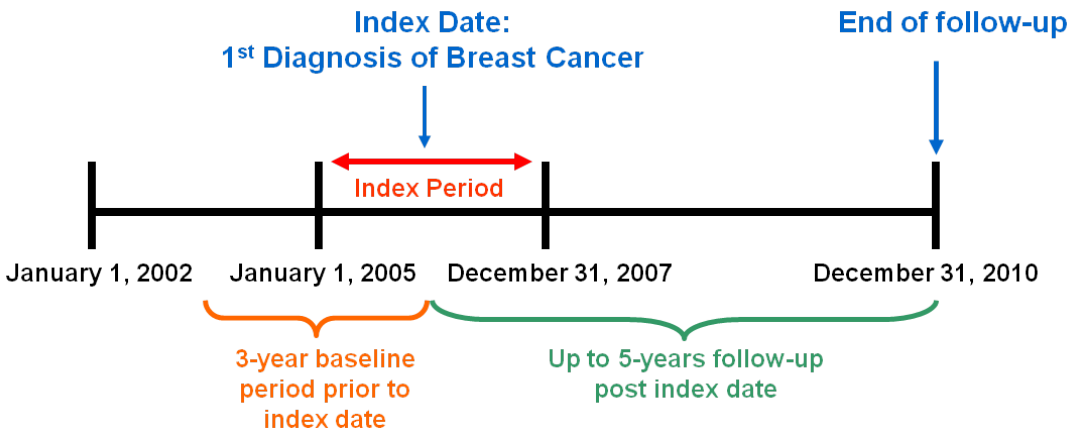


Table 1. ICD-9-CM Codes Used for the Determination of Mental Illness Status

Diagnosis	**ICD-9-CM codes**
Anxiety Disorder	308, 293.84, 300.0, 300.1, 300.2, 300.89
Depressive Disorder	296.2, 296.3, 300.4, 311, V79.0
Major psychiatric illness (Bipolar Disorder, Schizophrenia or Other Psychotic Disorder)	295, 297, 298, 293.81, 293.82, 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8, 296.9

Table 2. Demographic and clinical characteristics of early stage breast cancer patients by mental illness status

	With Mental Illness n=4651 (24.4%)	Without Mental Illness n=14,377 (75.6%)
Age at Diagnosis, Mean±SD	77.0±6.3	76.9±6.3
Age Group at Diagnosis, %		
68-74 years	40.5%	40.9%
75-84 years	46.2%	45.6%
85+ years	13.3%	13.4%
SEER State, %		
Connecticut	6.6%	6.4%
Michigan	5.4%	7.2%
Hawaii	0.8%	1.4%
Iowa	7.4%	6.3%
New Mexico	1.9%	1.9%
Washington	5.5%	5.5%
Utah	3.6%	2.2%
Georgia	11.6%	12.8%
California	28.5%	30.5%
Kentucky	9.0%	6.7%
Louisiana	6.7%	5.8%
New Jersey	11.9%	14.5%
Race, %		
White	91.0%	88.1%
African American	6.2%	7.0%
Asian or Pacific Islander	2.2%	4.1%
American Indian/Alaska Native Islander	0.3%	0.2%
Other	0.1%	0.1%
Unknown	0.2%	0.4%
Ethnicity, %		
Hispanic	4.8%	4.4%
Non-Hispanic	95.2%	95.6%
Marital Status, %		
Single (never married)	6.7%	6.5%
Married (including common law)	37.9%	44.6%
Separated	0.4%	0.4%
Divorced	8.1%	6.3%
Widowed	43.6%	38.3%

	With Mental Illness n=4651 (24.4%)	Without Mental Illness n=14,377 (75.6%)
Unknown	3.3%	4.0%
Census-based median income level, Mean±SD	49,163±22,795	52,536±24,753
Comorbid Conditions, %		
Myocardial Infarction	9.3%	5.6%
Congestive Heart Failure	23.7%	14.9%
Peripheral Vascular Disease	16.0%	11.3%
Cerebrovascular Disease	31.1%	20.7%
Chronic Pulmonary Disease	40.5%	28.3%
Rheumatologic Disease	9.1%	7.2%
Peptic Ulcer Disease	5.9%	3.3%
Mild Liver Disease	1.1%	0.8%
Moderate or Severe Liver Disease	1.0%	0.5%
Diabetes	35.5%	31.5%
Diabetes with Chronic Complications	8.3%	5.3%
Hemiplegia or Paraplegia	2.1%	0.9%
Renal Disease	9.1%	5.6%
AIDS	0.5%	0.3%
Number of Medical Comorbidities, %		
0	22.2%	34.2%
1-2	46.8%	46.8%
≥3	31.0%	18.9%
Charlson Comorbidity Index, Mean±SD	2.17±2.13	1.51±1.72
Tobacco use	6.4%	3.6%

