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The Effect Of Depression And Antidepressants On Cost, Survival And Adherence To Hormone Therapy In Breast Cancer

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THE EFFECT OF DEPRESSION AND ANTIDEPRESSANTS ON COST, SURVIVAL AND ADHERENCE TO HORMONE THERAPY IN BREAST CANCER

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DEDICATION

This dissertation is dedicated to my parents, sister and my friends in Columbia who have supported me during this process.

ABSTRACT

Introduction: Breast cancer patients with a depression diagnosis before or after cancer diagnosis have increased cost, shorter survival time and reduced adherence to hormone therapy. Treating depression in these patients should improve these outcomes; however, there is scarce literature on this topic. Currently, no study has determined the association of concurrent depression while adjusting for a history of depression or treating depression with antidepressants with cost, survival and adherence to hormone therapy. This study has two objectives: 1) to determine the association of concurrent depression with cost, survival and adherence to hormone therapy adjusting for a history of depression 2) to determine the association of antidepressant use with cost, survival and adherence to hormone therapy in patients with depression.

Methods: The SEER-Medicare dataset for 2005-2010 was used to address the study objectives. Breast cancer patients with hormone receptor positive cancers diagnosed from 2006 to 2009 were identified from the SEER cancer registry. Those who initiated hormone therapy within a year of cancer diagnosis were included in the initial population. A depression diagnosis was determined using ICD-9 codes. Those who had an ICD-9 code for depression within a year of cancer diagnosis were included in the final sample. Antidepressant use was determined from prescription drug claims and those who had at least one claim after a depression diagnosis were included in the final analysis. Generalized linear models (GLMs) were used to determine the association of

antidepressant use with adherence to hormone therapy and the incremental cost of antidepressant use among breast cancer patients with depression. Kaplan-Meier curves were used to determine the initial association of antidepressant use with survival.

Results: The final study population was 10,471 hormone receptor positive breast cancer patients who took hormone therapy within a year of breast cancer diagnosis. Of these patients, 10% had a diagnosis of depression within a year of breast cancer diagnosis. In breast cancer patients with depression, 62% took an antidepressant after their depression diagnosis. Depression was associated with a statistically significant decrease in adherence (OR 0.81; 0.71-0.93) in the adjusted model. Depression had a statistically significant 30% decrease in survival in the adjusted model. Depression was associated with increased cost ($21,978.75) in the adjusted model; however, this was not statistically significant. Adjusted general antidepressant use in breast cancer patients with depression had a non -significant reduction in the odds of adhering to hormone therapy (OR .79; .55-1.14). Those who took antidepressants for a year had a statistically significant increase in the likelihood of adhering to hormone therapy (OR 2.4; 1.61-3.65). Adjusted general antidepressant use was not associated with survival in breast cancer patients with depression. Continual antidepressant use for a year was associated with a statistically significant 60% increase in survival time in breast cancer patients with depression. Adjusted general antidepressant use was associated with a $27,840.50 increase in per patient per year cost; however, this difference is not statistically significant. Continual antidepressant use for 90+ days was associated with a statistically non-significant decrease in per patient per year total medical cost.

Conclusion: Concurrent depression is associated with worse outcomes in breast cancer patients adjusting for having a history of depression. Continual antidepressant use in breast cancer patients with depression is associated with improved adherence to hormone therapy and increased survival time. The benefit of antidepressant use is time dependent and those who with longer use of antidepressants show more improvement compared to those who do not. Antidepressant use increases per patient per year total medical cost; however, this is not a significant increase and continual use might be associated with decreased cost. Extended antidepressant use in the depressed cancer population provides positive benefits to these patients by improving adherence to hormone therapy and survival and potentially reducing cost.

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LIST OF ABBREVIATIONS

AI..... Aromatase Inhibitor

CYP2D6 .....Cytochrome P450 2D6

GLM .....Generalized Linear Model

PDC .....Percent Days Covered

SEER .....Surveillance Epidemiology and End Results Program

SERM .....Selective Estrogen Receptor Modulator

SNRI..... Selective Norepinephrine Reuptake Inhibitor

SSRI .....Selective Serotonin Reuptake Inhibitor

TCA..... Tricyclic Antidepressant

CHAPTER 1: INTRODUCTION

1.1 Overview

The aim of this chapter is to provide an overview of depression and antidepressant use in breast cancer patients. A description of breast cancer and its importance will introduce the study population for the dissertation. The key outcomes for this study are adherence to hormone therapy, survival and cost for breast cancer patients. Discussion of each outcome begins with the association of depression followed by the association of antidepressant use for those who are depressed. This chapter concludes with a statement about the gaps in the literature.

1.2 Breast Cancer in the United States of America

1.2.1 Introduction

Breast cancer is a disease that affects both men and women in the United States and all parts of the globe. It is also the most costly cancer in the United States[1]. Simply, breast cancer is uncontrolled growth of cells in breast tissue that form a tumor[2]. This disease is rare in men, but common in women. Female breast cancer is one of the most common cancers in the United States. If diagnosed at an early stage of tumor growth, female breast cancer has a good prognosis. Varieties of treatments are available to improve survival in these patients. There are still gaps in knowledge about the treatment of breast cancer patients despite the plethora of research on this topic[2].

1.2.2 Epidemiology

It is estimated that 12.3% of women will be diagnosed with breast cancer during their life with an estimated 231,840 women diagnosed in 2015 in the United States[3]. The Surveillance Epidemiology and End Results (SEER) program reports that female breast cancer has an 89.4% five-year survival rate (2005-2011)[3]. This survival rate leads to a higher prevalence of women with breast cancer in the United States, with an estimated 2,975,314 breast cancer cases in 2012[3]. Prevalence has likely increased over time as the death rate reduced from 26 per 100,000 women in 2001 to 21.3 per 100,000 women in 2012[3]. Breast cancer affects women differently based off various demographic characteristics. Women over 50, and Whites in the United States are most likely to develop breast cancer, while those who are Black have the highest mortality rate in breast cancer[2].

Breast cancer is the general term for cancer of the breast tissue[2]. This general term indicates several types of cancers of the breast, which have distinctive characteristics. These characteristics are the basis for distinct sub types, which have different treatments and survival probabilities. These subtypes are the presence of the estrogen receptor (ER+), progesterone receptor (PR+) , human epidermal growth factor receptor 2 (HER2+), or the absence of all 3 receptors (triple negative), or a mix of these combined[2]. The most common of these subtypes are ER+ and PR+ tumors[2, 4, 5]. The significance of ER+ and PR+ tumors is their need for estrogen and/or progesterone to grow[6]. These cancers express receptors for estrogen and/or progesterone that allow them to use these hormones to promote growth. Breast cancers with a majority of cells expressing one or both of these receptors are considered hormone receptor positive breast cancer or ER+/PR+[6]. Those who are hormone receptor positive have a better 5-year survival outlook compared to those who do not[7].

1.2.3 Treatment

Surgery, chemotherapy and radiation are general treatments for all sub types of breast cancer[2]. Surgery is defined as breast conserving surgery where minimal tissue is removed or a mastectomy where the entire breast is removed[2]. The type of surgery depends on the characteristics of the patient and cancer. Radiation is the use of high energy particles to kill cancer cells and generally follows breast conserving surgery and might follow a mastectomy depending on the characteristics of the cancer[2]. Chemotherapy is the use of cytotoxic drugs to kill cancer cells and can be given before (neo-adjuvant) or after (adjuvant) surgery[8]. Chemotherapy is generally the most effective with a combination of drugs; however there is no combination that is more effective than others[2].

Targeted therapy is generally given if the breast cancer sub type is sensitive to targeted therapy. The most common targeted therapy is hormone therapy to treat ER+ and PR+ breast cancers[2]. Women who take hormone therapy for ER+ and PR+ cancers have an increased survival benefit[9, 10]. Hormone therapy is given for at least 5 years as this time frame has been shown to provide the most survival benefit in these patients[10]. Adherence to hormone therapy is an issue even with the benefit of increased survival[11]. Approximately 62% of breast cancer patients who take hormone therapy adhere to the 5 year regimen[12]. Improvement is needed for patients to complete 5 years of hormone therapy.

1.2.4 Types of Hormone Therapy

Hormone therapy contains two major categories, selective estrogen receptor moderators (SERMs) and aromatase inhibitors (AIs) [2, 13, 14]. Each category has the benefit of interfering with the growth of breast cancer, but they also have unique side effects.

Tamoxifen is the most common drug in the SERM category[14]. SERMs are estrogen receptor antagonist because they block the estrogen receptor in breast cells. By blocking the

estrogen receptor, SERMs prevent tumors from using estrogen to promote growth[6, 15]. Tamoxifen is the SERM of choice for treating ER+/PR+ breast cancer[13, 15]. Tamoxifen has serious side effects which include blood clots, stroke, hot flashes, fatigue, mood swings and night sweats, which contribute to non-adherence to tamoxifen therapy[14, 16].

Anastrozole, letrozole, and exemestane are common drugs in the AI category. AIs reduce estrogen in the body by blocking aromatase, a cytochrome P450 enzyme that creates estrogens from adrenal androgens and testosterone[15, 17]. Anastrozole and letrozole are non-steroidal AIs that form a temporary bond with aromatase that keeps aromatase from making estrogens[15]. Exemestane is a steroidal AI that binds to aromatase and permanently inhibits aromatase from creating estrogens[15]. Due to the clinical effectiveness of these AIs, they are now an alternative treatment to tamoxifen for postmenopausal and advanced cancers[13, 17]. AIs also have serious side effects, which include heart problems, osteoporosis, joint pain and hot flashes, which also contribute to non-adherence of AI therapy[14, 16].

1.2.5 Adherence to Treatment

SERMs alone, AIs alone, or SERMs followed with AIs as therapy for at least 5 years show the best improvement in survival and reduction of recurrence[6, 13, 18]. Adherence to hormone therapy is a concern due to drug side effects and the length of time to gain the benefit of survival[19-22]. Menopausal symptoms and sides effects such as cognitive symptoms and musculoskeletal pain associated with hormonal therapy have been shown to be factors in reducing adherence to hormone therapy[19, 20]. Studies observing adherence show a decrease in adherence over time for both SERMs and AIs[12, 22-24]. Reduced adherence over time is a concern as women have poorer survival with reduced adherence[12, 22, 23], or conversely, those who are adherent show improved survival[9, 25-28].

Several studies have identified factors that predict non-adherence[22, 23, 29-32]. Side effects were the most common reason for non-adherence found in these studies[29, 30, 32]. Other reasons affecting adherence to hormone therapy include number of comorbidities, tumor size, using both a SERM and AI, and age. One study did find that a decrease in the quality of life was a predictor of non-adherence[29]. Adherence to hormone therapy is associated with several factors, which include patient characteristics, switching to an AI from a SERM and quality of life.

Non-persistence or discontinuing therapy is a particular type of non-adherence that is also important in hormone therapy[13, 33]. A person can be considered persistent but not adherent if they consistently take hormone therapy for 5 years but do not adhere to the recommended regimen during this time. For example, a person may have been 10 days late to refill their hormone therapy but they do not stop taking it completely. This person would be persistent but not adherent. Studies have found that non-persistence is an issue for breast cancer patients taking hormone therapy[12, 13, 33, 34]. These studies report that age, comorbidities and poverty level were associated with non-persistence. A study by Hadji indicated a switch of therapy and depression were also associated with non-persistence[33].

1.2.6 Cost

Breast cancer costs are categorized as direct or indirect cost. Direct costs include all medical expenses incurred by breast cancer patients. These costs can be breast cancer specific, all cost incurred by the patient or broken down to medical, pharmacy and other cost. Indirect cost includes loss of productivity, time family spends caring for the patient, and life style changes due to breast cancer.

Direct breast cancer cost was estimated to be $18.1 billion in 2014 in the United States[1]. Continuing care, including hormone therapy, cost $7.6 billion (42%) of the total cost for breast

cancer in 2014. Within the first year of diagnosis, 39% of Medicare payments were direct cost of treatment in breast cancer patients in 2002.

Breast cancer also has a high indirect cost. Employers in the United States lost $12.1 billion in 2005 due to breast cancer deaths for those over 20[1]. This estimate excludes other indirect cost such as lifestyle changes. Lifestyle changes would include increased exercise, such as yoga classes, and cosmetic changes (wigs). The patient incurs these extra costs, but they are not accounted for in medical cost or loss of work for an employer.

Direct and indirect costs of female breast cancer make it the most costly cancer in the United States[35] As indirect costs are hard to measure, studies have focused on direct cost, particularly the cost associated with hormone therapy. Non-adherence to hormone therapy is a major contributor to the high cost of breast cancer[36]. Those who were not adherent to hormone therapy had significantly higher medical cost during the 4 years of hormone therapy observed. There was no statistical difference in total cost (medical plus pharmacy) between those who were adherent and those who not adherent[36].

. *1.2.7 Summary*

Breast cancer affects many women in the United States and has several sub types that allow for specific treatments depending on the category. The most common sub type is hormone receptor positive, which is treated with hormone therapy. Adherence to hormone therapy is an issue due to the length of time of the therapy and side effects. Breast cancer is also the most costly cancer in the United States with non-adherence to hormone therapy contributing to the high cost of breast cancer.

1.3 Depression and Breast Cancer

Around 25% of breast cancer patients will be diagnosed with depression[37-42]. The prevalence of depression in breast cancer ranges from 5% to 50% depending on the population studied and how depression was classified[37-43]. Diagnosing depression is difficult as those taking chemotherapy have side effects that overlap with symptoms of depression[42]. There is also evidence that those taking hormone therapy will exhibit depressive symptoms as well[44]. Chemotherapy and rapid decline of estrogen due to hormone therapy is linked to cognitive impairment and depression[40, 41, 45]. There is also evidence that breast cancer patients are prone to depression due to a change in cytokine levels from the cancer and chemotherapy[45-49].

The prevalence of depression in breast cancer is a concern due to its effect on adherence and survival. Studies have established that depression has a negative effect on adherence in chronic diseases such as diabetes and hypertension[50]. The association of depression with adherence to hormone therapy in breast cancer is not consistently reported in the literature. A diagnosis of depression was associated with no effect or decreased odds of non-adherence to hormone therapy according to a review by Van Liew[16]. Van Liew's review indicated that having at least on comorbid condition was a predictor of better adherence. Other views on the association of depression with adherence to hormone therapy are seen in other studies outside of Van Liew's review[20, 33, 51, 52]. These studies indicate a negative association of depression with adherence to hormone therapy. Further, a meta-analysis of the literature showed depression is negatively associated with adherence to hormone therapy[53]. Van Liew's study is likely indicating that those who have a comorbid condition (i.e. depression), are more likely to be monitored by a physician and will be more adherent to hormone therapy as they are seeing a physician more often compared to if they did not have the comorbid condition.

Depression also has a negative impact on survival in breast cancer patients. Goodwin found a 42% increase in the risk of 3 year mortality for those who were depressed in the SEER-Medicare population[54]. Studies that used different datasets report similar results[55-57]. There is a biological mechanism for reduced survival in depressed cancer patients. Studies show that breast cancer patients have increased levels of cortisol, a hormone that controls glucose intake by cells, which could lead to tumor cells exhibiting resistance to cortisol stimulation. This resistance allows tumor cells to dominate glucose absorption and grow[58]. Those who are depressed also exhibit increased levels of neuroendocrine hormones related to stress that promote tumor growth as well[58, 59]. Breast cancer patients who exhibit depression after surgery have an impaired immune system response to breast cancer cells, indicating they are not able to fight off the cancer and potentially lead to a shorter survival time[59].

Cancer patients with depression have higher cost compared to those without depression. Breast cancer survivors who have depression show almost double the cost compared to those who do not have depression[60].

1.3.1 Summary

Depression in breast cancer is a concern it negatively affects adherence to hormone therapy, survival and cost. Those with depression have poor survival for two reasons. The first is depression is associated with poor adherence to hormone therapy. Adhering to hormone therapy improves survival and it has been shown that breast cancer patients who do not adhere to hormone therapy have worse survival compared to those who do adhere to hormone therapy. Depression also potentially weakens the body's ability to fight breast cancer and lead to poor survival since the cancer will take over the body if allowed. Those with depression also incur higher cost from increased healthcare utilization (direct medical and pharmacy) either by increased hospitalizations or increased physician visits and additional prescriptions.

1.4 Treatment of depression in breast cancer

1.4.1 Overview

Antidepressants and group therapy are two treatment modalities for depression in breast cancer patients[61, 62]. Several studies show that group therapy is effective in treating depression symptoms in the breast cancer population[62-66]. Antidepressants are also effective in treating depression in breast cancer patients[67-70].

Antidepressants have potential additional benefits in breast cancer beyond treating depression. They have been shown to help alleviate menopausal symptoms, hot flashes, etc., in breast cancer patients on hormone therapy[71]. This is probably due to their estrogenic effects[72]. Antidepressants also show anti-tumor effects *in vitro*[73].

Some antidepressants interact negatively with hormone therapy. The most commonly prescribed antidepressant, selective serotonin reuptake inhibitor (SSRI), negatively interact with tamoxifen. Tamoxifen is metabolized by cytochrome p450 2D6 (CYP2D6) into its active metabolites, which have a 100 fold increase in the ability to block the estrogen receptor[74]. SSRIs inhibit CYP2D6, which reduces the active metabolites of tamoxifen in breast cancer patients on tamoxifen therapy[74]. Studies have addressed the potential negative interaction of SSRIs with tamoxifen. Three studies found no effect of SSRIs on tamoxifen's protective effect against recurrence[75-77]. One study reported the SSRI paroxetine did block tamoxifen's protective effect on survival[78]. Following these studies, an editorial by Breibart indicated that certain SSRIs, like paroxetine, should not be given concurrently with tamoxifen as they are considered strong inhibitors of CYP2D6. SSRIs considered milder inhibitors of CYP2D6 could be given concurrently with tamoxifen[79]. This concern is reflected in a transition from use of SSRIs regarded as strong inhibitors to those that are weak inhibitors of CYP2D6 in tamoxifen users over time[80].

1.4.2 Depression treatment and cancer outcomes

As stated previously, depression is associated with worse outcomes; therefore, treating depression should be associated with improved outcomes. In the scare literature determining an association of depression treatment with outcomes, treating depression potentially improves outcomes in those with depression. Breast cancer patients with depression who were treated with the antidepressant fluoxetine showed improved completion of both chemotherapy and hormone therapy[81]. Depressed metastatic breast cancer patients who had reduced depression scores had improved survival[82]. Treating depression in breast cancer has mixed results on cost. One study finds no difference between the treated (group therapy) and untreated groups for both cost and utilization[83]. A literature review indicated that psychosocial interventions are inexpensive and do not significantly increase cost in the treated group and found that this intervention was cost effective as it increased quality adjusted life years[84]. A Canadian study in cancer patients reported a 23% reduction in total cost in breast cancer patients with depression who received group therapy[85]. In diabetes, a chronic condition like cancer, treating depression systematically showed increased total cost in the first year but reduced total cost by the second year[86]. Another study found short term cost for treating depression with group therapy is significantly higher while those on antidepressants are not significantly higher[87]. At this time, it is unknown how treating depression with antidepressants over the course of hormone therapy will influence cost.

Treating depression with group therapy or antidepressants potentially improves adherence to hormone therapy and survival in breast cancer. Breast cancer patients with depression do have higher cost if they are treated with antidepressants or group therapy; however, if treatment persists over time, cost could be reduced.

1.5 Summary

Breast cancer is a costly disease that affects a large proportion of women. Breast cancer has several sub types that are characterized by distinct clinical markers. The most common sub type is hormone receptor positive where the cancer cells express the estrogen and/or the progesterone receptor. These cancers are able to use hormones to promote their growth so the traditional therapy is to block these receptors either directly using SERMs or at the source using AIs. Due to side effects and length of hormone therapy, adherence and persistence to hormone therapy are clinically important issues. There is no consensus on how depression affects adherence and persistence in breast cancer; however, it is likely that there is a negative association of depression with adherence to hormone therapy. Cost and survival are both negatively affected by depression. Treating depression potentially improves adherence and survival and initially raises cost; however, cost might be reduced over time.

There are gaps in the knowledge of how depression and antidepressant use impact adherence to hormone therapy, cost and survival in breast cancer patients. The association of depression with adherence to hormone therapy, survival and cost adjusting for a history of depression is not known. The association of antidepressant use with adherence to hormone therapy, survival and cost in the majorly depressed population is not known.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter will present the current literature that describes the effect of depression and depression treatment on adherence to hormone therapy, survival and cost in breast cancer patients. This chapter will begin with a description of adherence, survival and cost followed by a detailed analysis of the relevant studies. Each analysis will include the purpose of the study, source of the data, study population, how relevant variables were operationalized, sample size, analysis used, relevant results, discussion of results and overall conclusion from the study. For each subsection, non- significant results are presented first followed by significant results. Each subsection will conclude with a summary of the presented studies followed by the identification of the gap in the literature. Each major section will conclude with a summary of all presented literature and the gaps found in the presented literature. This chapter will conclude with the aims and hypotheses of this study.

2.2 Definitions of Outcome Variables

2.2.1 Adherence

Medication adherence is the extent to which a patient follows their treatment regimen over a period of time[51]. Non-persistence or discontinuation is defined by an extended period of time between prescription drug fills, for the same drug, and indicates a patient stopped taking their therapy[33]. The length of time that defines when a person is non-persistent ranges from 90 to over 180 days between prescriptions in breast cancer patients[33, 52]. A patient who is not persistent is also considered non- adherent. Pill count, electronic monitoring, self- report, medication

possession ratio and percent days covered are ways to measure adherence in breast cancer patients taking hormone therapy[20, 22, 51, 88].

2.2.2 Survival

Survival in cancer has two components, namely length of time from diagnosis to death, and cause of death, specifically cancer-specific or other cause[54, 55, 57, 89].

2.2.3 Cost

Cost can be calculated several ways in the health care setting depending on the perspective. From a societal perspective, cost would include all direct medical cost in addition to other indirect cost. Examples of indirect cost are absence and loss of productivity to a company due to illness and transportation to and from a health care facility. From the patient perspective, cost would include direct medical out-of-pocket cost in addition to the transportation and loss of salary due to illness. In the literature, the focus is generally on direct medical cost.

2.3 Association of Depression with Hormone Therapy Adherence, Survival and Cost in Breast Cancer

2.3.1 Association of depression and adherence to hormone therapy

Table 2.1 summarizes several studies that examined the association between adherence to hormone therapy and depression. There is lack of consistency in the conclusions about the association of depression with adherence to hormone therapy. Studies ranged from a significant improvement in adherence to hormone therapy to a significant reduction in adherence to hormone therapy for those who are depressed.

Four studies found improvement (significant and non-significant) in adherence to hormone therapy for those who were depressed[33, 51, 90, 91]. All four studies were in European populations and two used the same dataset. Only two of these studies were designed to determine an association of depression with adherence[33, 90]. The study by Huiart is unique in the breast cancer literature as it focuses on a younger population (<40 years of age)[90]. This study is not generalizable to the general breast cancer population because most breast cancer patents are older (>60), and there are differences in how those who are 40 are affected by breast cancer compared to those who are over 60. Huiart's study also has a smaller sample of 246, with only 49 being depressed, which also limits generalizability. It is likely that these results (RR=.8 for non-persistence) would be significant with a larger sample size. Hadji's study is in the elderly population, but focuses on the type of care a patient received in Germany[33]. This study is in the elderly population and is generalizable to these patients. Of note, the hazard ratio of .92 for depression is closer to one compared to Huiart's study, but with a sample of 12,412; a significant result is expected. A distinct difference between these two studies is Huiart identified depression at 10 months after breast cancer diagnosis compared to Hadji who identified depression before breast cancer diagnosis. A potential explanation for consistently observing an indication of a positive association of adherence to hormone therapy with depression is those who are depressed are more likely to see a physician more often, which would lead to them to be more adherent to hormone therapy because they are seeing a physician more regularly compared to those who are not depressed. Of interest, Ziller's study indicated a differential effect of baseline depression on hormone therapy adherence between those on tamoxifen vs AIs[51]. The design of this study was to characterize these patients in a non-experiment setting, not determine predictors of non-adherence. Those on tamoxifen with baseline depression showed improved adherence to therapy (non-significant OR=1.22) compared to those on AIs with baseline depression who showed reduced adherence to therapy (non-significant OR=.96). With samples larger than 65 and 72 for tamoxifen and AI users, respectively, these results would likely become significant. Like Hadji's

work, this study was in the elderly population and potentially generalized to the general breast cancer population.