Table 3. Tumor characteristics of patients with early-stage breast cancer by mental illness status

	With Mental Illness n=4651	Without Mental Illness n=14,377
AJCC Stage at Diagnosis, %		
I	57.3%	59.8%
IIa	26.4%	25.1%
IIb	10.5%	9.6%
IIIa	5.8%	5.5%
ER/PR Status, %		
ER+/PR+	63.6%	65.5%
ER+/PR-	13.2%	13.0%
ER-/PR+	0.6%	0.7%
ER-/PR-	14.3%	13.2%
Other/Unknown	8.3%	7.6%
Histologic Grade, %		
Well differentiated	25.5%	25.7%
Moderately differentiated	42.2%	43.5%
Poorly differentiated	25.0%	24.0%
Undifferentiated	1.0%	0.9%
Unknown	6.3%	5.9%
Tumor size, %		
≤10 mm	30.1%	31.1%
>10 to ≤20 mm	37.5%	38.7%
>20 to ≤50 mm	28.4%	26.6%
>50 mm	4.0%	3.6%
Number of Positive Lymph Nodes, %		
0	63.4%	66.9%
1-3	17.5%	16.4%
4-9	4.6%	4.4%
≥10	14.3%	12.2%
Unknown	0.2%	0.1%

Table 4. Treatment received during the follow-up period by mental illness status

	With Mental Illness **n=4651**	**Without Mental Illness** **n=14,377**
Breast-conserving surgery, %	2476 (53.2%)	8024 (55.8%)
Adjuvant Chemotherapy	1057 (42.7%)	3026 (37.7%)
Adjuvant Radiation	2029 (81.9%)	6818 (85.0%)
Mastectomy, %	1762 (37.9%)	5084 (35.4%)
Adjuvant Chemotherapy	940 (53.3%)	2525 (49.7%)
Adjuvant Radiation	677 (38.4%)	1866 (36.7%)
No surgery, %	413 (8.9%)	1269 (8.8%)
Chemotherapy	200 (48.4%)	475 (37.4%)
Radiation	208 (50.4%)	673 (53.0%)
No recorded treatment with surgery, chemotherapy or radiation	117 (2.5%)	408 (2.8%)

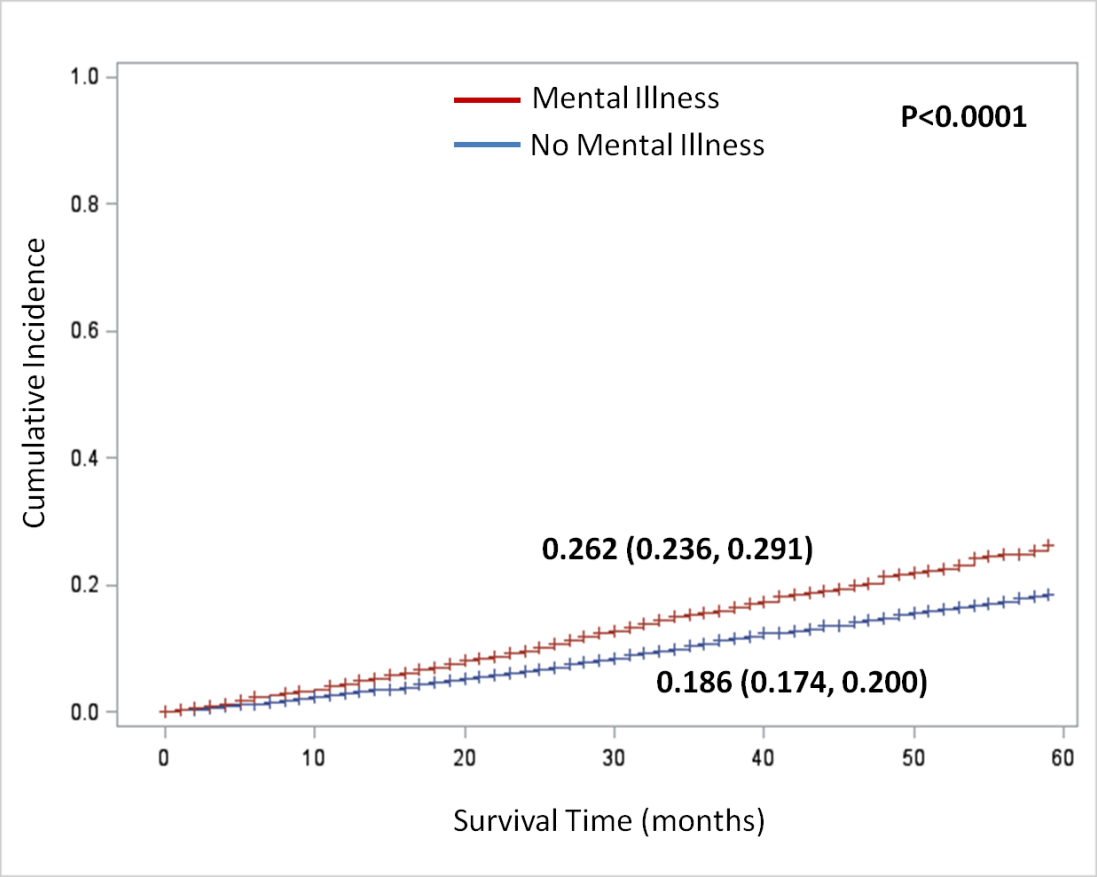
Table 5. Mean and median time to all cause and breast cancer-specific death for early stage breast cancer patients by mental illness status

	With Mental Illness n=4651	Without Mental Illness n=14,377
Time to death from any cause (months)		
Mean±SD	23.3±13.6	24.2±13.5
Median (Q1, Q3)	23 (12, 33)	23.5 (13, 34)
Time to death from breast cancer (months)		
Mean±SD	21.6±12.5	23.7±13.3
Median (Q1, Q3)	21 (12, 31)	23 (13, 33)

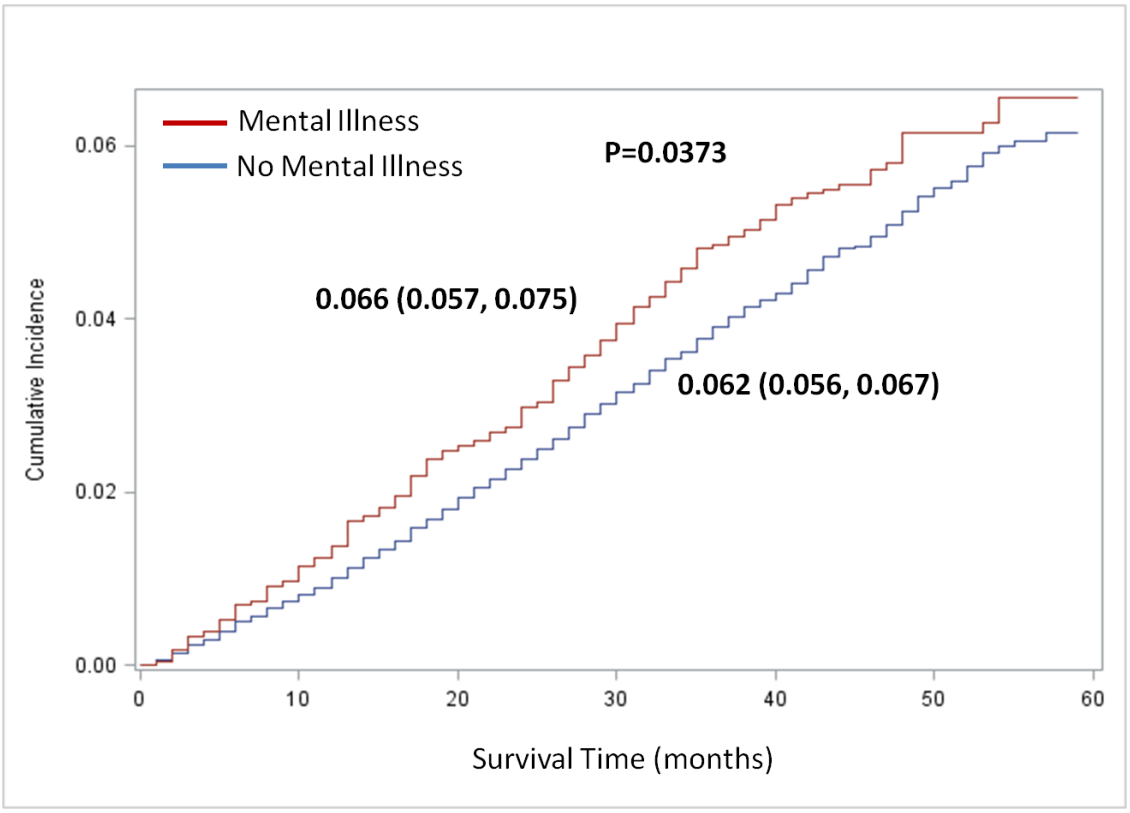
Q1=lower quartile; Q3=upper quartile.