A negative association of depression with adherence to hormone therapy was indicated in five other studies[20, 29, 52, 88, 92]. Of these studies, three showed a non-significant association of depression to adherence to hormone therapy[29, 52, 92]. The study by Grunfeld indicated that those who were not adherent to hormone therapy had a non-significant increase in depressed mood compared to those who were adherent, based on a sample with only 13 who were not adherent[92]. Like Ziller's work, this study aimed to characterize patients who were non- adherent to hormone therapy. The other two studies that showed a non-significant decrease in adherence to hormone therapy for those who were depressed did focus on predictors of adherence to hormone therapy[29, 52]. These studies did not directly measure depression and relied on self-report or medication use to distinguish patients who had depression. Concurrent depression was associated with increased risk of discontinuing therapy in both studies (non-significant). Kemp showed a significant increase in the risk of discontinuing therapy for those who were concurrent/newly depressed (HR=1.19) before adjusting for covariates such as tumor size and clinical stage. When adjusted for all covariates, this increased risk was not significant. Kemp also examined a history of depression and found a non –significant increase risk of discontinuing therapy[52].

Two studies were designed to determine the association of depression with adherence to hormone therapy, and they both found a significant negative association of depression with adherence[20, 88]. Both of these studies used a depression scale to determine depression status and used an alternative to pharmacy claims to determine adherence. Data were collected via electronic monitoring of pill caps and in person interviews in Bender's study. A strength of Bender's study is the use of random coefficients modeling, which allows the use of repeated measures for adherence over time. As adherence changes over time, this model allows for this variation in determining predictors of non-adherence. The parameter for univariate analysis

predicting adherence for the Beck depression score (a higher score indicates more severe symptoms) was -.8845 ($p<.01$) at baseline and -.3106 ($p>.05$) as a time dependent variable. This indicates that a higher Beck score at baseline is associated with reduced adherence ($p<.05$) and indicates a negative association over time ($p>.05$). This study's sample of 91 limits the power to detect statistically significant differences and a larger sample might have shown a statistically significant decrease in adherence for those who developed depression during the study. A limitation for this study is that the analysis did not account for the other variables in the study, which would alter the effect of the Beck score on adherence. Of note, adherence was a continuous variable and the analysis was for a 1% increase in days of therapy taken. This consideration indicates that the estimates are likely conservative estimates and those with more depressed symptoms have a significantly reduced likelihood of adhering to hormone therapy.

Klepin's study of cognitive factors associated with adherence to tamoxifen and raloxifen (Co-STAR) used 6 month follow-up information taken in-person and a baseline standardized neuropsychological test that consisted of several cognitive tests that covered different areas of cognition[88]. These areas include memory, verbal fluency and global function. This is a nested study from a randomized clinical trial examining differences in tamoxifen and raloxifen. Adherence was measured every 6 months by pill count when a patient came into the clinic for the randomized trial and was condensed to a single measure for the entire period in this follow up study. Multivariate logistic regression showed that a higher baseline depressive symptom score was associated with a significant 13% increase in the odds of non-adherence. This result indicates that more depressive symptoms at baseline are significantly associated with non-adherence to hormone therapy. Of note, this study was not in the breast cancer population, but those who were at risk for breast cancer. One limitation is the use of a condensed adherence variable instead of repeated measures. A more appropriate analysis would be the use of the 6-month measures in a repeated measures analysis instead of a single measure for up to 5 years.

There appears to be a negative association between depression and adherence. The studies that indicated a positive impact of depression on adherence do not provide support for this association in the general breast cancer population. The use of a young population or small sample size indicates limited external validity for Huiart and Ziller[51, 90]. The only claims analysis done that indicated a positive association assessed discontinuation and not adherence[33, 91]. In the claims analysis they did not account for a potential increase in utilization of physician visits due to depression as a potential reason for the positive association observed. As these analyses included the type of physician practice a person visited, the negative effect of depression might have been observed in the poorer physician practice and the depression variable itself indicates the association of more physician visits with increased persistence. These studies do not support a strong positive association of depression with adherence to hormone therapy. Of the five studies indicating a negative association of depression and adherence to hormone therapy, three used prospectively collected data from a clinical trial or other project[20, 52, 88]. Only two of these studies directly obtained information on depressive symptoms[20, 88] and only one used a large sample size[88]. Only Bender, used a repeated measures analysis for adherence over time. As adherence to hormone therapy drops over time, using repeated measures allows for a more detailed analysis of predictors of non-adherence[22]. No study reports the association between depression and adherence to hormone therapy using a large database with a repeated measures design.

2.3.2 Depression and survival

Table 2.2 summarizes four studies that examined the association between survival and depression. All studies found a significant reduction in survival for those with depression. These studies focus on a prior diagnosis of depression and not concurrent depression. Each study provides a different perspective on the association between depression and survival in breast cancer patients.

Onitilo's study used a general approach that observed four groups of people from the NHANES population[55]. These groups were those with no cancer without depression, no cancer with depression, cancer with no depression; and cancer with depression. Mortality was determined either with the National Death Index or by a proxy interview that determined a patient's vital status. The authors reported hazard ratios of 1.42, 1.24 and 1.7 ($p<.05$ for all) for those with cancer without depression, no cancer with depression and cancer with depression, respectively compared to those with no cancer without depression adjusting for various demographic characteristics. The authors reported a breast cancer specific hazard ratio of 1.27 ($p>.05$) that adjusted for various demographic characteristics. The sample size of 136 for all breast cancer only patients is likely too small to detect significant differences between those with depression and those without depression. A limitation of this study is the inability to adjust for cancer specific confounders, which would influence survival, such as stage of cancer that is an indication of cancer severity. Another limitation of this study is the inability to determine if depression was diagnosed before or after breast cancer diagnosis.

Hjerl's more focused design found mixed results for the direct association of depression with survival in early and late stage breast cancer patients [89]. In the 10,382 women with early stage breast cancer those with depression before or after cancer diagnosis had relative risks of 1.23 ($p>.05$) and 1.73 ($p<.05$), respectively for death due to all causes. Relative risks for the 10,211 late stage breast cancer patients were 1.34 ($p<.05$) and .96 ($p>.05$) for those with depression before or after breast cancer diagnosis respectively. All risks were adjusted for clinical characteristics that would affect survival and those with late stage cancers were additionally adjusted for tumor size and the number of positive lymph nodes. This study indicated that depression increases the risk of death due to all causes in early stage breast cancer while only preoperative depression significantly increases the risk of death due to all causes in late stage cancer patients. This is the first study to indicate that the timing of depression may

have a differential effect on survival depending on the stage of cancer. The strength of this study is the large sample size and additional adjustments for confounders. Another strength is the generalizability to a broader breast cancer population; however, this study used data from 1978-1993 from Denmark. An updated study is needed to determine if these results are applicable to the current population.

Vodermaier focused on 1,646 early stage breast cancer patients from two cancer centers who did or did not have a prior diagnosis of depression[57]. Those with a prior diagnosis of depression had a 154% (p=.02) increased risk of death due to all- causes adjusting for clinical and demographic characteristics. A strength of this study is the comprehensive adjustment for confounders and a large enough sample size to generalize to a broader breast cancer population.

Goodwin's SEER-Medicare study is the only United States claims based study to examine the impact of depression on survival in breast cancer[54]. The purpose of this study was to determine if a prior diagnosis of depression had an effect on 3-year survival in breast cancer patients. The final population of 24,696 breast cancer patients was analyzed. A prior diagnosis of depression had a 142% increase in the risk death within 3 years of diagnosis ($p<.05$) adjusting for some con founders. A limitation of this study was that tumor type (ER/PR + etc.), initial surgery, radiation use, chemotherapy use, tumor size and grade were not included in the analysis. These are all important factors that affect survival in breast cancer. Of note, this study used data from 1993-1996 and an updated analysis is need to determine the impact of prior depression on the current United States breast cancer population. An important strength is the use of SEER-Medicare, which is a representative database for all Medicare breast cancer patients in the United States. A study is needed to determine the effect of prior depression on survival adjusting for all confounders in the current SEER-Medicare population.

The literature shows a prior diagnosis of depression is associated with a significantly increased risk of death in breast cancer patients. Only one study accounted for the effect of concurrent depression on survival, and was in a Denmark population from 1978-1993. The only United States claims study looked at a prior diagnosis of depression and did not fully adjust for all confounders. There is no claims based analysis in the United States to determine the impact of concurrent depression on survival that also adjusts for a history of depression and all confounders in breast cancer.

2.3.3 Depression and cost

Table 2.3 summarizes the studies that examine the association between cost and depression. Only two studies determined the incremental cost of depression in cancer, and neither specifically looked at breast cancer. Other studies did not determine the incremental cost of depression, only the cost in patients with depression compared to those without depression. Only one study specifically examined cost in women with breast cancer and depression.

The study that specifically assessed cost in depressed breast cancer patients reported that those with depression incurred $15,471 annually compared to $8,297 in breast cancer patients without depression[60, 93]. Jeffery used the Military Data Repository (MDR) for this study and calculated costs as the total cost the Department of Defense paid to providers during fiscal year 2009. The final sample included 11,014 cancer patients, 2,851 (26%) breast cancer, for analysis. Incremental cost of depression in cancer patients was not calculated, and each cancer was analyzed separately, but the results were not reported in the primary article. A news article on this paper reported breast cancer specific results[60]. A limitation of this study is the use of a military database, which is not generalizable to the general breast cancer population. This is the only study to show that depressed breast cancer patients incur higher cost compared to non-depressed breast cancer patients.

Only one study determined the incremental cost of depression in cancer, which includes breast cancer. Pan determined the incremental cost of depression in all cancer patients in the Medical Expenditure Panel Survey (MEPS) population[94]. Cost was calculated as total health expenditures, which include all insurance payments, and out of pocket payments by the patient and reported in 2009 dollars. Ordinary least squares (OLS) of log transformed cost and generalized linear models (GLM) with a log link and Gaussian distribution were used to determine the incremental effect of depression on cost. OLS showed a 32% increase in total cost, 16% increase in outpatient and 107% increase in prescription cost for those who were depressed adjusting for demographic and clinical confounders ($p<.001$ for all). GLM showed that those with depression incurred an extra $2,213 total cost ($p<.05$) and $913 ($p<.01$) prescription cost compared to those without depression adjusting for clinical and demographic confounders. GLM also showed that those who are depressed had a reduction of $329 for outpatient cost. One limitation of this study is the inability to account for cancer specific factors such as stage that will influence cost as those with more severe cancers will have higher cost compared to those with less severe cancers. A strength of this study is the generalizability to all United States cancer populations as MEPS is nationally representative. Another strength is the use of a GLM with a log link and a Gaussian distribution to account for the skewed nature of cost.

Jayadevappa used SEER-Medicare to the effect of depression on cost in men with prostate cancer[95]. Cost was calculated as direct medical cost Medicare paid in reimbursements and reported in 2009 dollars using a 5% discount rate. A generalized linear model with a log-link and gamma distribution reported the effect of depression on cost. Depression diagnosed during treatment showed significantly increased cost (1.52 odds to 1.34 odds) for the years 1 to 4 after cancer diagnosis and 1.43 odds the last year before death. Depression diagnosed after treatment showed significantly increased cost (1.51 odds to 1.89 odds) for years 2-5 and 1.26 odds the last year before death. A limitation of this study is the authors only report the odds and not the actual

cost even after they explain that is the advantage of using GLM. The authors did not take advantage of this tool to report the incremental cost of depression in prostate cancer. Another limitation is that they did not adjust for cancer specific variables such as stage, tumor size, or surgery type.

The literature shows that depression increases direct medical cost in cancer. Only one study showed the incremental cost of depression in cancer, and it was unable to account for cancer specific confounders. Two studies use a GLM to examine cost, which is an appropriate analysis to account for the skewed nature of cost. There is one study to compare the cost incurred by depressed breast cancer patients to non-depressed breast cancer patients; however, the study did not determine the incremental cost of depression and was in a select breast cancer population that did not reflect the general breast cancer population. No study in the literature determined the incremental cost of depression in breast cancer using generalized linear models.

2.3.4 Summary of Depression in Breast Cancer

The literature for depression and breast cancer shows that depression has negative effects on adherence to hormone therapy, survival and cost. The literature that examined the association between depression and adherence contains differing results. The studies that indicated a positive association between depression and adherence have two limitations: 1) a unique population not indicative of the general breast cancer population and 2) potentially increased monitoring due to more doctors' visits because of a depression diagnosis. Studies that showed a negative association of depression with adherence were in a prospective setting and generally used a single adherence measure. There has not been a retrospective claims study using repeated adherence measures to examine the effect of depression on adherence to hormone therapy. Studies examining the association of depression with survival all found a significant decrease in survival for those who were depressed. These studies focused on a prior diagnosis of depression and not

depression during breast cancer. The one generalizable United States study did not account for several confounders in their analysis. No study has examined the impact of depression during breast cancer on survival that accounts for all available confounders in the United States. Cancer patients with depression have increased cost and the only study that specifically observed breast cancer patients did not determine the incremental cost of depression and was in a unique population. Other studies that determined incremental cost of depression in cancer patients used a GLM, a model that is able to account for the skewed nature of cost without transforming cost before the analysis. The incremental cost of depression in breast cancer patients has not been determined using a GLM.

2.4 Breast Cancer and Treatment of Depression

2.4.1 Adherence and depression treatment

Table 2.4 summarizes three studies that examine the association between adherence to hormone therapy and antidepressant use. These studies show mixed results on this association that range from significant improvement to a significant reduction in adherence to hormone therapy; however, none of these studies focused on those who had a diagnosis of depression.

Two studies indicated a reduction in adherence to hormone therapy for those taking antidepressants[19, 24]. Trabulsi reported that antidepressants negatively affect adherence to hormone therapy in 4,715 elderly breast cancer patients[24]. Antidepressants at baseline reduced adherence by 4.7% (p=.004) adjusting for various clinical and demographic characteristics. A limitation is that depression was not controlled for in the analysis, which potentially indicates that antidepressants are a proxy for depression. Therefore, these results do not show the association of antidepressant use with adherence to hormone therapy in the depressed population. Another limitation of this study is the use of a single measure of adherence for 5 years instead of repeated

measures. Using a repeated measures analysis would allow patients to be followed over time. The study by Cluze did observe depressive symptoms and still found a reduction in adherence for those on antidepressants[19]. In the univariate analysis, antidepressants had a 1.91($p>0.2$) increase in the odds of early non-persistence while those with a CES-D score >23 (French cutoff for depression[96]) had a 0.76 ($p>0.2$) decrease in the odds of early non-persistence. Antidepressants also had a 1.36 ($p>.2$) increase in the odds of late non-persistence and depression had a 2.48($p>.2$) increase in the odds of late non-persistence. The p-value in the univariate analysis did not meet the required <.2 cutoff to be included in the multivariate analysis for antidepressant use and depression. As these odds ratios are not adjusted, antidepressant use is likely a proxy for those with major depression as indicated above. As depression was not accounted for in the analysis in both papers, antidepressants might decrease the risk of non-persistence in breast cancer patients with depression.

Navari's study is the only one that examined the effect of antidepressants on completion (adherence) to hormone therapy in 193 breast cancer patients with depressive symptoms[81]. The fluoxetine (antidepressant) group had a significantly higher rate of completing adjuvant therapy (87%) compared to placebo (50%) ($p<.01$). A limitation of this study is the short observation period, particularly for hormone therapy. As patients take hormone therapy for at least 5 years, the concern of non-adherence is after the first year or two. This study was also not in clinically depressed patients, but it is likely that those who are clinically depressed would benefit more from treatment than those who are not. Another limitation is it is not generalizable past early stage breast cancer patients with mild depressive symptoms. The strength of this study is its internal validity that comes with a double blind randomized controlled trial. This study indicates potential causality between fluoxetine treatment and completing adjuvant treatment at 6 months.

The literature is conflicted on the impact of antidepressants on adherence to hormone therapy; however, only one study observed those with any depressive symptoms. The two studies

that indicate a negative effect of antidepressants on adherence to hormone therapy do not account for a diagnosis of depression. In these studies, antidepressant use is likely a proxy for depression, which has been shown to negatively effects adherence to hormone therapy. The one study that established that antidepressants improve adherence was in a small sample and in the non-clinically depressed population. As an association was established in Navari's study, a large study in the clinically depressed population will determine if these results are generalizable to the larger breast cancer population. No claims-based study to determine the impact of antidepressant use on adherence to hormone therapy has been done in the clinically depressed breast cancer population.

2.4.2 Survival and depression treatment

Table 2.5 summarizes five studies that examine the association between survival and depression treatment. Three studies examined antidepressant use for depression treatment and two studies examined group therapy for depression treatment.

The two studies that examined group therapy were both randomized controlled trials and were not in a clinically depressed population[64, 82]. The study by Goodwin did not show any improvement in survival for those in group therapy (median 17.9 months survived) compared to control (median 17.6 months survived)[64]. Giese-Davis showed a significant increase in survival time for those who had lower depressive scores (median 53.6 months) compared to those did not (25.1 months)[82]. Of note, Giese-Davis did not determine if group therapy was effective in reducing depressive symptoms compared to the control group. These studies indicate that in the non-depressed population, survival is improved by decreasing depressive symptoms not with group therapy.

Of the three studies that examined the association of antidepressant use on survival, only one was in a group that exhibited depressive symptoms and none were in a clinically depressed

population[28, 70, 78]. In the two studies with no depressive symptoms, a mixture of results were reported. Weaver reported that those who use CYP2D6 inhibitors (half of which were antidepressants) reduced the risk of death by 17% ($p>.05$) adjusting for adherence and clinical and demographic characteristics[28]. There are two considerations when examining these results. The first is this was not in the depressed population and the reduction could be significant in the depressed population. The second is the effect could be due to the inhibitors that were not antidepressants examined in this study instead of the antidepressants. Also, there could be differential effects of specific antidepressants, which are not captured in this study. The study by Kelly indicates that there are differential effects of antidepressants on survival for breast cancer patients on tamoxifen[78]. The adjusted cox proportional hazards model indicated a potential positive association for the antidepressant fluoxetine and survival, reduced risk of death due to all causes by 5% ($p>.05$). The adjusted model indicated a negative association of other antidepressants with survival; most associations were not statistically significant. Paroxetine had a statistically significant 146% increase in the risk of death due to all causes. There are two important factors to consider in interpreting these results. The first is this may not be in the depressed population. Antidepressant use could be a proxy for depression, which is one reason why there is a potential negative association indicated in this study. If antidepressants are a proxy for depression, then there is no other variable in this study that would indicate depression is being treated by an antidepressant. This study would then be reporting the association of depression and not antidepressant use. Also, antidepressants could also be prescribed for other reasons that are not related to depression, such as treating menopausal symptoms[71]. In the depressed population, it is possible that antidepressant use improves survival. The second is this was in a tamoxifen only population and the only antidepressants examined were SSRIs. In tamoxifen users, there is a debate in the literature about the potential negative effects of SSRIs on tamoxifen metabolism and benefits[74, 76, 97, 98]. Published literature indicates that SSRIs fluoxetine and paroxetine potentially reduce the effectiveness of tamoxifen, but other SSRIs and other classes of

antidepressants do not reduce tamoxifen's effectiveness[98]. Of note, there has been no debate about SSRIs for those who use aromatase inhibitors.

Only one study examined the impact of antidepressant use on survival in cancer patients exhibiting depressive symptoms. Fisch reported a non-significant decrease in median survival time for those who took fluoxetine (6 months) compared to placebo (9 months) in a clinical trial by the Hoosier Oncology Group[70]. The strength of this study is the internal validity to determine causality for the effect of fluoxetine on survival. The randomized clinical trial design balances both observed and non-observed confounders between groups and the only difference between these groups is the taken drug. If there is only one difference between these groups, that difference is the cause for the reported results. One limitation is these patients were not clinically depressed, so there could be a positive effect of fluoxetine on survival. Of interest, the survival curves do cross in the second year of follow up with those on fluoxetine exhibiting a longer survival time compared to those on placebo. This indicates that a positive effect of antidepressant use is seen over time rather than immediately in depressed cancer patients.

The literature shows that a decrease in depressive symptoms is indicative of better survival. Antidepressants do improve depressive symptoms; however, the use of certain SSRIs in treating depression in tamoxifen users may not improve survival due to negative drug interactions. Only one study examined antidepressant use in those with depressive symptoms and indicated that any positive effect would be seen over time and not immediately in cancer patients. No study has examined the effect of antidepressant use on survival in the depressed breast cancer population.

2.4.3 The impact of depression treatment on direct medical cost

Table 2.6 summarizes the three studies that examine the association between direct medical cost and depression treatment. All studies observed group therapy as a treatment for depression.

Two studies looked at group therapy only and found no significant increase in cost for this intervention[83, 99]. Simpson's study indicated that the intervention significantly reduces cost for those who have high medical expenses; however, this was not in the depressed breast cancer population[99] . Lemieux's study indicated a non-significant reduction in cost for those who are distressed at baseline and took part in group therapy[83]. These studies were both in the Canadian breast cancer population and were not in the depressed population.

A U.K. study by Strong examined the cost of group therapy and indicated cost of antidepressant use as part of this intervention for depressed cancer patients[100]. The average total cost of the intervention was £334.86 ($670) per 6 months, which included antidepressant cost. Antidepressant costs were £70.11(~$140) vs £20.79(~$42) for those in group therapy or not, respectively. The difference is likely due to those in group therapy being more diligent in taking antidepressants compared to those who are not in group therapy. This is the only study to indicate cost of antidepressant use in depressed breast cancer patients. The results indicate that antidepressant users would not have significantly increased costs in the depressed population. A direct estimate of antidepressant cost in the United States cannot be made from this paper due to differing pricing policies in the U.K. versus the United States.

The literature for cancer and depression treatment is sparse and focuses on group therapy. There is an indication that antidepressant use would not significantly increase cost, and potentially reduce direct medical cost in the depressed population. There is no study in the

United States that has determined the effect of antidepressant use on direct medical cost in the depressed breast cancer population.

2.4.4 Summary of Antidepressant use in the Depressed Breast Cancer Population

The literature examining the impact of treating depression (group therapy or antidepressant) on adherence, survival and cost is sparse and focuses on those with depressive symptoms instead of those with a diagnosis of depression. Studies examining the impact of antidepressants on adherence do not account for a depression diagnosis or are in those with mild depressive symptoms. These studies indicate that antidepressants potentially increase adherence to hormone therapy in depressed breast cancer patients. Studies show that antidepressant use has mixed results with survival in breast cancer; however, they were not in the depressed population and only focused on one class of antidepressants. Treating depression improves survival, but no study has looked at all antidepressants and their effect in the depressed population. Antidepressant users would likely incur a non-significant increase in direct medical cost compared to non- users; however, the study was in a U.K. population, who have differing pricing policies compared to those in the United States. No study has determined the effect of antidepressant use on direct medical cost in the depressed breast cancer population.

2.5 Overall Summary

Depression negatively affects hormone therapy adherence, survival and cost in breast cancer patients. The studies that indicate a positive association of depression with adherence to hormone therapy are in a unique population and do not take into consideration increased monitoring by physicians due to a diagnosis of depression. Studies that indicate a negative association of depression with adherence to hormone therapy used electronic monitoring and pill counts to measure hormone therapy adherence only looked a prior diagnosis of depression and a

single measure of adherence. No study has used a repeated measures analysis to determine the effect of concurrent depression on adherence to hormone therapy in breast cancer. The literature suggests that a history of depression negatively effects survival; however, only one study has examined the effect of concurrent depression with survival and it was not in a United States population. No study in the United States has examined the effect of concurrent depression on survival in breast cancer patients. Depression increases cost in breast cancer; however, the incremental cost of depression in these patients has not been reported. Literature that examined the impact of antidepressant use on adherence, survival and cost in the depressed breast cancer population is sparse. The literature indicates that treating depression may improve adherence and survival but increase cost. The effect of antidepressant use on direct medical cost in the depressed population is unknown. There are three questions from this literature review: 1) is adherence to hormone therapy improved in the depressed population that uses antidepressants? 2) is survival improved in the depressed population that uses antidepressants? 3) what is the impact of antidepressant use in those with a diagnosis of depression on cost?

2.6 Specific Aims and Hypotheses

This study has three aims:

1) To explore the association of depression and antidepressant use with hormone therapy adherence in hormone receptor positive breast cancer patients

    H1A: Breast cancer patients with depression will have lower adherence to hormone therapy then those without depression.