Figure 2. Cumulative incidence and 95% confidence interval for all-cause and breast cancer-specific death in early stage breast cancer patients with and without mental illness

a. All-cause death

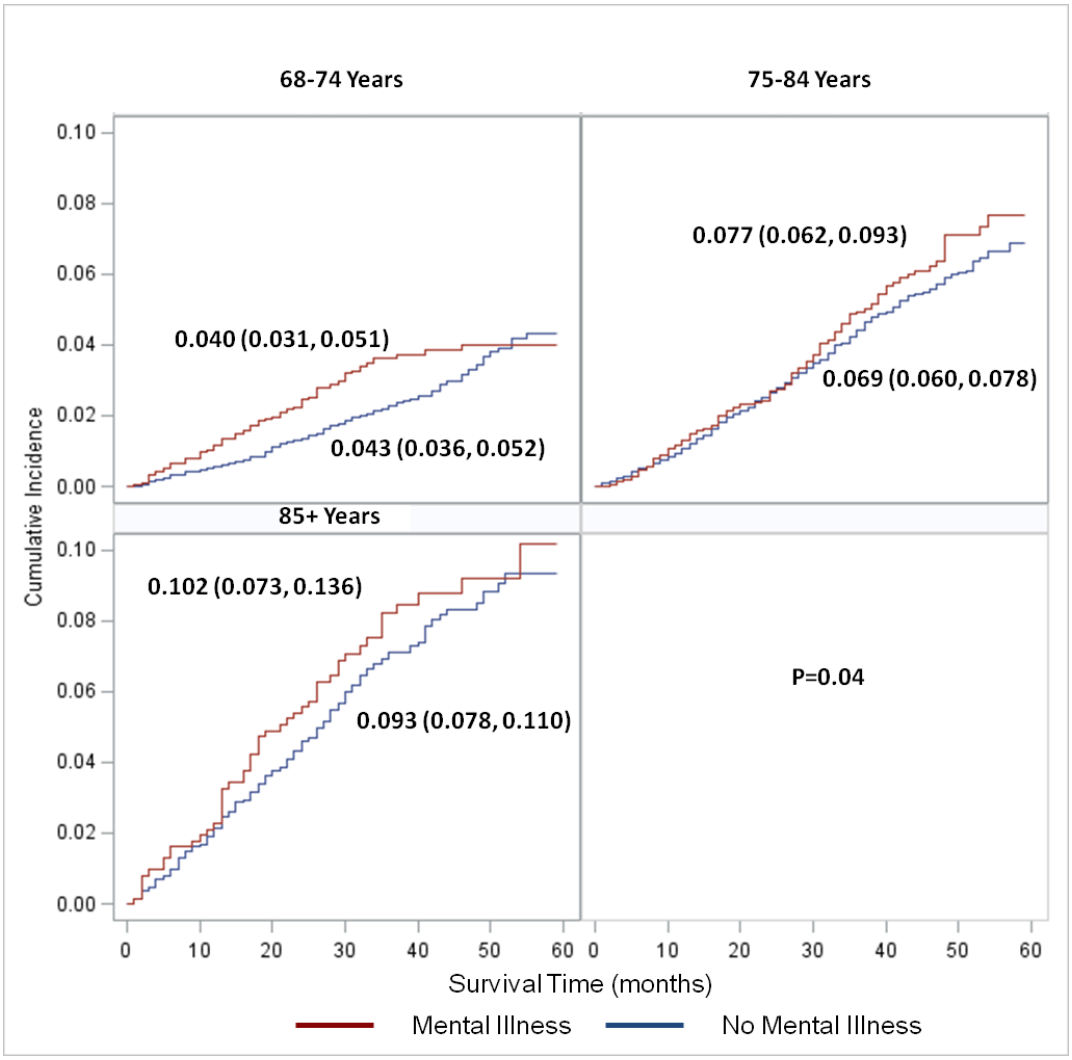


b. Breast cancer-specific death



NOTE: The y-axis has been scaled to range from 0 to 0.06.

c. Breast cancer-specific death by age group



NOTE: The y-axis has been scaled to range from 0 to 0.10.