    H1B: Breast cancer patients with depression and taking antidepressants will have improved adherence to hormone therapy then those with depression not taking

antidepressants

2) To explore the association of depression and antidepressant use with survival in hormone receptor positive breast cancer patients

   H2A: Breast cancer patients with depression will have a shorter survival time compared to those without depression

   H2B: Breast cancer patients with depression and taking antidepressant will have increased survival compared to those with depression and not taking antidepressants

3) To explore the association of depression and antidepressant use on direct medical cost in hormone receptor positive breast cancer population

   H3A: Breast cancer patients with depression will have increased cost compared to those without depression

   H3B: Breast cancer patients with depression and taking antidepressants will have reduced direct medical cost compared to those with depression and not taking antidepressants

Table 2.1: Studies Examining the Association of Depression and Adherence to Hormone Therapy

Author (year)	**Data source**	**Outcome Measure**	**Sample Size**	**Relevant Results**
Ziller (2008)	Clinic information from Marburg Germany	Adherence	89	Depression has a non-significant increase in adherence in tamoxifen group and non- significant decrease in adherence in AI group
Huiart (2012)	French National Health Insurance System	Compliance and persistence	288	A CES-D score of 23+ associated with non - significant decrease in risk of non- persistence
Hadji (2013)	Disease Analyzer Database (IMS Health) in Germany	Treatment discontinuation within 3 years	12,412	Depression associated with a significant decrease in risk of discontinuing therapy
Kostev (2014)	Disease Analyzer Database (IMS Health) in Germany	Discontinuation of treatment	6,626	Depression associated with a significant decrease in the risk of discontinuing therapy
Grunfeld (2005)	Guy's Hospital Breast Clinic database	Adherence	110	Depression not significantly associated with adherence
Aiello Bowles (2012)	COMBO study	Discontinuation and duration of therapy	538	Depression or mood changed associated with non-significant increase in the odds of discontinuing therapy
Bender (2014)	Comprehensive Breast Program in Pittsburgh	Adherence	91	A higher Beck score at baseline associated with significant decrease in adherence
Kemp (2014)	linked data from 45 and up study to various claims	Time to discontinuation of therapy	1,531	Pre-existing depression associated with non - significant increase in the risk of discontinuing therapy in unadjusted and adjusted models New depression associated with significant increase in the risk of discontinuing therapy in unadjusted model for initial therapy New depression associated with non- significant increase in the risk of discontinuing

Author (year)	Data source	Outcome Measure	Sample Size	Relevant Results
				therapy in adjusted models
Klepin (2014)	Co-STAR cohort from STAR trial	Adherence	1,479	A higher GDS score associated with a significant increase in the odds of non-adherence

Table 2.2: Studies Examining the Association of Depression and Survival

	Data source	**Outcome Measure**	**Sample Size**	**Relevant Results**
Onitilo (2006)	NHANES 1	All- cause mortality	10,025	Those with cancer and depression have a significantly higher risk of dying compared to those without cancer or depression In breast cancer, there is a non- significant increase in the risk of dying in the depressed group compared to non- depressed
Hjerl (2003)	Danish Breast Cancer Cooperation Group	All- cause, natural and unnatural mortality	20,593	Depression before surgery is associated with an increased risk of death Depression after surgery is associated with increased risk of death in early stage cancer patients but a non-significant decrease in late stage
Vodermaier (2014)	Prospective Canadian study	All -cause and breast cancer specific mortality	1,646	Those with depression have a slightly significant increase in the risk of all -cause mortality and a non-significant increase in breast cancer specific mortality Depression is significantly associated with an increased risk of mortality in early stage patients
Goodwin (2004)	SEER	3 year hazard of death	19,645	Depression significantly increased 3 year hazard of death

Table 2.3: Studies Examining the Association of Depression and Cost

Author (year)	**Data source**	**Outcome Measure**	**Sample Size**	**Relevant Results**
Bambauer (2007)	MCBS	Cost related non-adherence	13,835	Those with cancer and depression had significantly higher cost related non-adherence
Pan (2015)	MEPS	Total health care expenditures	4,766	Cancer patients with depression have higher unadjusted expenditures Cancer patients with depression have significantly higher total and prescription cost after adjusting for various characteristics
Jayadevappa (2012)	SEER-Medicare	Direct medical cost	50,147	Men with depression during treatment of prostate cancer have significantly higher cost all around Men with depression during or after treatment of prostate cancer have significantly higher long term cost
Jeffery (2012)	Military Data Repository	Total cost to DoD	11,014	Cancer patients with depression had lower unadjusted total cost but higher mean per patient cost
Jancin (2014)	News report of Jeffery talk	Total cost to DoD	2,851	Breast cancer patients with depression have twice the unadjusted cost as those without depression

Table 2.4: Studies Examining the Association of Depression Treatment and Adherence to Hormone Therapy

Author (year)	**Data source**	**Outcome Measure**	**Sample Size**	**Relevant Results**
Navari (2007)	Clinical trial	Completion of treatment at 6 months	193	Mildly depressed breast cancer patients on the antidepressant fluoxetine showed significantly higher 6 month completion of any cancer treatment
Cluze (2011)	Cohort Elippse 40 study	Tamoxifen interruption	161	Tamoxifen patients on antidepressants had a non-significant increase in the odds of interruption
Trabulsi (2014)	MED-ECHO databases	Medication adherence to antiestrogen therapy	4,715	Those on antidepressants showed a significant reduction in adherence to antiestrogen therapy in breast cancer

Table 2.5: Studies Examining the Association of Depression Treatment and Survival

Author (year)	**Data source**	**Outcome Measure**	**Sample Size**	**Relevant Results**
Kelly (2010)	linked prescription drugs and cancer registry in Ontario	Breast specific and all- cause mortality	24,430	Paroxetine showed significantly increased hazard of death from breast cancer and all causes Other antidepressants showed a non- significant increase or decrease in hazard of death from breast cancer and all causes
Weaver (2013)	NC Medicaid-cancer registry	Cancer related death	857	Using a CYP2D6 inhibitor (antidepressant etc.) is associated with a non-significant decrease risk of death
Fisch (2003)	Hoosier Oncology group	All- cause mortality	129	Those with depressive symptoms and taking fluoxetine show a non-significant decrease in survival compared to placebo
Goodwin (2001)	RCT in Canada	Survival	235	Breast cancer patients in group therapy show no difference in survival Group therapy did reduce depressive symptoms
Kissane (2007)	Australian Hospital data	Survival	227	Breast cancer patients in group therapy show no difference in survival Group therapy did reduce cases of depression
Giese-Davis (2011)	RCT in California	All- cause mortality	101	An increasing depressive score (CES-D) is associated with an increased risk of death A decreasing depressive score is associated with improved survival

Table 2.6: Studies Examining the Association of Depression Treatment and Cost

Author (year)	**Data source**	**Outcome Measure**	**Sample Size**	**Relevant Results**
Strong (2008)	UK RCT	Health care cost Intervention cost	200	Average direct cost of intervention was $523 Those in group therapy for depression had slightly higher cost
Lemieux (2006)	Breast Expressive Supportive Therapy study	Direct health care cost	125	Intervention of therapy had a non- significant higher cost If patient distressed at baseline then therapy had a non - significant lower cost
Simpson (2001)	RCT in Canada	Billed cost	89	No difference between therapy and control for mean billed cost Therapy group had significantly lower billed cost for those in the upper quartile of billed cost

CHAPTER 3 METHODS

3.1 Introduction

This chapter will describe the methods used to determine the final sample, define the main independent and dependent variables, and covariates and describe the type of analyses used for this study. Details on the data source, sample selection, variable operationalization, confounders and analysis are covered in this chapter. This is a retrospective cohort design and an explanation of this design and its application to this study will be discussed in this chapter.

3.2 Data source

The merged SEER-Medicare data set was used for this study. SEER-Medicare is a comprehensive data set that is comprised of the SEER cancer registry and Medicare Claims.

The Surveillance Epidemiology and End Results program (SEER) is a comprehensive cancer registry for the United States that started in 1973. SEER collects detailed information on incident cancer cases, which includes primary tumor site, stage, first course of treatment and vital status. SEER also routinely collects detailed demographic information for these incident cancer cases. SEER currently covers ~30% of the United States population in all geographic region and the data is used in calculating population rates (survival, incidence etc) for the United States[101].

Medicare is a federal health insurance program for those who are 65 and older or those with end stage renal disease or other disabilities. Medicare claims include Part A, Part B and Part D claims. Medicare patients have the option of enrolling in Parts A and B (government

insurance) or in Part C (HMO, private insurance). Part A claims consist of inpatient hospital claims and Part B claims consist of outpatient hospital claims and physician visit claims. Parts and B have claims information starting in 1991. Part A and B claim information includes cost of the claim to Medicare, procedure performed, diagnosis for procedure and the date of the claim. Part D is prescription drug coverage that contains drug claims since July 2006. Part D claim information includes the date of dispensing the drug, generic and brand name of the drug, and the days supplied.

SEER data was merged with Medicare claims using last name and social security number by CMS and the final data de-identified. The merged dataset is considered representative of the United States population. The final dataset contained unique patient identifiers to link between SEER data and Medicare claims[101]. The data was provided in four files: SEER, Part A, Part B and Part D. SEER-Medicare data for 2005-2010 was used for this study.

3.3 Study Design

This is a retrospective cohort design. Patient information was collected one year prior to and up to four years after breast cancer diagnosis. This design is used because this study uses previously collected information and follows a past cohort of breast cancer patients (2006-2009), from a specific point in time, date of diagnosis, forward to the most current time available[102].

Based off previous studies, the conceptual framework uses identified socio-demographic and clinical factors that are related to depression in breast cancer patients. These factors are income, stage at diagnosis, treatment (radiation, chemotherapy, type of surgery), comorbidities, marital status, age, race and type of hormone therapy used[103, 104]. In order to determine the association of depression, these factors are adjusted for in the analysis.

3.3.1 Sample Flow Chart

The following chart represents the populations of this study to answer the main hypotheses.

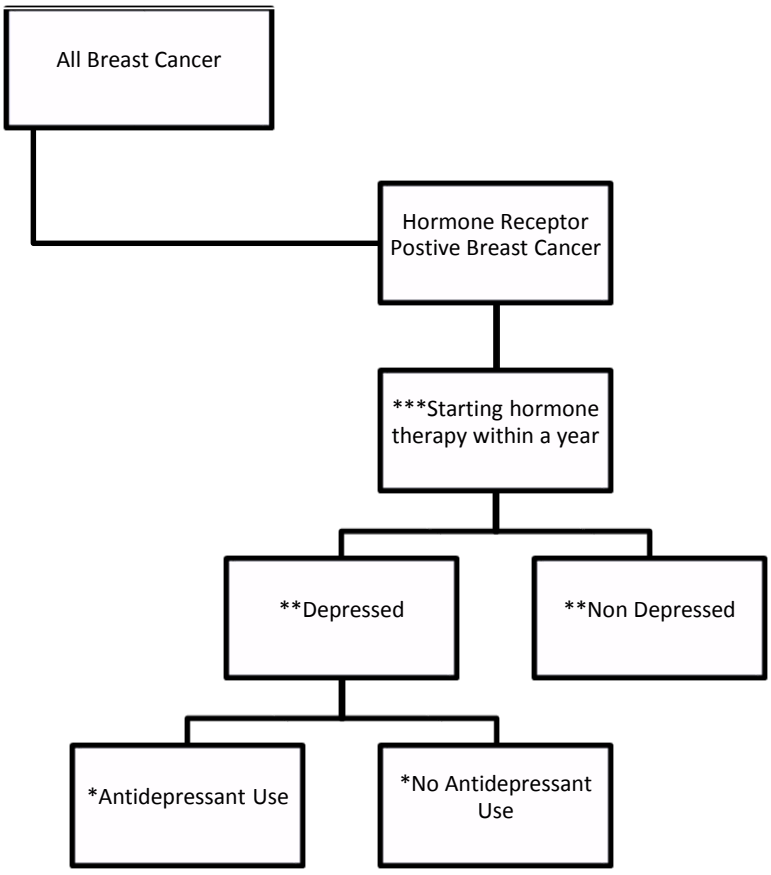

Figure 3.1: Sample Selection Framework

The groups with asterisks beside them are the populations of interest for this study. The primary study population has three asterisks beside it. The populations with two asterisks were used to test the hypotheses that depression reduces adherence to hormone therapy, and survival and increases cost. The populations with one asterisk were used to test the hypotheses that those with depression and taking antidepressants have decreased cost and improved survival and adherence to hormone therapy compared to those with depression and not taking antidepressants.

3.4 Sample selection

3.4.1 Initial breast cancer population

The breast cancer population was identified from the SEER registry using the provided cancer site code for breast cancer (46) for those diagnosed from 2006-2009. Estrogen and progesterone receptor status was determined from the registry using provided indicator variables for these biomarkers. Those with known estrogen or progesterone receptor positive status were included in the final sample. Of these patients, those with non- metastatic breast cancer and who were at least 65 at diagnosis were kept for analysis. Metastatic status was determined using the 7th edition of the AJCC breast cancer staging system of those with stage IV were considered metastatic[105]. Age was determined by a provided recode variable that indicated an age group at diagnosis. The included age groups were 65-69,70-74, 75-79, 80-84 and 85+. Of these patients, only those on hormone therapy were included.

3.4.2 Hormone therapy use

Hormone therapy was determined by a SERM or AI claim in Medicare Part D within a year of cancer diagnosis. SERMS and AIs were identified using the brand name of the drug. For example, a claim of arimidex for patients taking anastrozole. A frequency of brand names was done and matched with hormone therapy agents presented by breastcancer.org and the Susan G Komen website. Patients with hormone receptor positive breast cancer starting hormone therapy within a year were followed in Medicare for a minimum of 1 year and up to 4 years. Hormone therapy was classified as SERM only or aromatase only. Those who had claims for both were excluded.

3.4.3 Final sample for analysis

The final sample included only those who were continuously enrolled in part A and part

B from 1 year prior to cancer diagnosis through year post cancer diagnosis. The sample was restricted to those who were not enrolled in an HMO at all during this time- period as HMO's are private insurers, and those enrolled in an HMO will not have available information during this time. This requirement was to determine co-morbidities 1 year prior to the cancer diagnosis and to determine depression up to a year post diagnosis. Women with a diagnosis for schizophrenia, 295.xx, or bipolar disorders,(296.xx) excluding 296.2 and 296.3, or those with any antipsychotic medication claim during the year before cancer diagnosis were excluded from the study. Those with unknown stage or grade were also excluded from the final sample.

3.5 Primary independent variables

3.5.1 Depression

Patients with ICD-9 codes 311, 296.2, 296.3, and 300.4 from a hospital or physician claim were classified as being depressed. To be included in the depressed population, a patient had at least one claim within a year after cancer diagnosis. Depression was classified as either yes or no. Those with a depression claim within a year before cancer diagnosis were considered to have a history of depression.

3.5.2 Antidepressant Use

Antidepressant use was identified using drug name in part D claims. Antidepressants were classified as a selective serotonin reuptake inhibitor (SSRI), SNRI, TCA or miscellaneous. Depressed breast cancer patients on antidepressants had to have at least one antidepressant claim after their depression diagnosis to be included in the analyses to determine the effect of antidepressant use on cost, survival and adherence to hormone therapy.

To distinguish between those who used antidepressants consistently or not, a variable indicating the number of 30-day supply fills for an antidepressant was included. Those with more

than a 30-day supply were counted in intervals of 30 based of their supply. For example, a person with a 60-day supply would have a count of two for that claim.

Continuous antidepressant use was categorized as those who continuously used an antidepressant for less than 90, 90, 180 or 365+ days.

3.6 Primary Dependent Variables

3.6.1 Adherence to hormone therapy

Hormone therapy adherence rate was determined using the percent days covered (PDC) for the duration of medication use by a breast cancer patient[22]. Adherence was measured for up to 4 years of therapy. Adherence was measured on a quarter (90 days) by quarter basis until not continuously enrolled in part D or end of study. Using this method, PDC = (days covered)/ (duration of medication use). The duration of medication use is calculated from the start of hormone therapy to the end of the indicated quarter. This is equivalent to 90 multiplied by the quarter number. For example, the duration of medication use for the third quarter is 270, 90*3. The quarter number increases each quarter, so the sixth quarter represents one and half years on hormone therapy. In each interval, those classified as adherent had a PDC≥ 80% in order to be consistent with published literature on hormone therapy adherence[22, 36, 51]. Adherence was measured while the patient was continuously enrolled in part D and was stopped if the patient was no longer enrolled in part D. This restriction was applied to ensure complete information was available to measure adherence to hormone therapy. If a person was not enrolled in Part D, a refill might not be captured and a person who would be classified as adherent would be classified as non-adherent.

3.6.2 Persistence

A breast cancer patient with a gap of 90 or more days between the end of their last supply and their next fill date for hormone therapy was classified as non-persistent[19, 33, 90]. This time frame was chosen to be consistent with published literature.

3.6.3 Cost

Total direct medical cost was calculated as the sum of pharmacy, physician and hospital cost for provided services per patient per year from cancer diagnosis. Cost was from the payer's perspective (Medicare's), and was the amount paid for services or drugs by Medicare. Cost was inflation adjusted to 2010 U.S. dollars using the Consumer Price Index inflation calculator[106]. The analysis used accounts for the skewed nature of cost and further details are in the analysis section.

3.6.4 Survival

Survival was determined from the cancer registry and was measured in months from cancer diagnosis until death or December 31, 2012, which is the last day the registry has information on these patients. This is a longer follow up time as the registry reports this information instead of using available claims for cost and adherence to hormone therapy.

3.7 Additional covariates

Patient co-morbidity was measured using the Charlson co-morbidity score a year before their breast cancer diagnosis. ICD-9 codes were used to determine patients' co-morbidity score with a higher score indicating more severe co-morbidities[107]. Co-morbidity scores were classified as 0, 1 or 2+[23]. Age, race, geographic location and median income of zip code were used to account for socio-demographic status for a person. Age at the time of breast cancer diagnosis

was categorized as 65-69, 70-74, 75-79, 80-84 and 85+. Race was categorized as white, black or other[108]. Geographic location was determined by two variables. The first indicated urban setting or not. The second indicated SEER location, classified as northeast, north central, west and north central as defined by SEER[109]. The median income of the zip code was classified as under $30K, between $30K and $50K, and over $50K previously defined in work done with SEER-Medicare[11]. Those with unknown income were not included. Cancer stage and grade were also included to account for cancer severity. Cancer stage and grade were categorical variables.

3.8 Analysis

Descriptive statistics were used to illustrate sample characteristics and differences between those with depression and those without depression. These statistics were also used to characterize antidepressant users and non- users in the depressed population. Chi-square statistics were used to compare categorical variables across groups and the two-sample t-test was used to compare continuous variables across groups. For all regression models, an a priori selection of variables based off the conceptual framework were used. To test the hypothesis that those with antidepressant use will have improved adherence to hormone therapy in the depressed population, a generalized linear regression with logit-link and binomial distribution for repeated measures was used. This analysis is similar to logistic regression and does yield odds ratios from the parameter estimates. A generalized linear regression with log-link and gamma distribution for repeated measures of total cost was used to test the hypothesis that those on antidepressants will incur lower cost in the depressed population and to determine the incremental cost of depression. Kaplan Meier estimates were used to determine the initial association of depression and antidepressant use in the depressed population with persistence and survival. Kaplan-Meier estimates and a time interaction variable in the cox proportional hazards model were used to test the proportional hazards assumption. If proportional hazards were indicated (curves did not cross

and the interaction variable was not statistically significant), the association of depression and antidepressant use in the depressed population was reported from the adjusted Cox proportional hazards model. If proportional hazards were not indicated, (curves did cross and the time interaction variable was statistically significant), the distribution was determined using a linear survival model that fits different distributions. The distribution with the best fit (lowest AIC value) was used to estimate the association of depression and antidepressant use in the depressed population, adjusting for clinical and demographic characteristics.

The following model is the general form used for the analysis for the association of depression with adherence to hormone therapy. Y indicates the probability of adhering to hormone therapy so e^β is the adjusted odds ratio for the parameter[110, 111]. For this study, e^ β_1 is the estimate of interest as it indicates the odds of adhering to hormone therapy if a person has depression adjusting for demographic and clinical characteristics[110].

Log (Y/1-Y) = β_1 *depression + β_2 * age + β_3 *race + β_4 *co-morbidity + β_5 *SEER site + β_6 *urban + β_7 *cancer stage + β_8 *chemotherapy + β_9 *radiation+ β_{10} *cancer grade + β_{11} *history of depression + β_{12} *count indicating repeated measures

The following model is the general form used for the analysis for the association of depression with survival. H_i represents an individual's hazard of death and t indicates length of time a person survives. H_0 is the baseline hazard function. No assumption is needed for the baseline hazard function when there are proportional hazards between groups and H_0 is not in the model. If proportional hazards are not indicated, then H_0 is in the model as a baseline hazard function for the sample. For this study, e^(β_1) is the estimate of interest as it indicates the risk of death if a person has depression adjusting for demographic and clinical characteristics[112].

$H_i(t)$ = H_0 * (e^(β_1 *depression + β_2 * age + β_3 *race + β_4 *co-morbidity + β_5 *SEER site + β_6

*urban + β_7 *cancer stage + β_8 *chemotherapy + β_9 *radiation+ β_{10} *cancer grade + β_{11} *history of depression))

The following model is the general form used for the analysis for the association of depression with cost. Y represents total cost per patient per year and Log (E(Y|variable)) is the log cost based off the log link used for this association. For this study, β_1 is the estimate of interest as it indicates the increase in cost a person has depression adjusting for demographic and clinical characteristics[113]. The intercept in this case is baseline cost for the sample and estimates are added to the intercept for the total cost[94].

Log (E(Y|variable)) = intercept+ β_1 *depression + β_2 * age + β_3 *race + β_4 *co-morbidity + β_5 *SEER site + β_6 *urban + β_7 *cancer stage + β_8 *chemotherapy + β_9 *radiation+ β_{10} *cancer grade + β_{11} *history of depression + β_{12} *count indicating repeated measures

The following model is the general form used for the analysis for the association of antidepressants with adherence to hormone therapy in the depressed population. Y indicates the probability of adhering to hormone therapy so e^β is the adjusted odds ratio for the parameter[110, 111]. For this study, e^ (β_1 is the estimate of interest as it indicates the odds of adhering to hormone therapy if a person has depression adjusting for demographic and clinical characteristics.

Log(Y/1-Y) = β_1 *antidepressants + β_2 * age + β_3 *race + β_4 *co-morbidity + β_5 *SEER site + β_6 *urban + β_7 *cancer stage + β_8 *chemotherapy + β_9 *radiation+ β_{10} *cancer grade + β_{11} *history of depression + β_{12} * number of 30 day antidepressant supplies + β_{13} * count indicating repeated measures

The following model is the general form used for the analysis to determine the association of antidepressants with survival in the depressed population. H_i represents an individual's hazard of death and t indicates length of time a person survives. H_0 is the baseline hazard function. No assumption is needed for the baseline hazard function when there are proportional hazards between groups and H_0 is not in the model. If proportional hazards are not indicated, then H_0 is in the model as a baseline hazard function for the sample. For this study, $e^{(\beta_1)}$ is the estimate of interest as it indicates the risk of death if a person with depression uses antidepressant adjusting for demographic and clinical characteristics[112].

$H_i = H_0 * e^{(\beta_1 *\text{antidepressants} + \beta_2 * \text{age} + \beta_3 *\text{race} + \beta_4 *\text{co-morbidity} + \beta_5 *\text{SEER site} + \beta_6 *\text{urban} + \beta_7 *\text{cancer stage} + \beta_8 *\text{chemotherapy} + \beta_9 *\text{radiation} + \beta_{10} *\text{cancer grade} + \beta_{11} *\text{history of depression} + \beta_{12} * \text{number of 30 day antidepressant supplies})}$

The following model is the general form used for the analysis to determine the association of antidepressants with cost in the depressed population. Y represents cost and Log (E(Y|variable)) is the log cost based off the log link used for this association. For this study, β_1 is the estimate of interest as it indicates the increase in cost a person with depression uses antidepressants adjusting for demographic and clinical characteristics[113]. The intercept in this case is baseline cost for the sample and estimates are added to the intercept for the total cost[94].

$\text{Log}(E(Y|\text{variable})) = \text{intercept} + \beta_1 *\text{antidepressants} + \beta_2 * \text{age} + \beta_3 *\text{race} + \beta_4 *\text{co-morbidity} + \beta_5 *\text{SEER site} + \beta_6 *\text{urban} + \beta_7 *\text{cancer stage} + \beta_8 *\text{chemotherapy} + \beta_9 *\text{radiation} + \beta_{10} *\text{cancer grade} + \beta_{11} *\text{history of depression} + \beta_{12} * \text{number of 30 day antidepressant supplies} + + \beta_{13} * \text{count indicating repeated measures}$

CHAPTER 4 RESULTS

4.1 Overview

This chapter begins with a description of breast cancer patients with and without a diagnosis of depression followed by a description of those breast cancer patients with depression who use antidepressants and those who do not. Results related to hypotheses H1A-H3B will follow and addressed separately. For each hypothesis, the association of depression is estimated followed by the test of the hypothesis. A concluding statement indicates if the results support the indicated hypothesis. Results are presented in the following order: 1) the association of depression and antidepressant use with adherence to hormone therapy 2) the association of depression and antidepressant use with survival and 3) the association of depression and antidepressant use with cost in breast cancer patients.