Table 6. Adjusted hazard ratios and 95% confidence intervals comparing the rate of death for those with and without mental illness

a. All-cause mortality*

	HR	95% CI
Mental Illness vs. no Mental Illness	1.43	1.32, 1.56
By mental illness type		
Anxiety only vs. no mental illness	1.16	1.005, 1.34
Depression only vs. no mental illness	1.44	1.27, 1.63
Anxiety and depression vs. no mental illness	1.29	1.09, 1.52
Major psychiatric illness vs. no mental illness	2.27	1.94, 2.65
Subgroup Analysis		
By age groups (years)†		
68-74	1.56	1.30, 1.87
75-84	1.46	1.29, 1.64
85+	1.31	1.12, 1.52

b. Breast cancer-specific mortality†

	HR	95% CI
Mental Illness vs. no Mental Illness	1.12	0.96, 1.30
By mental illness type		
Anxiety only vs. no mental illness	0.95	0.73, 1.22
Depression only vs. no mental illness	1.21	0.96, 1.51
Anxiety and depression vs. no mental illness	1.04	0.76, 1.41
Major psychiatric illness vs. no mental illness	1.40	1.02, 1.92
Subgroup Analyses		
By age group (years)†		
68-74	1.25	0.94, 1.66
75-84	1.09	0.88, 1.34
85+	1.08	0.78, 1.49
By stage		
I	0.89	0.64, 1.25
IIa	1.01	0.76, 1.34
IIb	1.09	0.80, 1.49
IIIa	1.40	1.03, 1.89
By ER/PR status		
ER+/PR+	1.18	0.93, 1.49
ER+/PR-	0.98	0.65, 1.49
ER-/PR+	0.90	0.31, 2.64

	HR	95% CI
ER-/PR-	1.03	0.78, 1.34
By Grade		
Well differentiated	1.02	0.61, 1.71
Moderately differentiated	1.02	0.77, 1.35
Poorly differentiated	1.03	0.84, 1.28
Undifferentiated	2.35	0.73, 7.59
By Number of Positive Lymph Nodes		
0	1.03	0.78, 1.35
1-3	1.08	0.80, 1.45
4-9	1.36	0.96, 1.92
≥10	1.01	0.75, 1.38

*****Adjusted for age, income, race, ethnicity, SEER location, and marital status.

[†]Adjusted for income, race, ethnicity, SEER location, and marital status.

Table 7. Descriptive analysis examining potential reasons for relationship between major psychiatric illness and increased rates of breast cancer death

	Major Psychiatric Illness n=619	No Mental Illness n=14,377
AJCC Stage at Diagnosis, %		
I	52.1%	59.8%
IIa	29.2%	25.1%
IIb	11.3%	9.6%
IIIa	7.3%	5.5%
ER/PR Status, %		
ER+/PR+	62.8%	65.5%
ER+/PR-	12.4%	13.0%
ER-/PR+	0.7%	0.7%
ER-/PR-	13.6%	13.2%
Other/Unknown	10.5%	7.6%
Histologic Grade, %		
Well differentiated	24.2%	25.7%
Moderately differentiated	40.9%	43.5%
Poorly differentiated	26.3%	24.0%
Undifferentiated	0.8%	0.9%
Unknown	7.8%	5.9%
Tumor size, %		
≤10 mm	26.7%	31.1%
>10 to ≤20 mm	34.6%	38.7%
>20 to ≤50 mm	32.6%	26.6%
>50 mm	6.1%	3.6%
Number of Positive Lymph Nodes, %		
0	54.3%	66.9%
1-3	17.9%	16.4%
4-9	4.8%	4.4%
≥10	22.9%	12.2%
Unknown	0.1%	0.1%
Breast-conserving surgery	48.0%	55.8%
Adjuvant Chemotherapy	45.8%	37.7%
Adjuvant Radiation	71.4%	85.0%
Mastectomy	40.2%	35.4%
Adjuvant Chemotherapy	59.8%	49.7%
Adjuvant Radiation	39.4%	36.7%
No surgery	11.8%	8.8%
Chemotherapy	54.8%	37.4%