The hypotheses to be tested are:

> H1A: Breast cancer patients with depression will have lower adherence to hormone therapy then those without depression.
>
> H1B: Breast cancer patients with depression and taking antidepressants will have improved adherence to hormone therapy then those with depression not taking antidepressants
>
> H2A: Breast cancer patients with depression will have a shorter survival time compared to those without depression

H2B: Breast cancer patients with depression and taking antidepressant will have increased survival compared to those with depression and not taking antidepressants

H3A: Breast cancer patients with depression will have increased cost compared to those without depression

H3B: Breast cancer patients with depression and taking antidepressants will have reduced direct medical cost compared to those with depression and not taking antidepressants

4.2 Baseline Characteristics

The SEER registry included 147,081 women with breast cancer satisfying the preliminary inclusion criteria. The majority (72%) had a diagnosis of hormone receptor positive cancer. After restricting the population to those 65 and older, not diagnosed at autopsy, not enrolled in an HMO and took hormone therapy within a year of cancer diagnosis, 10,471 were further identified as depressed (N=1,073) or not depressed (N=9,398) (figure 4.1). The enrollment and metastatic restriction is where the most patients were lost in the final selection for the sample population (figure 4.1). Of the 10,471 hormone receptor positive breast cancer patients taking hormone therapy, 8,522 (81%) took an AI and 1,949 (19%) took a SERM. The depressed population made up 10% of the final study sample, which is consistent with the 7% found in Goodwin's study in the general SEER-Medicare breast cancer population[54]. The depressed population differed significant from the non-depressed population on several factors. These include a history of depression, more co-morbidities, and more severe cancer (table 4.1). Consistent with more advanced cancer is the choice of a mastectomy, an invasive procedure, compared to breast conserving surgery. Consistent with Goodwin, those who are not married and white are more

prevalent in the depressed population. Those with radiation treatment are significantly fewer in the depressed population (table 4.1).

Of the 1,073 depressed patients, 664 (62%) had an antidepressant claim after their diagnosis of depression. For antidepressant users, 339 (51%) took an SSRI, 94 (14%) took an SNRI. 56 (8%) took a TCA and 175 (26%) took a different antidepressant. Those taking antidepressants had more history of depression, lower grade cancers, and were younger (table 4.2). No other significant differences were observed between antidepressant users and non-users.

4.3 Adherence to Hormone Therapy

4.3.1 Association of Depression with Adherence to Hormone Therapy

For reference, this section is testing hypothesis H1A: *Breast cancer patients with depression will have lower adherence to hormone therapy then those without depression*.

Consistent with previous studies, the number of patients who stayed adherent to hormone therapy reduced over time (figure 4.2). Table A.1 presents the number of patients observed in each quarter. Fewer patients (statistically significant) adhered to hormone therapy in the depressed group compared to the non-depressed group (figure 4.2). Depressed patients had significantly lower PDC values compared to the non-depressed group (table 4.3). Of note, the difference in mean PDC values between the depressed and non-depressed group consistently increased over the length of time a patient was on hormone therapy. In the GLM with a logit link and binomial distribution (test of H1A), depression was associated with a 19% reduction ($p<0.01$) in the odds of adhering to hormone therapy after adjusting for various clinical and demographic variables (table 4.4). Those with a history of depression had a 15% reduction ($p<0.01$) in the odds of adhering to hormone therapy. The repeated measures variable indicating the number of

measures a person had was associated with a 9% reduction ($p<0.0001$) in the odds of adhering to hormone therapy. Other factors that were significantly associated with reduced odds of adhering to hormone therapy were AI use, in a Midwest or South SEER site, and age>74 and in an urban area. Factors that were significantly associated with increased odds of adhering to hormone therapy were a mastectomy and a race that was neither black nor white.

Adherence to hormone therapy does reduce over time, which is shown in unadjusted counts and mean PDC values for each quarter and in the adjusted GLM model. Those with depression consistently have reduced adherence to hormone therapy over time, which is reflected in both unadjusted count and mean PDC values for each quarter. The unadjusted values and the adjusted value from the GLM model provide support for hypothesis H1A that patients with depression do have reduced adherence compared to those who do not have depression.

4.3.2 Association of Antidepressants with Adherence to Hormone Therapy

For reference, the hypothesis tested in this section is H1B: *Breast cancer patients with depression and taking antidepressants will have improved adherence to hormone therapy then those with depression not taking antidepressants*

The sample size for the test of hypothesis H1B is in table A.2 and reflects the number of patients analyzed in each quarter. In breast cancer patients with depression (depressed sample), antidepressant users had higher PDC values compared to non-users, but the difference was not statistically significant (table 4.5).

There was little difference in the percent of patients who were adherent to hormone therapy between antidepressant users vs non-users for quarters 1-7. Antidepressant users were consistently more adherent to hormone therapy compared to non-users starting at quarter 8 in the depressed sample (figure 4.3). Antidepressant users had a significantly higher percentage of patients who adhered to hormone therapy (55%) compared to non-users (45%). These results

indicate that antidepressant use is associated with improved adherence to hormone therapy in the depressed sample; however, this difference varies across the period of treatment.

To determine the association of antidepressant use with adherence to hormone therapy (test of H1B), a GLM was used for repeated measures to adjust for confounders. After adjusting for clinical and demographic characteristics, antidepressant use was associated with a non-significant 21% decrease in the odds of adhering to hormone therapy. The indicated negative association potentially reflects the severity of depression, as those with more severe depression are more likely to be on antidepressants. Figure 4.3 suggests that duration of antidepressant use is an important factor to consider as a benefit was shown only after 8 quarters of hormone therapy adherence measures. To account for the benefit of extended antidepressant use, patients were classified by the length of time they continually used antidepressants (<90 days, 90-179 days, 180-364 days, 365+ days). In the GLM model, antidepressant users who continually took an antidepressant for a year had a 340% increase in the odds of adhering to hormone therapy ($p<0.0001$) compared to non-users (table 4.6). This marked increase in the probability of adherence to hormone therapy indicates that those who are depressed and use antidepressants benefit from long- term use of antidepressants.

Those on antidepressants have improved adherence over time in the depressed sample; however, this benefit is seen for continual use of antidepressants over time. The results do not fully support the stated hypothesis that breast cancer patients with depression and taking antidepressants have better adherence compared to those not taking antidepressants.

4.3.3 Persistence to Hormone Therapy

Those with depression consistently had a significantly shorter time in persisting with hormone therapy (median 23 months), compared to those without depression (median 27 months) (figure 4.4). The proportional hazards assumption was met and the adjusted association of

depression with persistence to hormone therapy was assessed with the Cox proportional hazards model. Those with depression had a non-significant 106% increase in the risk of non-persistence to hormone therapy adjusting for clinical and demographic characteristics. Those with a history of depression had a 115% increase ($p<0.05$) in the risk of non-persistence to hormone therapy. Other factors significantly associated with non-persistence to hormone therapy are charlson score (2+), stage (2+), grade (3+), from a western SEER site, and age (85+). A mastectomy is the only factor that is associated with a significantly reduced risk of non-persistence (7% reduction).

Those who have a history of depression have a significant increase in non-persistence while those with concurrent depression have a non-significant increase in non-persistence. As the majority of depressed patients also have a history of depression, this result could indicate that chronic depression is the reason for non-persistence rather than newly diagnosed depression. A condensed variable that combines history of depression with concurrent depression to reflect this close association was considered; however, as the focus of this study is the association with depression with and without a history of depression, the condensed variable was not used.

In the depressed population, those on antidepressants had increased time persisting with hormone therapy (median 24 months) than those who did not take an antidepressant (median 21 months) (figure 4.5). Those who continually used antidepressants had increased persistence from 90 days of antidepressant use (median 24 months) to 1 year of antidepressant use (median 32 month) (figures 4.6-4.8). General antidepressant use was associated a non-significant 104% increase in the risk of non-persistence to hormone therapy (table 4.8). Surprisingly, those who used antidepressants continuously for 180 days had a significant 131% increase in the risk of non-persistence. This could be due to side effects, inability to handle multiple medications over a period of time or other reasons that are not able to be determined at this time. Those who continually used antidepressants for a year showed a significant 45% reduction in the risk of non-persistence to hormone therapy. This indicates that the length of time on antidepressants is

critical for depressed patients to benefit from this therapy. Other factors significantly associated with non-persistence are stage (3+), chemotherapy use and age (85+). No other factors were significantly associated with persistence.

Persistence and adherence are connected, as those who are not persistent are not adherent. The persistence to hormone therapy results reflect adherence to hormone therapy results: depression reduces adherence to hormone therapy and persistence to hormone therapy, and antidepressant use for a year improves adherence to hormone therapy and persistence to hormone therapy in patients with depression. These results indicate that it is continual use of antidepressants, not general use, which improves adherence to hormone therapy. The overall results support hypothesis H1A (depression reduces adherence to hormone therapy) but do not support hypothesis H1B (general antidepressant use improves adherence to hormone therapy).

4.4 Survival

4.4.1 Association of Depression with Survival

For reference, the hypothesis tested in this section is H2A: *Breast cancer patients with depression will have a shorter survival time compared to those without depression.*

The depressed population had lower survival compared to the non-depressed population (mean 57 months vs 63 months). The longer survival time reflects SEER data reported through 2012 for these patients instead of 2010 in the claims. Those in the depressed group always had lower survival compared to the non-depressed group (figure 4.9). The proportional hazards assumption was not met for this population. In order to adjust the association of depression with survival for confounders, a test for the underlying distribution of the hazard function was done. The underlying hazard distribution for this population was determined to be lognormal after

testing potential distributions and choosing the best fit based off the lowest AIC value. A parametric model using this underlying distribution was used to determine the adjusted association of depression with survival. Those with depression had a 31% decrease in survival after adjusting for clinical and demographic characteristics ($p<0.05$) (table 4.9). Those with a history of depression had a non -significant 7% decrease in survival. This is not consistent with Goodwin's finding for a history of depression and survival; however, Goodwin did not look at concurrent depression or adjust for clinical factors. As the majority of those with depression also have a history of depression, it is likely that Goodwin's result (HR= 1.42) is split between the two variables in this analysis and any other difference is likely attributed to further adjustment for clinical variables that decrease survival. Other factors associated with a significant decrease in survival were Charlson score (1+), stage (1+), grade (2+), a southern SEER site, black, age (74+), and income (30K+). Factors associated with a significant increase in survival time were having a mastectomy, radiation therapy, a race other than white or black, in an urban area and married.

Concurrent depression significantly reduces survival in breast cancer patients and over time those who are depressed are less likely to survive compared to those who are not depressed. The results support hypothesis 2A stating depression does negatively affect survival.

4.4.2 Association of antidepressants with Survival

For reference, the hypothesis to be tested is H2B: *Those with depression and taking antidepressant will have increased survival compared to those with depression and not taking antidepressants.*

In the depressed sample, antidepressant use had a similar mean survival time (57 months) compared to the non-users (56months). General antidepressant use did not have any effect on survival in breast cancer patients with depression (figure 4.10). As previously determined, the length of time antidepressants are used is a critical factor in determining a benefit for using them

in the depressed population. Antidepressants users for at least 90 days had a mean survival time of 58 months and overlap with non-users, which reflects the original full antidepressant population (figure 4.11). This indicates that 90 days is not enough time to gain any survival benefit from taking antidepressants if depressed. Antidepressant users for under 90 days had a mean survival time of 32 months and a marked drop in survival time after 10 months was indicated in this population (figure 4.11). These results potentially indicate that if a depressed person is going to use an antidepressant, they are better off not taking it than taking it for less than 90 days. The proportional hazards assumption was not met and further adjustment was done using the underlying log normal distribution. After adjusting for confounders, 90 day antidepressant users had a non -significant 151% increase in survival compared to antidepressant users for less than 90 days. Antidepressant non-users had a non-significant 169% increase in survival compared antidepressant users for under 90 days after adjusting for confounders (table A.5). Antidepressant users for 180 days had a mean survival time of 60 months compared to 52 months for antidepressant non-users. Those who continuously used an antidepressant for 180 days always had a better survival time. As seen with the 90 -day users, antidepressant users for less than 180 days had the worst survival (figure 4.12). Adjusted estimates were determined using the underlying log normal distribution. In this model, antidepressant use for less than 180 days had a non- significant 18% decrease in survival compared to no antidepressant use adjusting for confounders. Antidepressant use for 180 days had a non-significant 13% increase in survival adjusting for confounders (table A.6). Antidepressant users for at least a year had a mean survival time of 58 months compared to 56 months in antidepressant users under 1 year. Antidepressant users for a year always had better survival replicating the 90 and 180-day results. In this instance, non-users of antidepressants and non-continual users were similar to each other (figure 4.13). Adjustment using the underlying log normal distribution model showed that those who did not use antidepressants had a 55% decrease ($p<0.05$) in survival compared to those who did use an antidepressant for a year. Those who did not use an antidepressant for a year had a

60% reduction ($p<0.05$) in survival compared to those who did use an antidepressant for a year adjusting for confounders (table A.7). Any benefit from using antidepressants for those with depression likely occurs after the first 180 days of continuous use and the benefit appears to increase as the length of time of use increases.

The results do not support hypothesis H2B (survival is improved with general antidepressant use).

4.5 Cost

4.5.1 Unadjusted cost for those with Depression and those without Depression

For reference, the sample size for each year of cost is found in table A.3.

In the first year after breast cancer diagnosis, depressed patients had non-significant lower median cost. In subsequent years patients with depression had higher median cost which was statistically significant for years 2, 3 and 5 after cancer diagnosis (table 4.10). Over time, cost in both groups went down, particularly from year 1 to year 2 after cancer diagnosis. Those with depression might have lower cost in the first year due to not taking prescriptions or following through with chemotherapy or radiation treatment. After the first year, those with depression likely incur greater cost due to cancer recurrence (not taking hormone therapy or did not receive chemotherapy etc.) or hospitalization due to depression or other reasons.

4.5.2 Association of Depression with all cost

For reference, the hypothesis tested in this section is H3A: *Breast cancer patients with depression will have increased cost compared to those without depression.*

A depression diagnosis was associated with a non- significant increase in per patient per year cost after adjusting for clinical and demographic characteristics. Those with depression incurred $230,960.04 (intercept + depression estimate) per patient per year cost compared to $208,981.29 (intercept) for those without depression adjusting for clinical and demographic characteristics. The incremental cost of depression was $21,978.75 (depression cost – non-depression cost, $p>0.05$) per person per year adjusting for clinical and demographic characteristics (table 4.11). Surprisingly, depression did not significantly increase cost; however, as the model adjusted for other co-morbidities and cancer severity this is not as surprising. Both cancer stage and the comorbidity score significantly increased cost. Patients with depression do have more comorbidities and more severe cancers, so their cost will be higher due to these factors. It is likely that patients with depression already have doctor's visits planned and do not incur additional doctor's visits because they have depression. In this case, the comorbidity score and cancer stage variables capture these visits instead of the depression variable, which would indicate why the $21,978.25 is not significant.

The stated results do not support hypothesis H3A that depression increases cost; however, the estimate was positive and indicated an increase in cost for patients who have depression.

4.5.3 Unadjusted cost in the depressed population for those using antidepressants and those not using antidepressants

For reference, table A.4 indicates the sample size for each year for antidepressant users and non-users in patients with depression.

Those who took antidepressants had non-significant higher median cost in the depressed population in all years except year 2 after cancer diagnosis (table 4.12). In year 2, those on antidepressants had significantly higher costs. As depression was diagnosed within a year of

cancer diagnosis and antidepressant use was required to be after the depression diagnosis, the significant increase in cost in year 2 probably reflects the initiation of antidepressants. As some antidepressants are costly, the initiation is likely the reason for significantly higher cost. It is possible that antidepressant use over time decreases medical cost but the magnitude is not sufficient to offset the prescription cost of the antidepressant or potentially increased physician visits to continue using antidepressants.

4.5.4 Association of antidepressants with all Cost

For reference, the tested hypothesis is H3B: *Breast cancer patients with depression and taking antidepressants will have reduced direct medical cost compared to those with depression and not taking antidepressants*

Antidepressant users did not have significantly increased cost after adjusting for clinical and demographic characteristics (table 4.13). Antidepressant users incurred $178,082.11 per patient per year compared to $150,241.61 adjusting for clinical and demographic characteristics. The incremental cost for antidepressant use was $27,840.50. As mentioned earlier, these patients are likely seeing a doctor and are not incurring significantly increased cost. In addition to a single doctor's visit covering multiple comorbidities and cancer severity, antidepressant use could also keep patients out of the hospital and so would potentially reduce cost due to reduced hospital visits. As antidepressants are expensive, it is likely that the reduced cost from fewer hospital visits does not offset the increase in cost of the antidepressant. This balance would also explain why the increased cost is not statistically significant. As the benefit of antidepressant use was seen over time in previous results, the duration of antidepressant was taken into account in this analysis. Those who continually used antidepressants for at least 90 days indicated reduced cost. Cost were reduced more at 180 days of antidepressant use compared to the other categories with an $11,551.12 ($p>0.05$) reduction. This non-significant decrease is likely indicative that the cost of antidepressant use is greater than the benefit of reduced hospital visits or other medical

complications. It is possible that depressed patients will see a greater reduction in cost for continual use of antidepressants from their perspective.

For H3B, these results do indicate a potential reduction in cost for long- term antidepressant use; however, this reduction was not significant. The results indicate that H3B (cost is reduced with general antidepressant use) is not supported. It is possible that a cost utility study in this population will show that the extra cost of antidepressant use is worth the additional quality adjusted life years gained from antidepressant use.

4.6 Summary

The presented results established that those with depression have reduced adherence to hormone therapy, reduced survival and increased cost. These results also establish that treating the depressed population with antidepressants for at least 180 days improves adherence to hormone therapy and improves survival. From Medicare's perspective, long-term antidepressant might reduce cost over several years; however, it is likely that antidepressant use is a cost effective treatment for depressed breast cancer patients.

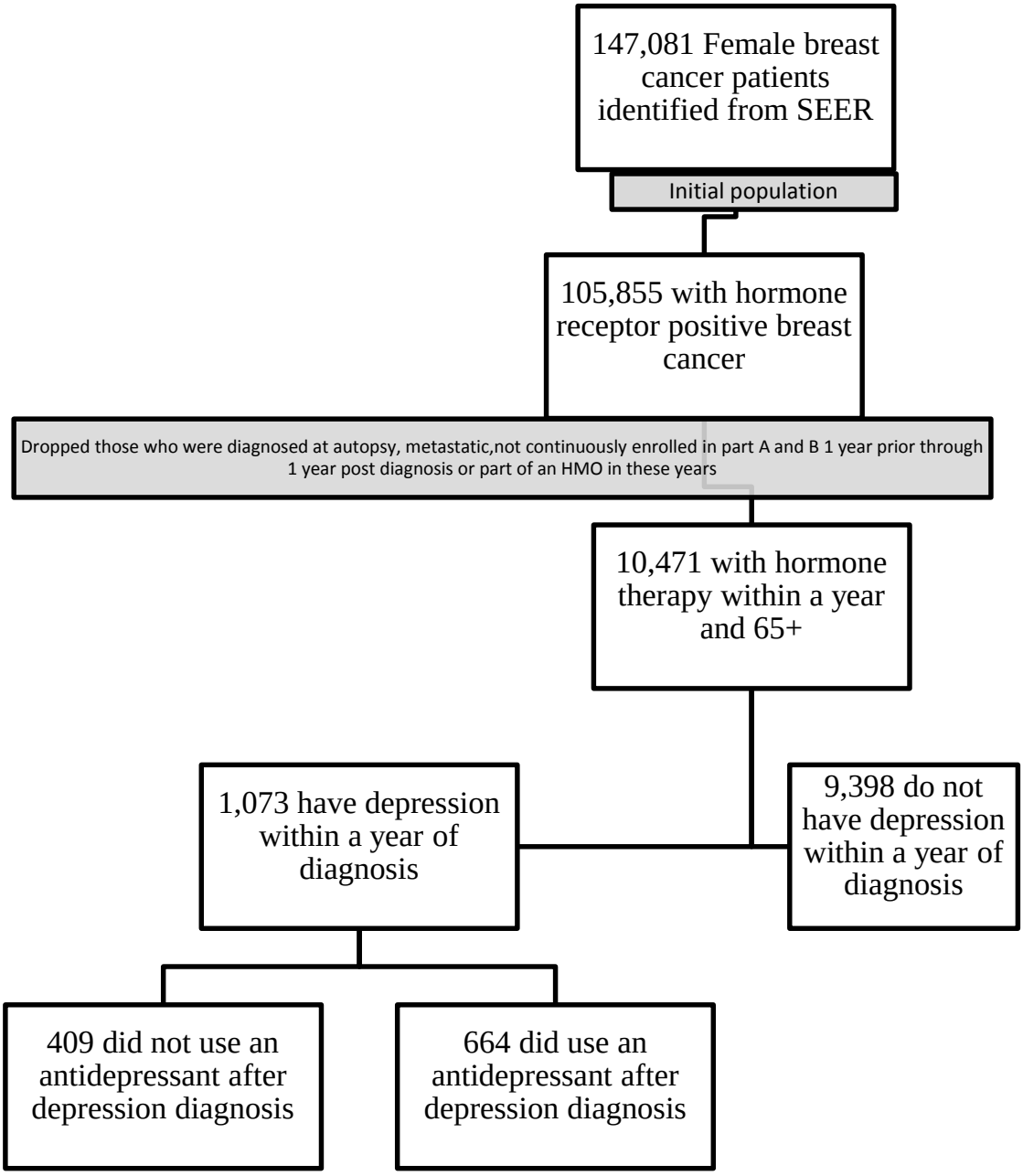

Figure 4.1 Sample Selection

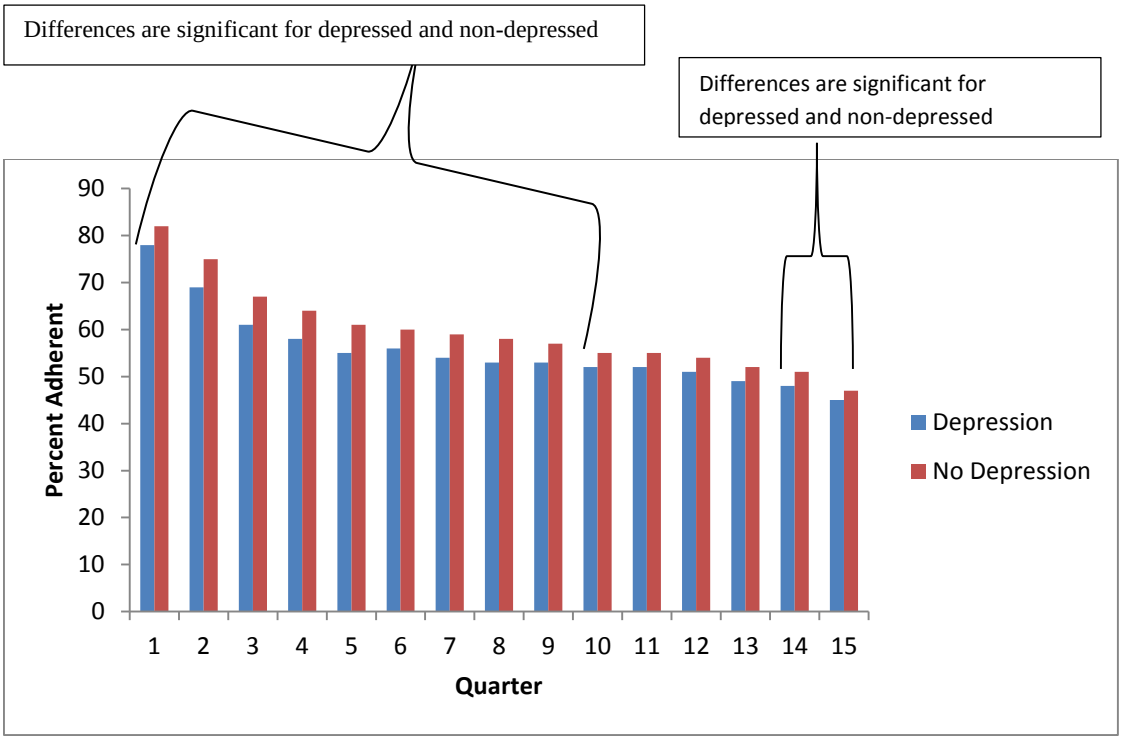

Figure 4.2 Percent of Patients Adherent to Hormone Therapy Over Time in the Depressed and Non-Depressed Population: Percent patients who are adherent to hormone therapy by quarter from start of hormone therapy in the depressed and non-depressed populations. Chi-square analysis was used to determine significant differences between those with depression and no depression by quarter.