	Major Psychiatric Illness n=619	No Mental Illness n=14,377
Radiation	37.0%	53.0%
No recorded treatment with surgery, chemotherapy or radiation	3.4%	2.8%

CONCLUSION

In conclusion, the results of the analysis demonstrated that patients with mental illness were slightly more likely to be white, have a lower income, use tobacco, and have more medical comorbidities. They also lacked protective factors such as being married. There were no significant differences in the risk of diagnosis, initial treatment, surgery, or adjuvant radiation delays for those with versus without mental illness. However, there was an increased risk of adjuvant chemotherapy delay in those with versus without mental illness. When examining this relationship by mental illness type, patients with comorbid anxiety and depression had an increased risk for a diagnosis delay, while those with major psychiatric illness had a significantly increased risk of an initial treatment delay. Patients with mental illness had a significantly higher rate of all-cause mortality, and the relationship remained for each category of mental illness. Although the presence of mental illness overall did not significantly impact the rate of breast cancer death, a significantly higher rate was observed for patients with major psychiatric illness compared to those without mental illness. Based on these results, it is critical that patients with mental illness are carefully monitored by an interdisciplinary care team, including their primary care physician, an oncologist and a psychiatrist. Ultimately, in order to ensure optimal medical monitoring and care is provided, patients may need assistance with coordination of their medical services.

APPENDIX

Procedure	**ICD-9-CM codes**	**CPT Codes**	**HCPCS Codes**
Breast-conserving Surgery	85.2x	19110, 19120, 19125, 19126, 19160, 19162, 19301, 19302	
Mastectomy	85.4x	19180, 19182, 19200, 19220, 19240, 19303, 19304, 19305, 19306, 19307	
Chemotherapy	v58.11, v87.41', v07.3, v66.2, v67.2, 99.25	96400, 96401, 96402, 96405, 96406, 96408, 96409, 96410, 96411, 96412, 96413, 96414, 96415, 96416, 96417, 96420, 96422, 96423, 96425, 96440, 96445, 96446, 96450, 96542, 96545, 96549, 0519F, 36640, 36823, 4180F, 51720, 61517	C1086, C1167, C1178, C8953, C8954, C8955, C9205, C9213, C9262, C9414, C9415, C9417, C9418, C9419, C9420, C9421, C9422, C9423, C9424, C9425, C9426, C9427, C9429, C9431, C9432, C9433, C9436, C9437, C9438, C9440, G0355, G0356, G0357, G0358, G0359, G0360, G0361, G0362, G0921, G0922, G0923, G0924, G0925, G0926, G0927, G0928, G0929, G0930, G0931, G0932, G8371, G8372, G8373, G8374, G8381, G9021, G9022, G9023, G9024, G9025, G9026, G9027, G9028, G9029, G9030, G9031, G9032, J0128, J0207, J0594, J0640, J0641, J0894, J1050, J1051, J1190, J1453, J1675, J1825, J1830, J1950, J3315, J3490, J3590, J7150, J8510, J8520, J8521, J8530, J8540, J8560, J8565, J8600, J8610, J8700, J8705, J9000, J9001, J9010, J9015, J9017, J9020, J9025, J9027, J9031, J9033, J9035, J9040, J9041, J9045, J9050, J9055, J9060, J9062, J9065, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097, J9098, J9100, J9110, J9120, J9130, J9140, J9150, J9151, J9155, J9160, J9165, J9170, J9171, J9178, J9180, J9181, J9182, J9185,

Procedure	ICD-9-CM codes	CPT Codes	HCPCS Codes
			J9190, J9200, J9201, J9202, J9206, J9207, J9208, J9209, J9211, J9212, J9213, J9214, J9215, J9216, J9217, J9218, J9219, J9225, J9226, J9230, J9245, J9250, J9260, J9261, J9263, J9264, J9265, J9266, J9268, J9270, J9280, J9290, J9291, J9293, J9300, J9302, J9303, J9305, J9310, J9320, J9330, J9340, J9350, J9357, J9360, J9370, J9375, J9380, J9390, J9395, J9600, J9999, Q0083, Q0084, Q0085, Q2017, S0165, S0172, S0176, S0177, S0178, S0182, S1016, S2107, S5019, S5020, S9329, S9330, S9331
Radiotherapy	V58.0, V66.1, V67.1, 92.2x, 92.3x, 92.4x	77371-77373, 77401-77499, 77750-77799	G0173, G0174, G0251, G0339, G0340

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