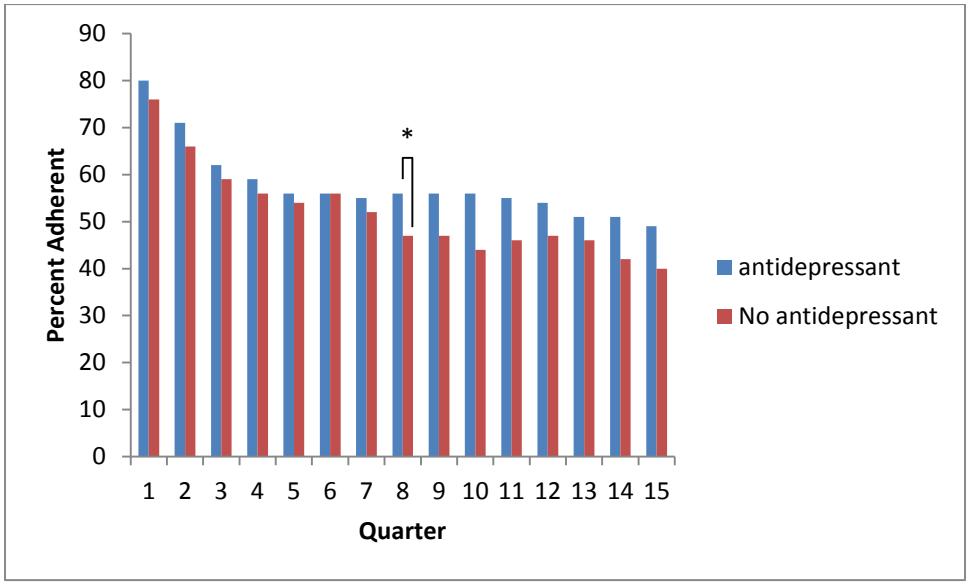

Figure 4.3 Adherence in Antidepressant Users and Non-Users in the Depressed population: * indicates significant difference from chi-square analysis between users and non-users by quarter

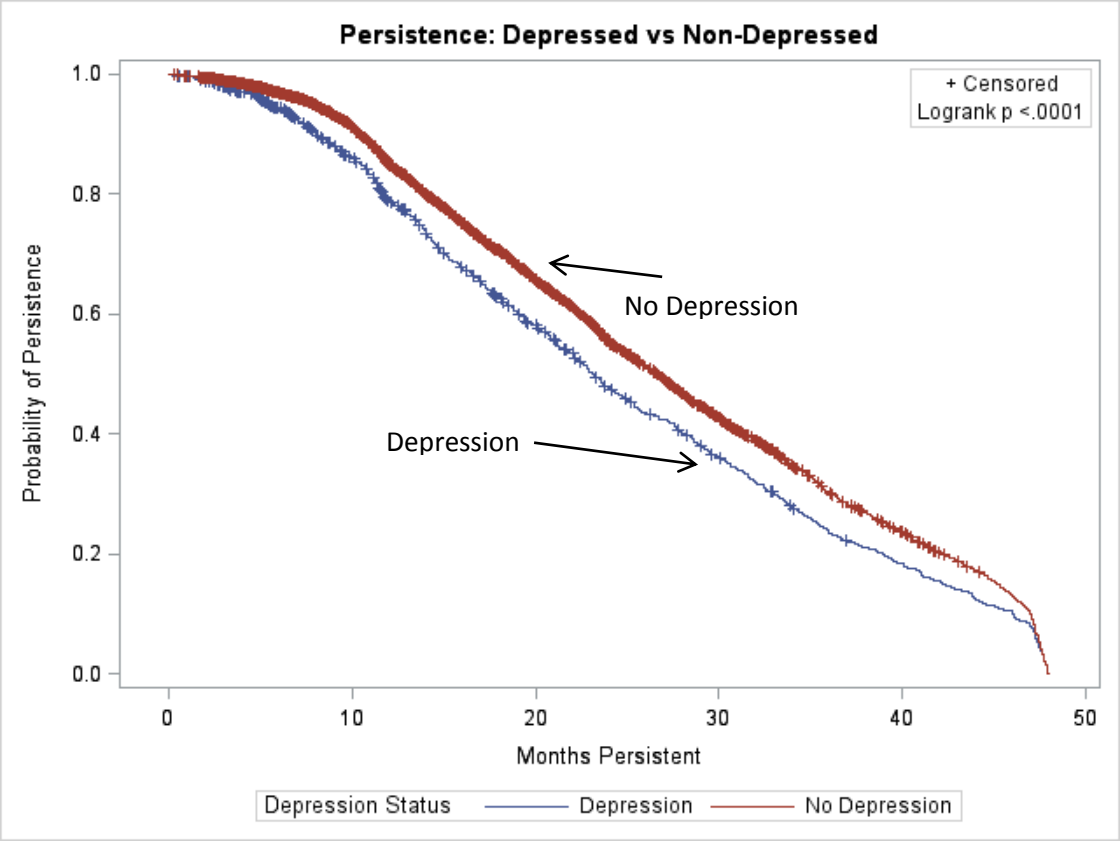

Figure 4.4 Persistence in the Depressed and Non-Depressed Population: Kaplan-Meier estimates for time of persisting with hormone therapy

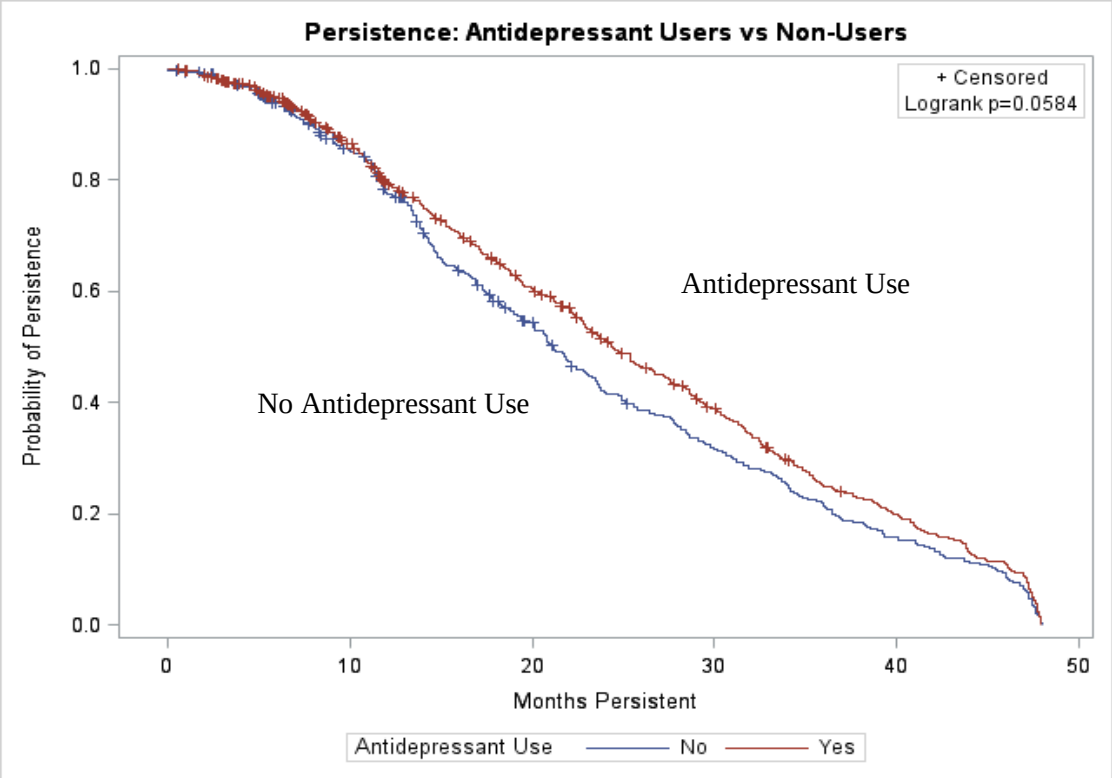

Figure 4.5 Time to Non-persistence for Antidepressant Users and Non-Users in the Depressed Population: Kaplan-Meier estimates for persistence in antidepressant users and non-users in the depressed population

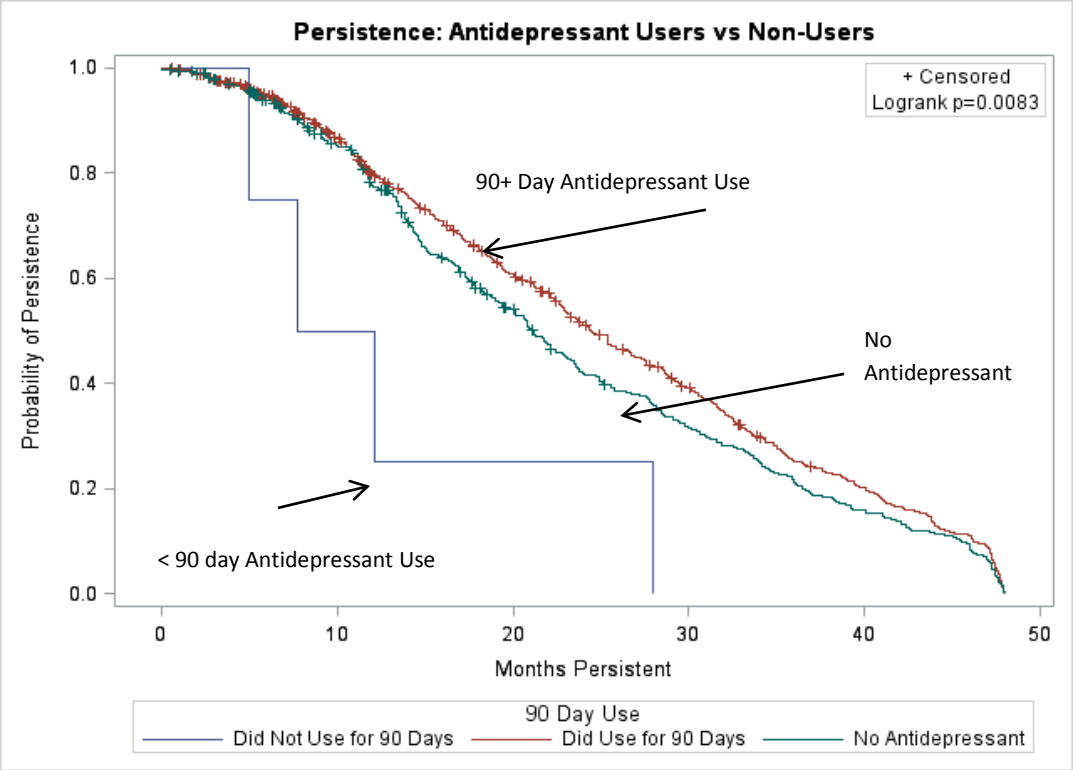

Figure 4.6: Time to Non-persistence of Hormone Therapy in the Depressed Population for Antidepressant users for 90+ days: Kaplan-Meier estimates for persistence in antidepressant users for at least 90 days, less than 90 days and non-users in the depressed population

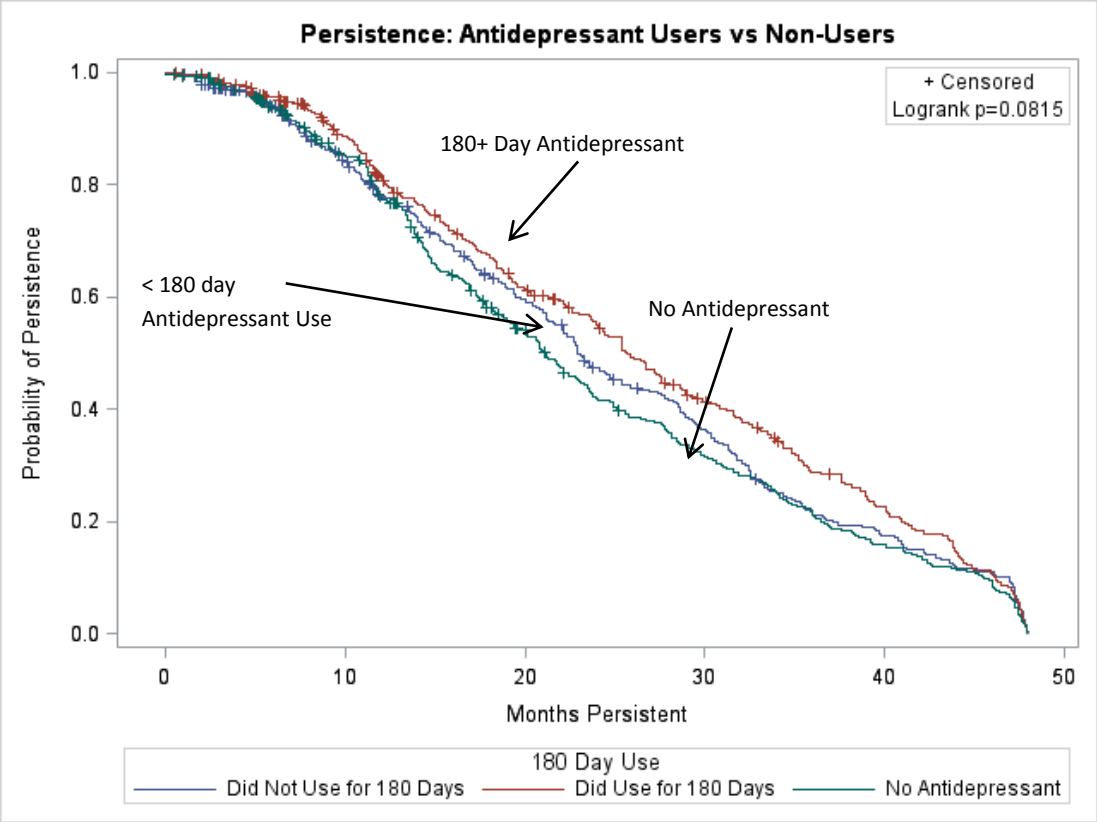

Figure 4.7: Time to Non-persistence of Hormone Therapy in the Depressed Population for Antidepressant users for180+ days: Kaplan-Meier estimates for persistence in antidepressant users for at least 180 days, less than 180 days and non-users in the depressed population

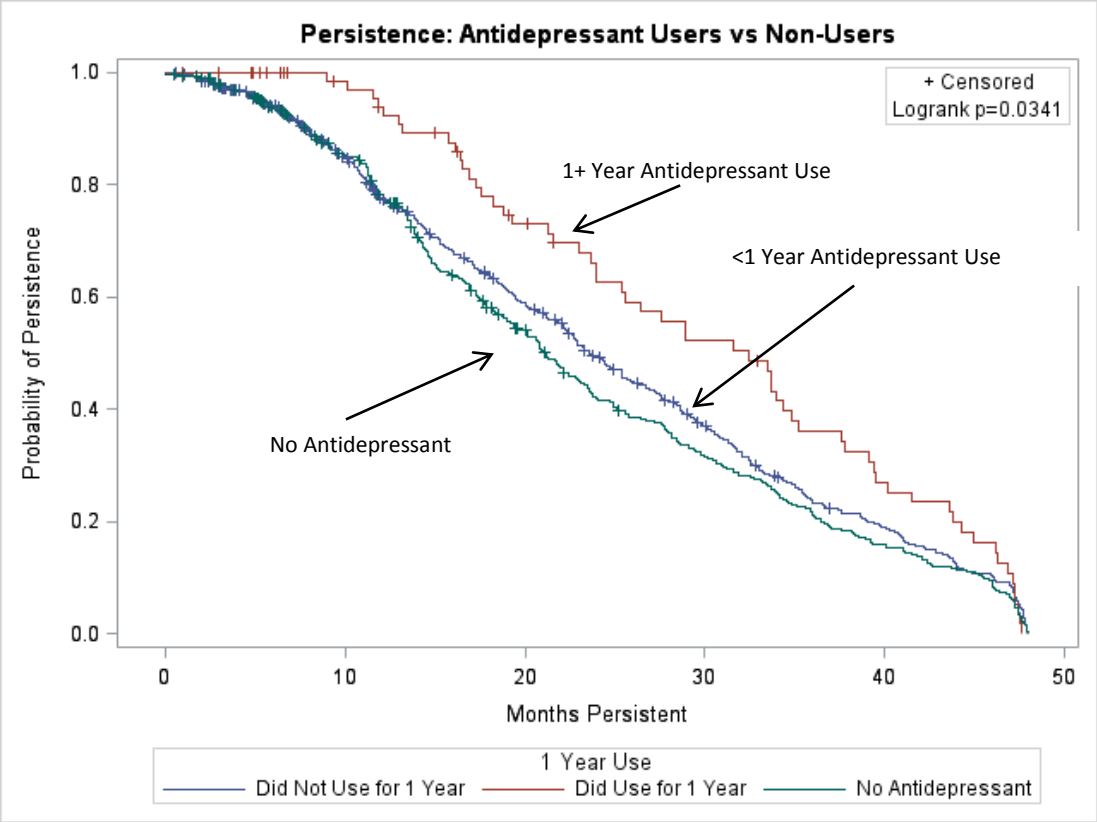

Figure 4.8: Time to Non-persistence of Hormone Therapy in the Depressed Population for Antidepressant Users for at least 1 Year: Kaplan-Meier estimates for persistence in antidepressant users for at least 1 year, less than 1 year and non-users in the depressed population

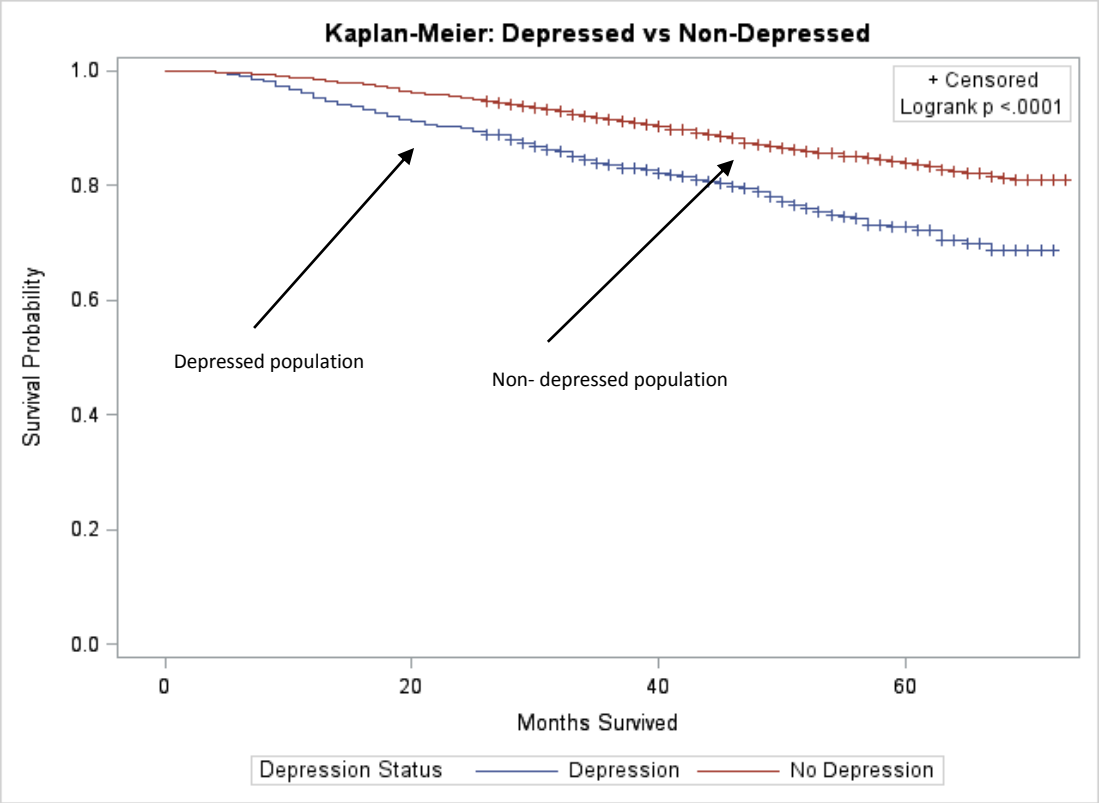

Figure 4.9 Survival in the Depressed and Non-Depressed Populations: Kaplan-Meier estimates for months survived since breast cancer diagnosis in the depressed and non-depressed populations

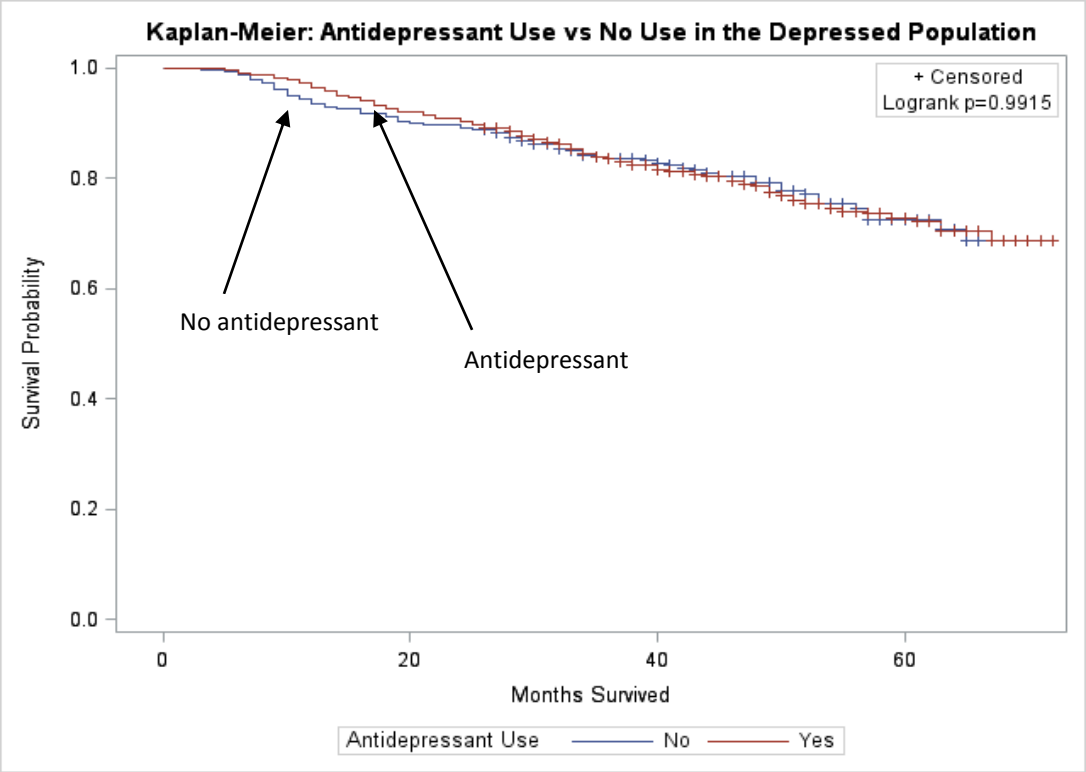

Figure 4.10 Survival for Antidepressant Users and Non-Users in the Depressed Population: Kaplan-Meier estimates for months survived since breast cancer diagnosis in the depressed population for those on antidepressants or not on antidepressants.

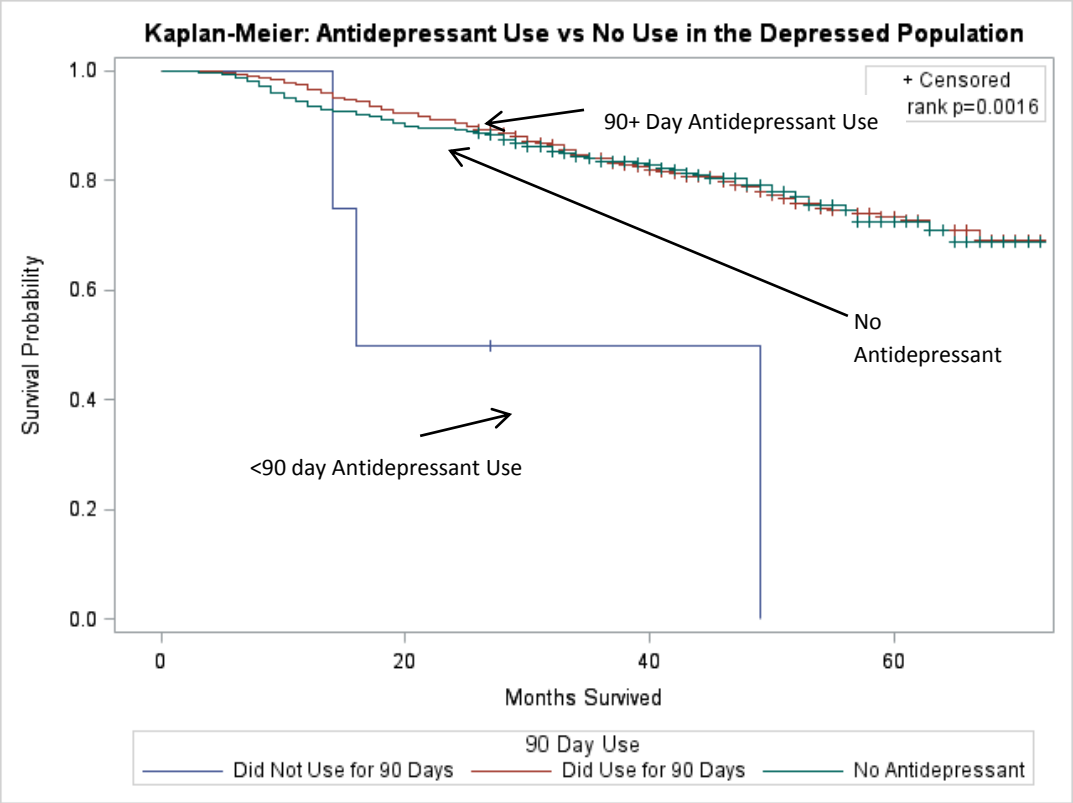

Figure 4.11 Survival in the Depressed Population for Those Who Continuously Use Antidepressants for 90 Days: Kaplan-Meier estimates for months survived since breast cancer diagnosis in antidepressant users for at least 90 days, less than 90 days and non-users in the depressed population

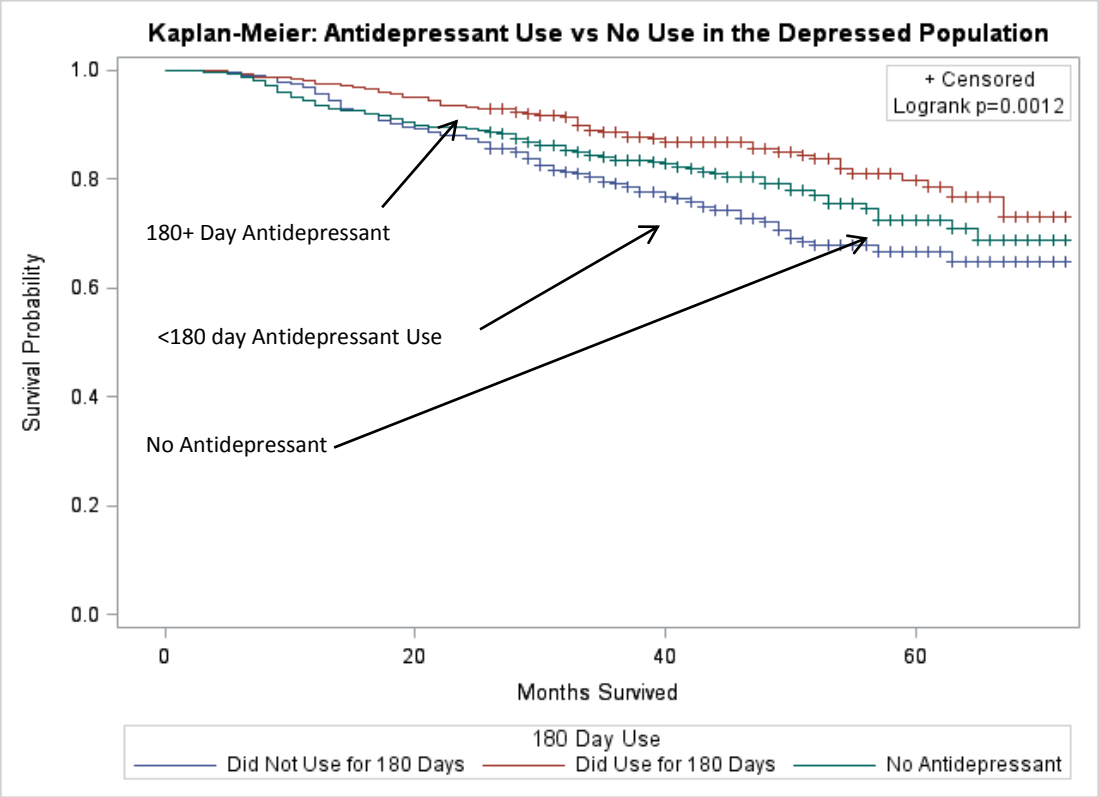

Figure 4.12: Survival in the Depressed Population for Those Who Continuously Use Antidepressants for 180 days: Kaplan-Meier estimates for months survived since breast cancer diagnosis in antidepressant users for at least 180 days, less than 180 days and non-users in the depressed population

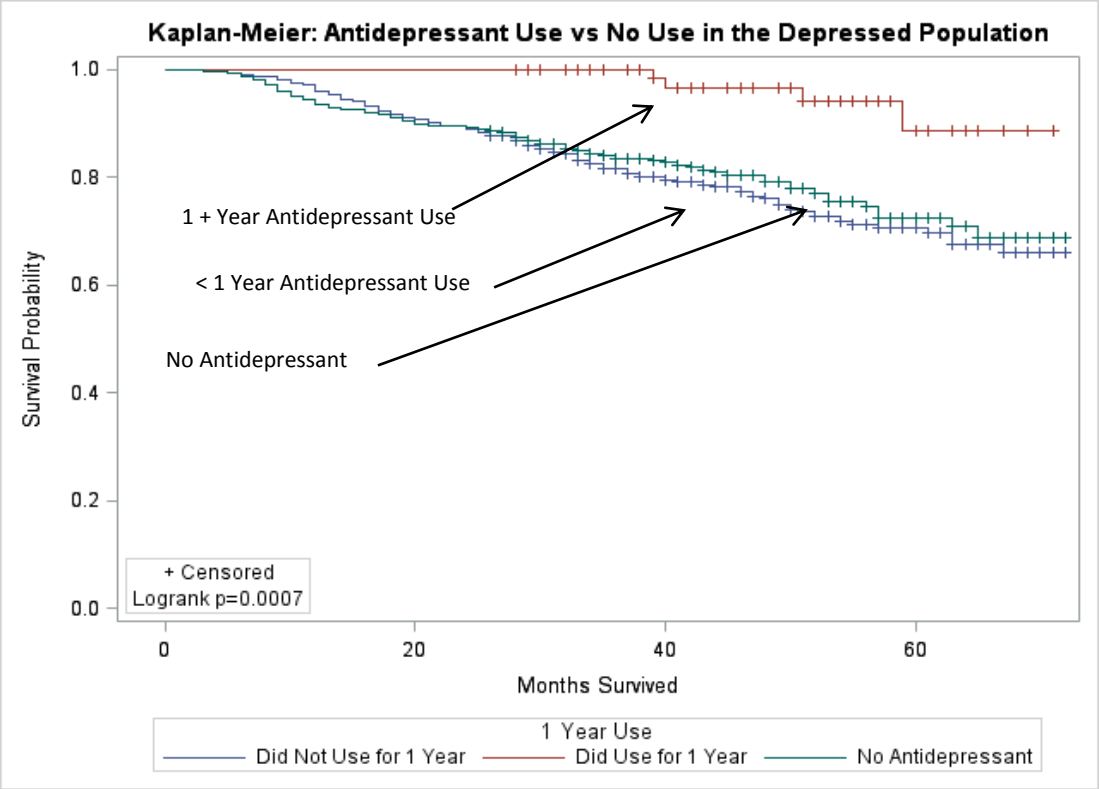

Figure 4.13 Survival in the Depressed Population for Those Who Continuously Use Antidepressants for 1 Year: Kaplan-Meier estimates for months survived since breast cancer diagnosis in antidepressant users for at least 1 year, less than 1 year and non-users in the depressed population

Table 4.1: Baseline Characteristic of the Depressed and Non-Depressed Populations

	Non-Depressed (N= 9,398)	**Depressed (N= 1,073)**	**p-value**
History of Depression*	8.62	43.71	**<.0001**
Hormone therapy type			**0.7**
SERM only	18.7	18.17	
AI only	81.3	81.8	
Charlson Score *			**0.001**
0	58.84	53.31	
1	7.81	9.69	
2+	33.35	37	
Stage *			**<.0001**
0	6.39	4.57	
1	54.83	49.3	
	30.93	34.76	
3	7.84	11.37	
Grade			**0.33**
1	28.15	26.47	
2	51.29	51.35	
3+	20.56	22.18	
Tumor Size in mm*	18.72	20.82	**0.0002**
Initial surgery*			**<.0001**
breast conserving	62.16	53.96	
mastectomy	37.84	46.04	
Radiation therapy*	49.8	44.36	**0.0007**
Chemotherapy	19.4	20.97	**0.22**
SEER site *			**0.002**
orth east	22.43	21.9	
North central	12.1	13.05	
South	25.15	29.73	
West	40.32	35.32	
Race*			**0.0002**
White	85.12	89.75	
Black	6.9	4.94	
Other	7.98	5.31	
Age			**0.071**
65-74	54.01	52.38	
75-84	36.77	36.25	
85+	9.21	11.37	
Urban	87.71	87.33	**0.72**
Married *	43.2	37.28	**0.0002**

	Non-Depressed (N= 9,398)	Depressed (N= 1,073)	p-value
Median Income of Zip Code*			**0.0016**
<30K	12.92	15.75	
30-49K	45.58	47.81	
50K+	41.5	36.44	

Table 4.1: Those with an * indicate significant differences at p<.05 between groups. Chi-square analysis was used to compare between those who were depressed and not depressed.

Table 4.2 Baseline Characteristics of Antidepressant Users and Non-Users in the Depressed Population

	No Antidepressant (N=409)	**Antidepressant (N=664)**	**p-value**
History of Depression*	37.9	47.29	**0.003**
Hormone therapy type			**0.79**
SERM only	18.58	17.92	
AI only	81.42	82.08	
Charlson Score			**0.103**
0	49.39	55.72	
1	11.25	8.73	
2+	39.36	35.54	
Stage			**0.399**
0	5.38	4.07	
1	46.7	50.9	
2	35.21	34.49	
3	12.71	10.54	
Grade *			**0.007**
1	21.03	29.82	
2	55.01	49.1	
3+	23.96	21.08	
Initial surgery			**0.154**
breast conserving	56.72	52.26	
mastectomy	43.28	47.74	
Radiation therapy	43.03	45.18	**0.49**
Chemotherapy	20.54	21.23	**0.785**
SEER site			**0.23**
North east	25.18	19.88	
North central	12.22	13.55	
South	28.12	30.72	
West	34.47	35.84	
Race			**0.455**
White	91.2	88.86	
Black	4.4	5.27	
Other	4.4	5.87	
Age*			**0.045**
65-74	51.1	53.16	
75-84	34.47	37.35	
85+	14.43	9.49	
Urban	88.26	86.75	**0.468**
Married	34.23	39.16	**0.105**
Median Income of Zip			**0.688**

	No Antidepressant (N=409)	Antidepressant (N=664)	p-value
Code			
<30K	15.89	15.66	
30-49K	46.21	48.8	
50K+	37.9	35.54	
Antidepressant Type	**N/A**		**N/A**
SSRI		51.1	
SNRI		14.2	
TCA		8.4	
other		24.4	

Table 4.2: Those with an * indicate significant differences at p<.05 between groups. Chi-square analysis was used to compare between antidepressant users and non-users.

Table 4.3: Mean PDC values for Depressed and Non-Depressed Patients by Quarter

Quarter	Depression	No Depression
*1	86.81	89.87
*2	80.48	84.78
*3	77.21	81.34
*4	74.56	78.83
*5	73.07	77.56
*6	71.98	76.60
*7	71.30	75.72
*8	70.13	74.96
*9	68.44	74.49
*10	67.73	73.76
*11	66.77	73.18
*12	66.86	72.36
*13	65.96	71.98
*14	63.85	70.74
*15	61.27	69.46

Table 4.3: The * indicates a significant difference ($p<.05$) between mean PDC values for the depressed and non-depressed group from the students t-test.

Table 4.4 Adherence to Hormone Therapy in the Depressed Population

	Odds ratio	95% CI
Repeated Measure *	0.911	0.91-0.92
Depression *	0.81	0.71, 0.93
History of Depression*	0.85	0.75, 0.96
Hormone therapy type		
SERM only		
*AI only**	0.60	0.53, 0.67
Charlson Score		
0		
1	1.01	0.87, 1.16
2+	0.99	0.91, 1.07
Stage		
0		
1	1.01	0.84, 1.20
2	1.10	0.91, 1.33
3	0.94	0.74, 1.19
Grade		
1		
2	1.05	0.96, 1.15
3+	1.04	0.93, 1.17
Initial surgery		
breast conserving		
*mastectomy **	1.15	1.04, 1.28
Radiation therapy	1.05	0.95, 1.15
Chemotherapy	0.91	0.82, 1.01
SEER site		
North east		
*North central**	0.72	0.63, 0.83
*South**	0.86	0.76, 0.97
West	0.99	0.89, 1.10
Race		
White		
Black	1.10	0.92, 1.30
*Other **	1.50	1.28, 1.77
Age		
65-74		
*75-84**	0.87	0.80, 0.94
*85+**	0.85	0.74, 0.99
Urban	0.85	0.74, 0.98
Married	1.06	0.98, 1.15

	Odds ratio	95% CI
Median Income of Zip Code		
<30K		
30-49K	1.01	0.88, 1.15
50K+	0.91	0.79, 1.05

Table4.4: Those with an * indicate significant results at p<.05. Blank cells indicate referent group in analysis.

Table 4.5 Mean PDC Values for Antidepressant Users and Non-Users in the Depressed Population

Quarter	Antidepressant	No antidepressant
1	86.74	86.93
2	80.89	79.81
3	77.76	76.31
4	75.50	72.99
5	73.77	71.85
6	71.93	72.09
7	71.68	70.59
8	71.03	68.41
9	69.55	66.40
10	68.54	66.21
11	67.78	64.89
12	67.97	64.84
13	67.60	62.89
14	64.38	62.93
15	61.35	61.14

Table 4.5: Differences in the mean PDC value for antidepressant users and non-users in the depressed population were tested with the student's t-test. There were no significant difference at $p<.05$.

Table 4.6 Adherence to Hormone Therapy for Antidepressant Users and Non-Users in the Depressed Population

	Odds Ratio	**95% CI**
Repeated Measure	0.90	0.88, 0.92
Antidepressant	0.79	0.55, 1.13
Antidepressant Use		
< 90 days		
90-179 days	1.21	0.73, 1.99
180-364 days	1.08	0.70, 1.66
*365+ days**	2.42	1.61, 3.65
History of Depression	0.94	0.74, 1.21
Hormone therapy type		
SERM only		
*AI only**	0.69	0.48, 0.99
Charlson Score		
0		
1	0.97	0.62, 1.51
2+	1.05	0.81, 1.36
Stage		
0		
1	0.75	0.42, 1.36
2	0.82	0.44, 1.51
3	0.71	0.34, 1.47
Grade		
1		
2	0.89	0.74, 1.30
3+	1.08	0.76, 1.55
Initial surgery		
breast conserving		
*mastectomy **	1.76	1.30, 2.39
Radiation therapy	1.12	0.83, 1.50
Chemotherapy	0.78	0.57, 1.08
SEER site		
North east		
North central	0.86	0.56, 1.31
*South**	0.64	0.45, 0.93
West	0.89	0.64, 1.24
Race		
White		
Black	0.83	0.47, 1.46

	Odds Ratio	95% CI
Other	1.42	0.83, 2.44
Age		
65-74		
75-84	0.84	0.64, 1.09
85+	0.86	0.55, 1.33
Urban	0.80	0.52, 1.22
Married	0.93	0.71, 1.21
Median Income of Zip Code		
<30K		
30-49K	1.05	0.73, 1.50
50K+	0.86	0.57, 1.29

Table 4.6: An * indicates significant results at p<.05. Blank cells indicate referent group in analysis.

Table 4.7 Risk of Non-Persistence in the Depressed Population

	Hazard Ratio	95% CI
Depression	1.06	0.98, 1.14
History of Depression*	1.28	1.19, 1.37
Hormone therapy type		
SERM only		
AI only	0.98	0.93, 1.04
Charlson Score		
0		
1	1.07	0.98, 1.16
*2+**	1.13	1.08, 1.18
Stage		
0		
*1**	1.14	1.04, 1.25
*2**	1.17	1.06, 1.29
*3**	1.40	1.24, 1.59
Grade		
1		
2	1.04	0.98, 1.09
*3+**	1.08	1.01, 1.15
Initial surgery		
breast conserving		
*mastectomy **	0.93	0.88, 0.98
Radiation therapy	0.97	0.91,1.02
Chemotherapy*	1.17	1.10, 1.25
SEER site		
North east		
North central	1.08	0.99, 1.18
South	1.07	1.00, 1.15
*West **	1.10	1.04, 1.17
Race		
White		
Black	1.01	0.92, 1.10
Other	0.96	0.88, 1.04
Age		
65-74		
75-84	1.00	0.96, 1.05
*85+**	1.24	1.14, 1.34
Urban	0.97	0.90, 1.04
Married	0.97	0.92, 1.01

	Hazard Ratio	95% CI
Median Income of Zip Code		
<30K		
30-49K	0.99	0.92, 1.07
50K+	1.03	0.95, 1.11

Table 4.7: An * indicates significant results at p<.05. Blank cells indicate referent group in analysis.

Table 4.8 Risk of Non-Persistence for Antidepressant Users in the Depressed Population

	Hazard Ratio	95% CI
Antidepressant	1.04	0.85, 1.27
Antidepressant Use		
< 90 days		
90-179 days	1.12	0.87, 1.45
*180-364 days**	1.32	1.02, 1.69
*365+ days**	0.55	0.44, 0.70
History of Depression	1.09	0.95, 1.26
Hormone therapy type		
SERM only		
AI only	0.86	0.71, 1.02
Charlson Score		
0		
1	1.23	0.97, 1.56
2+	1.06	0.91, 1.22
Stage		
0		
1	1.32	0.94, 1.84
2	1.29	0.91, 1.82
*3**	1.83	1.23, 2.74
Grade		
1		
2	1.01	0.86, 1.20
3+	1.04	0.85, 1.28
Initial surgery		
breast conserving		
mastectomy	0.86	0.72, 1.02
Radiation therapy	0.91	0.77, 1.08
Chemotherapy*	1.42	1.18, 1.72
SEER site		
North east		
North central	1.05	0.81, 1.35
South	1.19	0.97, 1.47
West	1.20	0.99, 1.46
Race		
White		
Black	1.26	0.90,1.76
Other	1.24	0.92, 1.68

	Hazard Ratio	95% CI
Age		
65-74		
75-84	0.92	0.78, 1.06
*85+**	1.46	1.16, 1.83
Urban	0.98	0.77, 1.25
Married	.98	0.85, 1.14
Median Income of Zip Code		
<30K		
30-49K	0.99	0.79, 1.24
50K+	1.00	0.78, 1.28

Table 4.8: An * indicates significant results at p<.05. Blank cells indicate referent group in analysis.

Table 4.9 Adjusted Estimate for Survival in the Depressed Population

	Estimate	95% CI
Depression *	-0.36	-0.48, -0.25
History of Depression	-0.07	-0.18, 0.04
Hormone therapy type		
SERM only		
AI only	0.07	-0.03, 0.17
Charlson Score		
0		
*1**	-0.29	-0.42, -0.16
*2+**	-0.40	-0.48, -0.32
Stage		
0		
*1**	-0.47	-0.68, -0.25
*2**	-0.69	-0.91, -0.47
*3**	-1.23	-1.47, -0.98
Grade		
1		
*2**	-0.14	-0.23, -0.05
*3+**	-0.27	-0.39, -0.16
Initial surgery		
breast conserving		
*mastectomy **	0.17	0.07, 0.26
Radiation therapy*	0.42	0.33, 0.51
Chemotherapy	-0.01	-0.12, 0.09
SEER site		
North east		
North central	0.001	-0.14, 0.14
South	-0.07	-0.18, 0.05
West	0.05	-0.05, 0.15
Race		
White		
*Black **	-0.19	-0.33, -0.05
*Other **	0.18	0.02, 0.34
Age		
65-74		
*75-84**	-0.51	-0.60, -0.42
*85+**	-1.02	-1.14, -0.90

	Estimate	95% CI
Urban	0.12	-.01, 0.24
Married *	0.25	0.17, 0.34
Median Income of Zip Code		
<30K		
30-49K	0.03	-0.09, 0.15
50K+	0.08	-0.06, 0.21

Table 4.9: An * indicates significant results at p<.05. Blank cells indicate referent group in analysis. The natural exponent of estimates represents percent reduction or increase in survival.

Table 4.10 Unadjusted Costs for Depressed and Non-Depressed Patients

Year From Breast Cancer Diagnosis	**Non-Depressed**	**Depressed**	**p-value**
1 (N=9,398 , N=1,073)	$ 830,524.43	$ 771,597.74	0.34
2 (N= 8,985 , N=970)	$ 33,057.19	$ 60,376.09	<.0001
3 (N=6,713 , N=664)	$ 22,918.75	$ 38,931.67	<.0001
4 (N= 4,151 , N=395)	$ 18,296.51	$ 24,830.93	0.12
5 (N= 1,979 , N=166)	$ 6,388.32	$ 12,285.88	0.03

Table 4.10: Median per patient per year cost that Medicare paid from date of breast cancer diagnosis is reported. Year represents number of years since breast cancer diagnosis. The first N value indicates the number of non-depressed patients and the second N value indicates the number of depressed patients in that year. P-value is reported from Wilcoxon ranked sum test for non-parametric distributions.

Table 4.11 General Linear Model Estimates for Per Patient per Year Cost for Those Who are Depressed

	Parameter Estimate	95% CI
Intercept	12.25	11.74, 12.75
Repeated Measure	-1.46	-1.41, -1.50
Depression	0.10	-0.06, 0.26
History of Depression	-0.14	-0.285, 0.004
Hormone therapy type		
SERM only		
AI only	0.09	-0.09, 0.27
Charlson Score		
0		
*1**	0.25	0.03, 0.46
*2+**	0.43	0.28, 0.58
Stage		
0		
1	0.15	-0.09, 0.39
*2**	0.41	0.14, 0.68
*3**	0.42	0.11, 0.73
Grade		
1		
2	-0.11	-0.30, 0.07
3+	-0.02	-0.24, 0.20
Initial surgery		
breast conserving		
*mastectomy **	0.16	0.01, 0.31
Radiation therapy*	0.23	0.09, 0.37
Chemotherapy*	0.19	0.03, 0.36
SEER site		
North east		
*North central**	-0.47	-0.68, -0.25
*South**	-0.30	-0.48, -0.11
West	-0.05	-0.21, 0.12
Race		
White		
*Black **	0.52	0.18, 0.86
Other	0.20	-0.15, 0.55
Age		
65-74		
75-84	-0.02	-0.17, 0.14
*85+**	-0.44	-0.62, -0.26

	Parameter Estimate	95% CI
Urban	0.11	-0.16, 0.38
Married	0.01	-0.12, 0.14
Median Income of Zip Code		
<30K		
*30-49K**	-0.42	-0.76, -0.08
*50K+**	-0.45	-0.83, -0.08
Total months in parts A and B	0.01	-0.01, 0.04
Total months in part D*	0.08	0.05, 0.12

Table 4.11: An * indicates significant results at p<.05. Blank cells indicate referent group in the analysis. The natural exponent of the estimate added to the intercept represents the total per patient per year cost to Medicare for that group.

Table 4.12 Unadjusted Costs for Antidepressant Users and Non-Users in the Depressed Population

Year From Breast Cancer Diagnosis	No antidepressant	Antidepressant	p-value
1 (N=409, N=664)	$ 771,597.74	$ 771,996.68	0.65
2 (N=367, N=603)	$ 43,211.73	$ 68,598.79	0.02
3 (N=240, N=424)	$ 30,458.02	$ 41,576.25	0.06
4 (N=132, N=263)	$ 21,750.93	$ 27,190.20	0.23
5 (N=56, N=110)	$ 6,176.56	$ 16,207.32	0.47

Table 4.12: Median per patient per year cost that Medicare paid in the depressed population from date of breast cancer diagnosis is reported. Year represents number of years since breast cancer diagnosis. The first N value indicates the number of patients in the no antidepressant group and the second N value indicates the number of patients in the antidepressant group for that year. P-value is reported from Wilcoxon ranked sum test for non-parametric distributions.

Table 4.13 General Linear Model Estimate for Cost in Antidepressant Users in the Depressed Population

	Parameter Estimate	95% CI
Intercept *	11.92	10.82, 13.01
Repeated measure *	-2.07	-1.88
Antidepressant	0.17	-0.19, 0.52
Antidepressant Use		
< 90 days		
90-179 days	-0.03	-0.40, 0.34
180-364 days	-0.08	-0.43, 0.26
365+ days	-0.05	-0.41, 0.31
History of Depression	-0.20	-0.46, 0.06
Hormone therapy type		
SERM only		
AI only	0.12	-0.16, 0.40
Charlson Score		
0		
1	0.42	-0.14, 0.99
*2+**	0.29	0.04, 0.53
Stage		
0		
1	0.13	-0.47, 0.74
2	0.39	-0.26, 1.04
3	0.10	-0.58, 0.78
Grade		
1		
*2**	0.52	0.25, 0.79
*3+**	0.59	0.28, 0.91
Initial surgery		
breast conserving		
mastectomy	0.15	-0.15, 0.45
Radiation therapy	0.21	-0.04, 0.46
Chemotherapy	-0.06	-0.36, 0.24
SEER site		
North east		
*North central **	-0.53	-0.91, -0.16
*South**	-0.54	-0.91, -0.17
West	0.13	-0.27, 0.53
Race		
White		
*Black **	0.98	0.43, 1.52

	Parameter Estimate	95% CI
Other	0.27	-0.38, 0.93
Age		
65-74		
*75-84**	-0.32	-0.61, -0.03
*85+**	-0.87	-1.26, -0.49
Urban	0.35	-0.003, 0.706
Married	-0.05	-0.34, 0.24
Median Income of Zip Code		
<30K		
*30-49K**	-0.59	-0.93, -0.26
*50K+**	-0.61	-0.97, -0.25
Total months in parts A and B*	0.06	0.01, 0.10
Total months in part D*	0.003	0.02, 0.13

Table 4.13: An * indicates significant results at p<.05. Blank cells indicate referent group in the analysis. The natural exponent of the estimate added to the intercept represents the total per patient per year cost to Medicare for that group.

CHAPTER 5 DISCUSSION

5.1 Introduction

The final chapter will provide a discussion of the results and insight for future research and broader applications. A summary of the results for adherence to hormone therapy, survival and cost will begin each section. For each outcome, a discussion of the effect of depression on that outcome will start followed by a discussion of the effect of antidepressant use in the depressed population on that outcome. After the discussion, limitations will be discussed and how they affect the results. The chapter will conclude with an overall summary and final conclusion.

5.2 Adherence to Hormone Therapy

5.2.1 The Association of Depression with Adherence to hormone therapy

Depression was significantly associated with decreased adherence to hormone therapy. A history of depression was also significantly associated with decreased adherence. In the literature, mainly prospective studies have been done to determine the association of depression with adherence to hormone therapy[20, 88, 92]. In these studies, the association of depressive symptoms was determined, not the association of clinical depression. Two of these studies[20, 88] find a significant decrease in adherence, which the current results corroborate. The third showed that non-adherers to hormone therapy had a higher prevalence of depressed mood but this was not significant in the multivariate model used to predict adherence[92]. A retrospective hospital study

by Ziller found that depression had non-significant differential effects on adherence depending on the type of hormone therapy[51]. Tamoxifen users had a non-significant increase in adherence while aromatase inhibitor users had a non-significant decrease in adherence. The current results reflect the finding by Ziller as aromatase inhibitors did have a significant reduction in adherence compared to the tamoxifen group. This study builds on the existing literature by confirming existing results in a previously unused data source with a different method of measuring adherence. While previous work used self-report, pill count, electronic monitoring pill caps or the medication possession ratio (MPR) [20, 51, 88, 92], percent days covered (PDC) was used in this study. While the MPR is generally used for estimating adherence in claims data, it can overestimate adherence[114]. Percent days covered is a simpler formula that removes the worry of counting a day twice as can happen with early fills using the MPR[114]. PDC has been used previously in measuring hormone therapy adherence in breast cancer[22, 36]; however, this is the first time it has been used in determining the association of depression with adherence to hormone therapy. Using this method, depression is associated with a decrease in adherence to hormone therapy. This is the first study to use repeated measures to determine the association of depression with adherence to hormone therapy in a large database. As adherence to hormone therapy drops over time, the use of repeated measures accounts for this decrease. This is seen with the significant negative value of the repeated measure variable in the model. The repeated measure variable corroborates the established studies that show adherence to hormone therapy drops over time[22, 33]. One limitation to note is that a causal relationship cannot be established in this study. As depression was not identified before the start of hormone therapy, the temporal criteria is not met for Hill's criteria for causation. There is a potential causal association between a history of depression and reduced adherence to hormone therapy. As it is definite that a history of depression is before the start hormone therapy, Hill's temporal sequence criteria for causality is met; however, Hill's other requirements to establish a causal relationship (specificity, strength

of association etc.) are not present in this study[115]. Physicians should screen newly diagnosed breast cancer patients for depression and determine their depression history. This screen would point to those at greater risk for not adhering to hormone therapy and needing more active follow up once hormone therapy is initiated.

5.2.2 The Association of Antidepressants in the depressed population with Adherence to hormone therapy

Continual antidepressant use was associated with significantly improved adherence to hormone therapy in the depressed sample. Since depression decreases adherence, treating depression is thought to improve adherence to hormone therapy. In the regression model, those with continual use of antidepressants had significantly improved adherence. Only two studies observed any association of antidepressant use and adherence[24, 81]. Navari found antidepressant use improved adherence to hormone therapy[81], and Trabulsi found that antidepressant use reduced adherence to hormone therapy[24]. Trabulsi did not control for depression, so antidepressant use likely became a proxy for depression and it is unknown how antidepressant use affects adherence to hormone therapy in the depressed population. Navari looked at those with depressed symptoms and found that antidepressant use improved adherence to hormone therapy. The association of antidepressant use in the depressed population is unknown from this study because Navari only looked at those with depressive symptoms. This is the first study to show any association of antidepressant use in the depressed population. There is a slight negative association with general antidepressant use and adherence to hormone therapy. The analysis did adjust for length of antidepressant use and this negative association could correlate to more severe depression because claims data does not capture information on depression severity. Future work in this area would be to adjust for depression severity in determining the association of depression with adherence to hormone therapy. This study established that any benefit of antidepressant use on adherence to hormone therapy is with prolonged use of antidepressants. Physicians who

prescribe antidepressants to breast cancer patients with depression should make it clear to the patient that they need to be diligent in taking their antidepressant if they want to get any benefit from taking the antidepressant regarding improving their adherence to hormone therapy. Diligence in taking one drug is associated with diligence in taking another drug as a patient who is taking one can easily take a second at the same time. It is possible that just the act of taking an antidepressant and not the antidepressant itself improves adherence to hormone therapy in patients with depression. Those who seek treatment for depression likely want to get better and be more diligent in taking hormone therapy regardless if the antidepressant actively reverses any chemical imbalance caused by depression[47, 116, 117]. Future work will be to determine if these results are consistent in other data sources and if an active ingredient in antidepressants is needed to achieve the results found in this study.

This is the first study to report an association between antidepressant use and adherence to hormone therapy in breast cancer patients with depression and provides a new field for research in breast cancer.

5.3 Persistence to Hormone Therapy

5.3.1 The Association of Depression with persistence to hormone therapy

Those with depression had an increased risk of non-persistence after adjusting for clinical and demographic characteristics. Those with a history of depression also had a significant association with non-persistence. This result reflects three of the six published studies[19, 29, 52]. This study builds on two of the published studies by using a more stable and direct measure of depression compared to the previous studies[29, 52]. Kemp used a questionnaire to determine depressed mood, which is influenced by when the person fills out the questionnaire and is not a measure of clinical depression. Aiello Bowles used antidepressant use to determine depression,

which is not an accurate way of determining depression. Antidepressants are generally used to treat depression, but they can be used for several purposes in addition to treating depression and the depressed sample is potentially overestimatmed[71]. Huiart and Cluze look at the association of tamoxifen discontinuation and depressive symptoms in the French population[19, 90]. This study builds on these studies as it is in the United States and uses a diagnosis of depression instead of depressed mood or antidepressant use for characterizing those with depression. The study by Huiart used the same data as Cluze but found a non-significant decrease in non-persistence[90]. An important distinction between these two studies is that Cluze looked at early vs late discontinuation of tamoxifen while Huiart looked at discontinuation in general. Cluze only found increased non-persistence in those who had late discontinuation of tamoxifen[19]. These results could indicate that those with depression are actually going to the doctor early on and are more motivated to continue therapy. This explanation is also a potential reason for the results seen in the studies by Hadji and Kostev[33, 91]. As the studies that show depression improves persistence are all in Europe, there could be a policy in place for those with depression getting better care, which would improve persistence. The one study in the United States showed decreased persistence for those with depression, which this study supports. Further study of differing policies between the United States and Europe for those with depression might yield the reason why the European studies indicate a positive association of depression with persistence and the United States studies indicate a negative association. By definition, those who are not persistent are not adherent, as those who do not take their medicine for an extended period will not meet the 80% requirement to be adherent. Hypothesis H1A is supported by results from adherence to hormone therapy and persistence to hormone therapy.

5.3.2 The Association of Antidepressants in the depressed population with persistence to hormone therapy

Those who used antidepressants continually had significantly improved persistence in the depressed population. Of interest, continual use of antidepressants was significantly associated with increased persistence after adjusting for clinical and demographic characteristics. General antidepressant use was associated with a non-significant increase in the risk of non-persistence when adjusting for clinical and demographic characteristics; however, as this was adjusted for time, it is likely that this increase in risk reflects more severe depression. This result supports the only previously reported study of antidepressant use and adherence by Cluze[19], which showed decreased persistence for those taking antidepressants. Building on Cluze's study, this study also accounts for length of time using antidepressants. Those using antidepressants longer show improved persistence compared to those who do not. A potential explanation is those who continue taking antidepressants have a more positive outlook on life, which could lead to them to be more persistent[23].

Results for the association of antidepressant use with adherence to hormone therapy and persistence to hormone therapy indicate that duration is a critical component in improving these outcomes in breast cancer patients with depression. As hypothesis H1B does not take into account the duration of antidepressant use, the results do not support H1B.

5.4 Survival

5.4.1 The Association of Depression with Survival

Depression was associated with a significant decrease in survival and a history of depression was also associated with a decrease in survival. This is consistent with published literature[54, 55, 57, 89]. The study by Hjerl examined the association of survival with post-operative depression , controlling for pre-operative depression[89]. As Hjerl's definition of pre and post-operative is based on diagnosis, this study looked at a similar definition of depression and found

similar results. Of the three United States based studies, two studies looked at concurrent depression[55, 57] and one looked at a history of depression[54]. Studies that observed concurrent depression did not adjust for a history of depression, which has a significant impact on survival[54, 89]. This is the first study to determine the association survival with depression adjusting for a history of depression. The values reported in this study reflect published work both with concurrent and a history of depression and are the first to report both in the United States. These results support hypothesis H2A that there is a negative association of depression with survival.

5.4.2 The Association of Antidepressants in the depressed population with Survival

Continual use of antidepressants significantly improved survival in the depressed sample with longer time taking antidepressants indicating improved survival. The Kaplan-Meier curves indicate that those who are on antidepressants but are not using them have worse survival compared to those who do not use them at all. This would indicate to physicians that if they prescribe breast cancer patients an antidepressant they should emphasize the importance of using the antidepressant. Interestingly, at 90 days those taking antidepressants continually are similar to those with no drug while at 365 days those not continually taking an antidepressant are similar to those without an antidepressant. As the 180-364 day curve is in between the 90-179 and the 365+ day curves, antidepressant use for over 90 days is necessary to improve survival in the depressed population. For physicians, if they prescribe antidepressants for the depressed population, they should prescribe for at least 180 days in order to improve survival in their patient. This time period potentially explains why there was no difference between fluoxetine users and placebo patients in the study by Fisch. In Fisch's study, fluoxetine was only given for 52 days, which falls into the 90 day window showing no difference between users and non-users in this study[70].

These results add to the existing literature of the impact of treating depression on survival. While the literature indicates that decreasing depression symptoms improves survival[82], it has not been shown that treating depression with group therapy or fluoxetine improves survival[64, 70]. It should be noted that the published results for fluoxetine and group therapy were not in the depressed population. One study found a negative association of SSRI (class of antidepressants) use on survival; however, this was not in the depressed population[78]. Another study that looked at some antidepressants and other drugs that inhibit CYP2D6 found a non-significant improvement on survival[28]. Again, this was not in the depressed population so the impact of antidepressants on survival in the depressed population was unknown until this study. The marked difference between those with continual antidepressant use and those with non-continuous use could explain why worse survival is indicated in published studies; these patients were not continual users of antidepressants.

As duration of antidepressant use is an important factor for improved survival, hypothesis H2B is not supported.

5.5 Cost

5.5.1 The Association of Depression with Cost

Those with depression had higher median direct medical cost compared to those without depression. No significant increase in cost was shown for those with depression in the model adjusting for clinical and demographic characteristics. The incremental cost of depression was $21,978.75, not significant, per patient per year. The non-significant increase in cost is possible because this study is from Medicare's perspective and is in the elderly population, who likely has multiple co-morbidities. These patients would already be going to the physician's office, so one visit would take care of multiple co-morbidities, which would not significantly impact cost. Also,

more advanced stage was associated with increased cost, indicating severity of cancer. As these factors are all correlated, the non -significant increase in cost for depression is explained as the significant increase is from more severe cancers and more co-morbidities are the cost drivers instead of depression. Another reason for the non-significant increase is those with depression might stop taking medications or stop visiting their physician. This would reduce cost because they are not utilizing these services; however, these patients are probably at a higher risk of being hospitalized and have increased cost at the hospital. The magnitude of increased cost for these patients depends on the difference between the increased hospital cost and reduced physician visit and pharmacy cost. Also, this study only calculated drug, physician visit, outpatient and inpatient hospital cost. Costs for home health services were not included. Those with depression might be more likely to use home health services but would not be captured in this study and could explain the non-significant increase in cost.

The only published cost for depression and breast cancer indicated that those with depression had an average yearly cost of $15,471 compared to $8,297 for the non-depressed group[60, 93]. The study was in breast cancer survivors from the military database and is did not report this as incremental cost. The published cost is to the Department of Defense (DOD) and not Medicare. There are key differences in these populations which would explain the differences in cost between this study and Jeffery's. Jeffery looked at veterans and a younger population compared to this study, which looked at the older population in Medicare. Those who are younger are likely to be more healthy and have lower medical cost compared to those who are older and in Medicare. This difference could explain the higher cost found in this study compared to Jeffery's. Also, Medicare and the DOD likely have different policies on what they will and will not cover for patients. This difference in coverage could also explain why there is a difference in these two studies as the DOD may not cover all the services Medicare does or has a different reimbursement policy that would explain differences in this study and Jeffery's.

Hypothesis H3A is not supported as depression did not significantly increase cost; however, the results do indicate an increase in cost for patients with depression. It is possible that in a younger population with fewer co-morbidities, depression significantly increases cost.

5.5.2 The Association of Antidepressants in the depressed population with Cost

Antidepressant use did not significantly increase cost in the depressed population. The incremental cost to Medicare for antidepressant use is $27,840.50 per patient per year. This non-significant increase in cost is consistent with literature for cost of psychosocial interventions in the breast cancer population[83, 99, 100]. Continual antidepressant use for 90+ days was associated with a non-significant reduction in cost. This indicates that these patients are probably reducing their cost because they are likely not having as many hospital visits but not enough to offset the cost of the antidepressant. As mentioned before, these patients already incur significant medical cost elsewhere and the additional drug cost is not a significant increase from Medicare's perspective. These results indicate that continual use of antidepressants potentially reduces the cost to Medicare.

5.6 Strengths

This study has two major strengths: external and statistical validity. This study has external validity (results generalizable to a broader population) due to the use of SEER-Medicare. SEER-Medicare is representative of the entire Medicare population and so these results are generalizable to the full Medicare breast cancer population with hormone receptor positive cancer. The analysis used has statistical validity; a relationship is established between depression or antidepressant use and some of the studied outcomes. The analysis uses a repeated measures design to follow patients over time, so it accounts for changes in the outcome over time. As adherence and cost change over time, repeated measures allows for a more accurate

representation of what happens in the general population, which also improves external validity. Repeated measures also increase the statistical power to detect differences and allows for multiple observations per person, which improves statistical validity as a smaller population can be used to detect statistically significant differences. Repeated measures plus the large sample size provides statistical power to detect significant differences between groups. Model assumptions were checked and appropriate analysis was done if assumptions were violated, which strengthens the statistical validity of this study as the proper analysis was done for the data.

This study is not able to establish causality, but there are strengths with the association of depression and survival that should be noted. The association of depression with survival fulfills some of Hill's criteria for causality but not all. Hill's criteria for strength, temporal order, biological plausibility and consistency are present as there is a marked increase in the risk of death for those with depression, there is a biological link of depression with survival, the literature consistently reports a negative association of depression with survival and depression is diagnosed before death. Hill's criteria for specificity is partially fulfilled because the analysis adjusts for various confounders that would impact survival, including a history of depression but cannot adjust for all factors that impact survival. Other strengths of this study is the adjustment for a prior diagnosis of depression and observing antidepressant use, general and continual, in the depressed sample. No United States study has reported the association of depression with adherence to hormone therapy, survival and cost adjusting for a prior diagnosis of depression. The literature reports a prior diagnosis of depression has a significant association with these outcomes. Adjusting for a prior diagnosis and several confounders allows for a more precise estimate for the association of depression with these outcomes. The association of antidepressant use in the depressed population has not been reported and is a strength of this study. Studies that report the association of antidepressant use with these outcomes in the non-depressed population could reflect a depression diagnosis instead of the treatment. The addition of a length of

antidepressant use adds strength to this study because it distinguishes those who are short term users from those with extend use. This addition captures the benefit of antidepressant use and the general antidepressant variable would likely capture the severity of depression. Hence, the negative association found in this study.

5.7 Limitations

The first limitation in this study is that depression is under reported in Medicare claims[54]. This is more evident in cancer patients, who are less likely to be diagnosed with depression due to the side effects of chemotherapy and radiation being similar to depression[37]. This limitation indicates that those who are in the non-depressed group are likely similar to those in depressed group. The more homogenous the groups, the less likely it is to find a difference between them. This limitation would likely reduce the power to detect differences between antidepressant users and non-users. However, the use of repeated measures and as both groups had a sample size over 300, this study was likely sufficiently powered to detect differences between users and non-users.

The second limitation is using claims to measure adherence. While previous work has been done using part D to measure use of hormone therapy, there are limitations to consider[11]. One important limitation is there is no guarantee that a person actually takes the medicine after they fill it at the pharmacy. Those with multiple fills are likely to be taking hormone therapy as it is unlikely a person would continue to spend money on something they are not using. Also, there is no way to determine why a person was not adherent or non-persistent. Was it due to side effects or some other reason? One reason could be a person was able to get free samples from their physician or a clinical trial[11]. Those who receive free samples would not have claims in part D and could be counted as non-adherent when they actually were. This would make it more

difficult to detect an association with adherence to hormone therapy, as the two groups would be more similar instead of different.

A limitation in looking at antidepressant use in the depressed population is the inability to control for other types of depression treatment. This limitation would potentially reduce differences between the two groups, and make it more difficult to detect an association of antidepressants with the studied outcomes in the depressed population. As it has been shown that group therapy is effective in reducing depressive symptoms[65], those in the non-antidepressant group could still benefit from reduced depressive symptoms by participating in group therapy. Those with depression generally had a history of depression and are likely already being treated with group therapy or antidepressants. As severity of depression is unable to be measured, the antidepressant variable and history variable could be capturing the association of depression severity in addition to what they intend to capture. As this study used a duration of antidepressant use variable in addition to a general use variable, the benefit of antidepressant use is likely captured in the use instead of the general variable and this study works with this limitation.

5.8 Policy Implications

These results indicate that time is an important factor with breast cancer patients. Adherence to hormone therapy reduces over time, survival reduces over time and cost reduces over time. Physicians treating breast cancer patients need to be more aware of the issue of adherence to hormone therapy reducing over time. As it is the long term use of hormone therapy that improves survival, effort should be made to focus on improving adherence to hormone therapy after the first year. Incentives could be put in place for physicians to see their patients more often or for patients to prove they are taking hormone therapy as prescribed. These incentives would hopefully lead to better adherence and improved survival in these patients. The

feasibility of such an incentive program should be tested and determined if the additional cost of the incentive is worth the gain in survival.

These results indicate that depression negatively affects adherence to hormone therapy, survival and cost. For breast cancer patients, depression screening should be considered as a routine protocol to identify those with depression and start them on antidepressants in order to improve their chances of survival. Physicians should be made aware that depression is an issue for breast cancer patients and these patients need increased guidance to stay with their hormone therapy treatment to improve survival. For physicians who want to prescribe antidepressants to treat patients with depression, they should be made aware that patients need to be on an antidepressant for at least 180 days to start benefiting from this drug. This study shows that cost is not significantly increased with continual use of antidepressants and over time cost may be reduced. Potential incentives could be put in place for physicians who treat depression in breast cancer with antidepressants for making sure patients stick with their regimen for at least 180 days. Going forward a cost effectiveness analysis should be done to determine the feasibility of screening breast cancer patients for depression and then using antidepressants as a treatment.

5.9 Conclusion

This study shows for the first time the association of depression with hormone therapy adherence, survival and cost in breast cancer patients while controlling for a history of depression. Consistent with the literature, this study shows that depression has a negative impact on adherence to hormone therapy, survival and cost. For the first time, the association of antidepressants with hormone therapy adherence, survival and cost in the depressed breast cancer population was examined. These results indicate that long term antidepressant use improves adherence and survival and potentially reduce cost.

Further study is needed to determine how robust these results are and if they are generalizable to entire breast cancer population and not just the Medicare breast cancer population.

In conclusion, extended antidepressant use in the depressed breast cancer population provides positive benefits to these patients by improving adherence to hormone therapy and survival.

REFERENCES

1. Cancer Trends Progress Report. In: Institute NC, editor. Bethesda, MD: NIH, 2015.

2. Society AC. Breast Cancer Facts & Figures 2013-2014. Atlanta: American Cancer Society, Inc, 2013.

3. SEER Stat Fact Sheets: Breast Cancer. Available from URL: http://seer.cancer.gov/statfacts/html/breast.html 2015].

4. Howlader N, Chen VW, Ries LA, et al. Overview of breast cancer collaborative stage data items--their definitions, quality, usage, and clinical implications: a review of SEER data for 2004-2010. Cancer. 2014;120 Suppl 23: 3771-3780.

5. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. CA Cancer J Clin. 2014;64: 52-62.

6. Komen SG. Hormone Therapies. Available from URL: http://ww5.komen.org/BreastCancer/HormoneTherapies.html 2015].

7. Komen SG. Table 36: Estrogen receptor status and overall survival. Available from URL: http://ww5.komen.org/BreastCancer/Table36Estrogenreceptorstatusandoverallsurvival.html 2015].

8. breastcancer.org. How Chemotherapy Works. Available from URL: http://www.breastcancer.org/treatment/chemotherapy/how_it_works 2015].

9. Makubate B, Donnan PT, Dewar JA, Thompson AM, McCowan C. Cohort study of adherence to adjuvant endocrine therapy, breast cancer recurrence and mortality. Br J Cancer. 2013;108: 1515-1524.

10. NCI. Hormone Therapy for Breast Cancer. Available from URL: http://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet 2015].

11. Riley GF, Warren JL, Harlan LC, Blackwell SA. Endocrine therapy use among elderly hormone receptor-positive breast cancer patients enrolled in Medicare Part D. Medicare Medicaid Res Rev. 2011;1.

12. Nekhlyudov L, Li L, Ross-Degnan D, Wagner AK. Five-year patterns of adjuvant hormonal therapy use, persistence, and adherence among insured women with early-stage breast cancer. Breast Cancer Res Treat. 2011;130: 681-689.

13. Barron TI, Connolly R, Bennett K, Feely J, Kennedy MJ. Early discontinuation of tamoxifen: a lesson for oncologists. Cancer. 2007;109: 832-839.

14. breastcancer.org. Hormonal Therapy. Available from URL: http://www.breastcancer.org/treatment/hormonal 2015].

15. Gonnelli S, Petrioli R. Aromatase inhibitors, efficacy and metabolic risk in the treatment of postmenopausal women with early breast cancer. Clin Interv Aging. 2008;3: 647-657.

16. Van Liew JR, Christensen AJ, de Moor JS. Psychosocial factors in adjuvant hormone therapy for breast cancer: an emerging context for adherence research. J Cancer Surviv. 2014;8: 521-531.

17. Buzdar AU, Robertson JF, Eiermann W, Nabholtz JM. An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane. Cancer. 2002;95: 2006-2016.

18. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998;351: 1451-1467.

19. Cluze C, Rey D, Huiart L, et al. Adjuvant endocrine therapy with tamoxifen in young women with breast cancer: determinants of interruptions vary over time. Ann Oncol. 2012;23: 882-890.

20. Bender CM, Gentry AL, Brufsky AM, et al. Influence of patient and treatment factors on adherence to adjuvant endocrine therapy in breast cancer. Oncol Nurs Forum. 2014;41: 274-285.

21. (EBCTCG) EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365: 1687-1717.

22. Wu J, Stafkey-Mailey D, Bennett C. Long-term Adherence to Hormone Therapy in Medicaid-enrolled Women with Breast Cancer. Health Outcomes Research in Medicine. 2012;3: e195-e203.

23. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol. 2010;28: 4120-4128.

24. Trabulsi N, Riedel K, Winslade N, et al. Adherence to anti-estrogen therapy in seniors with breast cancer: how well are we doing? Breast J. 2014;20: 632-638.

25. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat. 2011;126: 529-537.

26. McCowan C, Wang S, Thompson AM, Makubate B, Petrie DJ. The value of high adherence to tamoxifen in women with breast cancer: a community-based cohort study. Br J Cancer. 2013;109: 1172-1180.

27. Simon R, Latreille J, Matte C, Desjardins P, Bergeron E. Adherence to adjuvant endocrine therapy in estrogen receptor-positive breast cancer patients with regular follow-up. Can J Surg. 2014;57: 26-32.

28. Weaver KE, Camacho F, Hwang W, Anderson R, Kimmick G. Adherence to adjuvant hormonal therapy and its relationship to breast cancer recurrence and survival among low-income women. Am J Clin Oncol. 2013;36: 181-187.

29. Aiello Bowles EJ, Boudreau DM, Chubak J, et al. Patient-reported discontinuation of endocrine therapy and related adverse effects among women with early-stage breast cancer. J Oncol Pract. 2012;8: e149-157.

30. Liu Y, Malin JL, Diamant AL, Thind A, Maly RC. Adherence to adjuvant hormone therapy in low-income women with breast cancer: the role of provider-patient communication. Breast Cancer Res Treat. 2013;137: 829-836.

31. Wigertz A, Ahlgren J, Holmqvist M, et al. Adherence and discontinuation of adjuvant hormonal therapy in breast cancer patients: a population-based study. Breast Cancer Res Treat. 2012;133: 367-373.

32. Gotay C, Dunn J. Adherence to long-term adjuvant hormonal therapy for breast cancer. Expert Rev Pharmacoecon Outcomes Res. 2011;11: 709-715.

33. Hadji P, Ziller V, Kyvernitakis J, et al. Persistence in patients with breast cancer treated with tamoxifen or aromatase inhibitors: a retrospective database analysis. Breast Cancer Res Treat. 2013;138: 185-191.

34. Kimmick G, Anderson R, Camacho F, Bhosle M, Hwang W, Balkrishnan R. Adjuvant hormonal therapy use among insured, low-income women with breast cancer. J Clin Oncol. 2009;27: 3445-3451.

35. Cancer Trends Progress Report 2011/2012 Update. Available from URL: http://progressreport.cancer.gov/doc_detail.asp?pid=1&did=2011&chid=105&coid=1026&mid= [accessed February 20, 2014].

36. Wu J, Lu ZK. Hormone Therapy Adherence and Costs in Women with Breast Cancer. The American Journal of Pharmacy Benefits. 2013;5: 65-70.

37. Massie MJ. Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr. 2004: 57-71.

38. Brintzenhofe-Szoc KM, Levin TT, Li Y, Kissane DW, Zabora JR. Mixed anxiety/depression symptoms in a large cancer cohort: prevalence by cancer type. Psychosomatics. 2009;50: 383-391.

39. Badger TA, Braden CJ, Mishel MH. Depression burden, self-help interventions, and side effect experience in women receiving treatment for breast cancer. Oncol Nurs Forum. 2001;28: 567-574.

40. Reece JC, Chan YF, Herbert J, Gralow J, Fann JR. Course of depression, mental health service utilization and treatment preferences in women receiving chemotherapy for breast cancer. Gen Hosp Psychiatry. 2013;35: 376-381.

41. Fann JR, Thomas-Rich AM, Katon WJ, et al. Major depression after breast cancer: a review of epidemiology and treatment. Gen Hosp Psychiatry. 2008;30: 112-126.

42. Weinberger T, Forrester A, Markov D, Chism K, Kunkel EJ. Women at a dangerous intersection: diagnosis and treatment of depression and related disorders in patients with breast cancer. Psychiatr Clin North Am. 2010;33: 409-422.

43. Reich M, Lesur A, Perdrizet-Chevallier C. Depression, quality of life and breast cancer: a review of the literature. Breast Cancer Res Treat. 2008;110: 9-17.

44. Breckenridge LM, Bruns GL, Todd BL, Feuerstein M. Cognitive limitations associated with tamoxifen and aromatase inhibitors in employed breast cancer survivors. Psychooncology. 2012;21: 43-53.

45. Janelsins MC, Mustian KM, Palesh OG, et al. Differential expression of cytokines in breast cancer patients receiving different chemotherapies: implications for cognitive impairment research. Support Care Cancer. 2012;20: 831-839.

46. Seruga B, Zhang H, Bernstein LJ, Tannock IF. Cytokines and their relationship to the symptoms and outcome of cancer. Nat Rev Cancer. 2008;8: 887-899.

47. Kim SY, Kim JM, Kim SW, et al. Associations between plasma cytokines and depressive mood in patients with breast cancer. Int J Psychiatry Med. 2012;43: 1-17.

48. Kim JM, Kim SW, Stewart R, et al. Serotonergic and BDNF genes associated with depression 1 week and 1 year after mastectomy for breast cancer. Psychosom Med. 2012;74: 8-15.

49. Kim JM, Stewart R, Kim SY, et al. A one year longitudinal study of cytokine genes and depression in breast cancer. J Affect Disord. 2013;148: 57-65.

50. Grenard JL, Munjas BA, Adams JL, et al. Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. J Gen Intern Med. 2011;26: 1175-1182.

51. Ziller V, Kalder M, Albert US, et al. Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. Ann Oncol. 2009;20: 431-436.

52. Kemp A, Preen DB, Saunders C, et al. Early discontinuation of endocrine therapy for breast cancer: who is at risk in clinical practice? Springerplus. 2014;3: 282.

53. Mausbach BT, Schwab RB, Irwin SA. Depression as a predictor of adherence to adjuvant endocrine therapy (AET) in women with breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2015;152: 239-246.

54. Goodwin JS, Zhang DD, Ostir GV. Effect of depression on diagnosis, treatment, and survival of older women with breast cancer. J Am Geriatr Soc. 2004;52: 106-111.

55. Onitilo AA, Nietert PJ, Egede LE. Effect of depression on all-cause mortality in adults with cancer and differential effects by cancer site. Gen Hosp Psychiatry. 2006;28: 396-402.

56. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. Psychol Med. 2010;40: 1797-1810.

57. Vodermaier A, Linden W, Rnic K, et al. Prospective associations of depression with survival: a population-based cohort study in patients with newly diagnosed breast cancer. Breast Cancer Res Treat. 2014;143: 373-384.

58. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. Biol Psychiatry. 2003;54: 269-282.

59. Lutgendorf SK, Sood AK. Biobehavioral factors and cancer progression: physiological pathways and mechanisms. Psychosom Med. 2011;73: 724-730.

60. Jancin B. Concomitant depression in breast cancer survivors doubles health care costs 2014. Available from URL: http://www.obgynnews.com/home/article/concomitant-depression-in-breast-cancer-survivors-doubles-health-care-costs/8cb1169afdde707a0287e438e760e2a3.html [accessed 2015].

61. Callari A, Mauri M, Miniati M, et al. Treatment of depression in patients with breast cancer: a critical review. Tumori. 2013;99: 623-633.

62. Classen C, Butler LD, Koopman C, et al. Supportive-expressive group therapy and distress in patients with metastatic breast cancer: a randomized clinical intervention trial. Arch Gen Psychiatry. 2001;58: 494-501.

63. Giese-Davis J, Koopman C, Butler LD, et al. Change in emotion-regulation strategy for women with metastatic breast cancer following supportive-expressive group therapy. J Consult Clin Psychol. 2002;70: 916-925.

64. Goodwin PJ, Leszcz M, Ennis M, et al. The effect of group psychosocial support on survival in metastatic breast cancer. N Engl J Med. 2001;345: 1719-1726.

65. Kissane DW, Grabsch B, Clarke DM, et al. Supportive-expressive group therapy for women with metastatic breast cancer: survival and psychosocial outcome from a randomized controlled trial. Psychooncology. 2007;16: 277-286.

66. Kissane D. Beyond the psychotherapy and survival debate: the challenge of social disparity, depression and treatment adherence in psychosocial cancer care. Psychooncology. 2009;18: 1-5.

67. Laoutidis ZG, Mathiak K. Antidepressants in the treatment of depression/depressive symptoms in cancer patients: a systematic review and meta-analysis. BMC Psychiatry. 2013;13: 140.

68. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat. 2005;89: 243-249.

69. Torta RG, Ieraci V. Pharmacological management of depression in patients with cancer: practical considerations. Drugs. 2013;73: 1131-1145.

70. Fisch MJ, Loehrer PJ, Kristeller J, et al. Fluoxetine versus placebo in advanced cancer outpatients: a double-blinded trial of the Hoosier Oncology Group. J Clin Oncol. 2003;21: 1937-1943.

71. Boekhout AH, Beijnen JH, Schellens JH. Symptoms and treatment in cancer therapy-induced early menopause. Oncologist. 2006;11: 641-654.

72. Müller JC, Imazaki PH, Boareto AC, et al. In vivo and in vitro estrogenic activity of the antidepressant fluoxetine. Reprod Toxicol. 2012;34: 80-85.

73. Stepulak A, Rzeski W, Sifringer M, et al. Fluoxetine inhibits the extracellular signal regulated kinase pathway and suppresses growth of cancer cells. Cancer Biol Ther. 2008;7: 1685-1693.

74. Caraci F, Crupi R, Drago F, Spina E. Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. Curr Drug Metab. 2011;12: 570-577.

75. Azoulay L, Dell'Aniello S, Huiart L, du Fort GG, Suissa S. Concurrent use of tamoxifen with CYP2D6 inhibitors and the risk of breast cancer recurrence. Breast Cancer Res Treat. 2011;126: 695-703.

76. Lash TL, Pedersen L, Cronin-Fenton D, et al. Tamoxifen's protection against breast cancer recurrence is not reduced by concurrent use of the SSRI citalopram. Br J Cancer. 2008;99: 616-621.

77. Lash TL, Cronin-Fenton D, Ahern TP, et al. Breast cancer recurrence risk related to concurrent use of SSRI antidepressants and tamoxifen. Acta Oncol. 2010;49: 305-312.

78. Kelly CM, Juurlink DN, Gomes T, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ. 2010;340: c693.

79. Breitbart W. Do antidepressants reduce the effectiveness of tamoxifen? Psychooncology. 2011;20: 1-4.

80. Dusetzina SB, Alexander GC, Freedman RA, Huskamp HA, Keating NL. Trends in co-prescribing of antidepressants and tamoxifen among women with breast cancer, 2004-2010. Breast Cancer Res Treat. 2013;137: 285-296.

81. Navari RM, Brenner MC, Wilson MN. Treatment of depressive symptoms in patients with early stage breast cancer undergoing adjuvant therapy. Breast Cancer Res Treat. 2008;112: 197-201.

82. Giese-Davis J, Collie K, Rancourt KM, Neri E, Kraemer HC, Spiegel D. Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: a secondary analysis. J Clin Oncol. 2011;29: 413-420.

83. Lemieux J, Topp A, Chappell H, Ennis M, Goodwin PJ. Economic analysis of psychosocial group therapy in women with metastatic breast cancer. Breast Cancer Res Treat. 2006;100: 183-190.

84. Gordon LG, Beesley VL, Scuffham PA. Evidence on the economic value of psychosocial interventions to alleviate anxiety and depression among cancer survivors: a systematic review. Asia Pac J Clin Oncol. 2011;7: 96-105.

85. Carlson LE, Bultz BD. Efficacy and medical cost offset of psychosocial interventions in cancer care: making the case for economic analyses. Psychooncology. 2004;13: 837-849; discussion 850-836.

86. Simon GE, Katon WJ, Lin EH, et al. Cost-effectiveness of systematic depression treatment among people with diabetes mellitus. Arch Gen Psychiatry. 2007;64: 65-72.

87. Shen C, Shah N, Findley PA, Sambamoorthi U. Depression treatment and short-term healthcare expenditures among elderly Medicare beneficiaries with chronic physical conditions. J Negat Results Biomed. 2013;12: 15.

88. Klepin HD, Geiger AM, Bandos H, et al. Cognitive factors associated with adherence to oral antiestrogen therapy: results from the cognition in the study of tamoxifen and raloxifene (Co-STAR) study. Cancer Prev Res (Phila). 2014;7: 161-168.

89. Hjerl K, Andersen EW, Keiding N, Mouridsen HT, Mortensen PB, Jørgensen T. Depression as a prognostic factor for breast cancer mortality. Psychosomatics. 2003;44: 24-30.

90. Huiart L, Bouhnik AD, Rey D, et al. Early discontinuation of tamoxifen intake in younger women with breast cancer: is it time to rethink the way it is prescribed? Eur J Cancer. 2012;48: 1939-1946.

91. Kostev K, Waehlert L, Jockwig A, Jockwig B, Hadji P. Physicians' influence on breast cancer patient compliance. Ger Med Sci. 2014;12: Doc03.

92. Grunfeld EA, Hunter MS, Sikka P, Mittal S. Adherence beliefs among breast cancer patients taking tamoxifen. Patient Educ Couns. 2005;59: 97-102.

93. Jeffery DD, Linton A. The impact of depression as a cancer comorbidity: rates, health care utilization, and associated costs. Community Oncology. 2012;9: 216-221.

94. Pan X, Sambamoorthi U. Health care expenditures associated with depression in adults with cancer. J Community Support Oncol. 2015;13: 240-247.

95. Jayadevappa R, Malkowicz SB, Chhatre S, Johnson JC, Gallo JJ. The burden of depression in prostate cancer. Psychooncology. 2012;21: 1338-1345.

96. Fuhrer R, Rouillon F. THE FRENCH VERSION OF THE CENTER FOR EPIDEMIOLOGIC STUDIES-DEPRESSION SCALE. Psychiatrie and Psychobiologie. 1989;4: 163-166.

97. Desmarais JE, Looper KJ. Interactions between tamoxifen and antidepressants via cytochrome P450 2D6. J Clin Psychiatry. 2009;70: 1688-1697.

98. Cronin-Fenton D, Lash TL, Sørensen HT. Selective serotonin reuptake inhibitors and adjuvant tamoxifen therapy: risk of breast cancer recurrence and mortality. Future Oncol. 2010;6: 877-880.

99. Simpson JS, Carlson LE, Trew ME. Effect of group therapy for breast cancer on healthcare utilization. Cancer Pract. 2001;9: 19-26.

100. Strong V, Waters R, Hibberd C, et al. Management of depression for people with cancer (SMaRT oncology 1): a randomised trial. Lancet. 2008;372: 40-48.

101. Sciences NDoCCaP. About SEER-Medicare Data Files. Available from URL: http://healthcaredelivery.cancer.gov/seermedicare/aboutdata/ 2015].

102. Levin KA. Study design IV. Cohort studies. Evid Based Dent. 2006;7: 51-52.

103. Kim SH, Son BH, Hwang SY, et al. Fatigue and depression in disease-free breast cancer survivors: prevalence, correlates, and association with quality of life. J Pain Symptom Manage. 2008;35: 644-655.

104. Carpenter JS, Elam JL, Ridner SH, Carney PH, Cherry GJ, Cucullu HL. Sleep, fatigue, and depressive symptoms in breast cancer survivors and matched healthy women experiencing hot flashes. Oncol Nurs Forum. 2004;31: 591-5598.

105. AJCC. Breast Cancer Staging. Available from URL: https://cancerstaging.org/references-tools/quickreferences/Cancer%20Staging%20Poster%20Picture%20Library/BreastPoster1.jpg 2016].

106. News C. US Inflation Calculator. Available from URL: http://www.usinflationcalculator.com/ 2016].

107. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43: 1130-1139.

108. Wang X, Du XL. Socio-demographic and geographic variations in the utilization of hormone therapy in older women with breast cancer after Medicare Part-D coverage. Med Oncol. 2015;32: 154.

109. NCI. Number of Persons by Race and Hispanic Ethnicity for SEER Participants (2010 Census Data). Available from URL: http://seer.cancer.gov/registries/data.html 2015].

110. Tarpey T. Generalized Linear Models (GLM), 2012.

111. Newsome. Link Functions and the Generalized Linear Model, 2015.

112. Sill M. Chapter 5: Cox Proportional Hazards Model.

113. Partha D. Modeling Health Care Costs and Counts, 2013.

114. Barner JC. Medication Adherence: Medication Adherence:

Focus on Secondary Database Focus on Secondary Database

Analysis Analysis. ISPOR: ISPOR Student Network, 2010.

115. HILL AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? Proc R Soc Med. 1965;58: 295-300.

116. Antonioli M, Rybka J, Carvalho LA. Neuroimmune endocrine effects of antidepressants. Neuropsychiatr Dis Treat. 2012;8: 65-83.

117. Jacoby B. Facing Breast Cancer With a Positive Attitude. Available from URL: http://www.huffingtonpost.com/barbara-jacoby/facing-breast-cancer-with-a-positive-attitude_b_7634644.html.

APPENDIX A: ADDITIONAL INFORMATION

Table A.1 Sample Size for the Association of Depression with Adherence to Hormone Therapy

Quarter	Depressed	Non-Depressed
1	1,073	9,398
2	1,036	9,211
3	973	8,898
4	882	8,177
5	793	7,541
6	716	6,915
7	638	6,249
8	550	5,460
9	496	4,910
10	429	4,336
11	362	3,776
12	280	3,073
13	241	2,577
14	195	2,089
15	148	1,611

Table A.1: The number of patients identified in each quarter who have a measure of adherence to hormone therapy for those with and without depression

Table A.2 Sample Size for the Association of Antidepressant Use with Adherence to Hormone Therapy for those with Depression

Quarter	Antidepressant Use	No Antidepressant Use
1	664	409
2	643	393
3	605	368
4	549	333
5	503	290
6	458	258
7	416	222
8	361	189
9	322	174
10	280	149
11	235	127
12	180	100
13	157	84
14	124	71
15	91	57

Table A.2 Number of patients identified with depression who either took or did not take antidepressant for each quarter with a measure of adherence to hormone therapy

Table A.3 Sample Size for Per Patient Per Year Cost for Depressed and Non-Depressed Patients

Year	Depressed	Non-Depressed
1	1,073	9,398
2	970	8,985
3	664	6,713
4	395	4,151
5	166	1,979

Table A.3: The number of patients identified in each year who have a measure of cost for those with and without depression

Table A.4 Sample Size for Per Patient Per Year Cost for Antidepressant Users and Non-Users in Patients with Depression

Year	Antidepressant Use	No Use of Antidepressant
1	664	409
2	603	367
3	424	240
4	263	132
5	110	56

Table A.4: The number of patients with depression identified in each year with antidepressant use or no use who have a measure of cost

Table A.5 Association of 90 Day Use of Antidepressants with Survival

	Estimate	95% CI	
Antidepressant Category			
did not use for at least 90 days			
no antidepressant	0.99	-0.31	2.29
used for at least 90 days	0.93	-0.37	2.22
Hormone therapy type			
SERM only			
AI only	0.01	-0.27	0.29
Charlson Score			
0			
*1**	-0.63	-0.95	-0.30
*2+**	-0.37	-0.59	-0.15
Stage			
0			
*1**	-0.78	-1.47	-0.08
*2**	-1.05	-1.75	-0.35
*3**	-1.36	-2.09	-0.60
Grade			
1			
2	-0.22	-0.48	0.04
3+	-0.21	-0.52	0.10
Initial surgery			
breast conserving			
*mastectomy **	0.30	0.05	0.54
radiation therapy*	0.36	0.11	0.60
chemotherapy	0.07	-0.20	0.34
SEER site			
north east			
north central	0.09	-0.27	0.46
south	-0.01	-0.32	0.31
west	0.20	-0.09	0.47
Race			
white			
black	-0.33	-0.75	0.08
other	-0.17	-0.63	0.28
Age			
65-74			
*75-84**	-0.36	-0.59	-0.13
*85+**	-0.89	-1.21	-0.57

	Estimate	95% CI	
Urban	-.01	-0.36	0.34
Married *	0.29	0.06	0.53
Median Income of Zip Code			
<30K			
30-49K	0.11	-0.20	0.42
50K+	0.23	-0.12	0.59

Table A.5: An * indicates significant results at p<.05

Table A.6 Association of 180 Day Use of Antidepressants with Survival

	Estimate	95% CI	
Antidepressant Category			
no antidepressant			
did not use for at least 180 days	-0.21	-0.44	0.03
used for at least 180 days	0.12	-0.14	0.38
Hormone therapy type			
SERM only			
*AI only**	0.03	-0.25	0.31
Charlson Score			
0			
*1**	-0.61	-0.94	-0.29
*2+**	-0.37	-0.59	-0.15
Stage			
0			
*1**	-0.79	-1.48	-0.09
*2**	-1.04	-1.74	-0.34
*3**	-1.34	-2.09	-0.60
Grade			
1			
2	-0.21	-0.46	0.05
3+	-0.18	-0.49	0.13
Initial surgery			
breast conserving			
*mastectomy **	0.28	0.04	0.52
radiation therapy*	0.35	0.10	0.60
chemotherapy*	0.07	-0.20	0.34
SEER site			
north east			
north central	0.13	-0.24	0.49
south	0.04	-0.27	0.35
west	0.19	-0.10	0.47
Race			
white			
*black **	-0.34	-0.75	0.07
other	-0.18	-0.63	0.28
Age			
65-74			
*75-84**	-0.35	-0.58	-0.12
*85+**	-0.88	-1.20	-0.57
Urban	-.01	-0.36	0.34

	Estimate	95% CI	
Married *	0.29	0.06	0.52
Median Income of Zip Code			
<30K			
30-49K	0.13	-0.17	0.44
50K+	0.26	-0.09	0.61

Table A.6: An * indicates significant results at p<.05

Table A.7 Association of 1 Year Use of Antidepressants with Survival

	Estimate	95% CI	
Antidepressant Category			
used for at least 365 days			
*did not use for at least 365 days**	-0.92	-1.51	-0.33
*no antidepressant**	-0.79	-1.39	-0.19
Hormone therapy type			
SERM only			
*AI only**	0.03	-0.24	0.31
Charlson Score			
0			
*1**	-0.60	-0.92	-0.28
*2+**	-0.34	-0.56	-0.12
Stage			
0			
*1**	-0.81	-1.50	-0.12
*2**	-1.06	-1.76	-0.36
*3**	-1.37	-2.11	-0.63
Grade			
1			
2	-0.21	-0.47	0.04
3+	-0.19	-0.50	0.12
Initial surgery			
breast conserving			
*mastectomy **	0.30	0.05	0.54
radiation therapy*	0.37	0.12	0.61
chemotherapy*	0.07	-0.20	0.34
SEER site			
north east			
north central	0.12	-0.26	0.47
south	0.02	-0.28	0.33
west	0.20	-0.08	0.48
Race			
white			
black	-0.32	-0.73	0.09
other	-0.15	-0.60	0.31
Age			
65-74			
*75-84**	-0.35	-0.58	-0.13
*85+**	-0.87	-1.19	-0.56
Urban	-.02	-.38	0.33

	Estimate	95% CI	
Married *	0.27	0.04	0.5
Median Income of Zip Code			
<30K			
*30-49K**	0.12	-0.18	0.43
50K+	0.24	-0.11	0.59

Table A.7 An * indicates significant results at p<.05