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# The Impact of Medication Adherence on Non-Drug Healthcare Utilization and Costs



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**Title Page**

# The Impact of Medication Adherence on Non-Drug Healthcare Utilization and Costs

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## Abstract

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**Purpose:** To explore the impact of hormone therapy (HT) adherence on non-drug healthcare utilization and healthcare costs among breast cancer patients.

**Methods:** Women aged >= 65 with hormone-receptor positive breast cancer from 2007 through mid-2009 were identified using SEER-Medicare-linked database. We examined their HT adherence, non-drug healthcare utilization and healthcare costs for the first year of HT and each year thereafter for a total of five years. Based on the distribution of healthcare utilization and costs measures, we applied appropriate statistical modeling methods to predict the relationships between HT adherence and outcomes of our interests.

**Results:** 6,045 eligible Medicare beneficiaries that met our selection criteria were included. We found that patients who were adherent to HT were associated with lower healthcare utilization of all kinds (inpatient, outpatient and physician office visits), and significant reductions in many types of medical costs and neutral total healthcare costs despite the increased pharmacy costs. Half of total medical cost reduction came from savings in hospitalization costs.

**Conclusions:** Our study suggests that the added cost of HT adherence was all but offset by the reduced cost for other medical care. Our study provides evidence on the potential success of implementing value-based insurance design (VBID) plans among breast cancer patients to improve their long-term oral medication adherence. Policy makers should consider adherence improvement strategies such as VBID plans, given that the costs likely will not surpass the total savings.

**Precis**

Increased pharmacy costs associated with better hormone therapy adherence among breast cancer patients can be all but offset by the reduced costs for other categories of medical care.

**Strength and limitations**

1. First of its kind to reveal the impact of copayment reduction on HT adherence and persistence among the dual eligible breast cancer patients among Medicare patients in the US.
2. Followed postmenopausal women diagnosed with early stage hormone receptor positive breast cancers for their full course of AIs treatment. The results help us understand the factors that impact patients' response to taking AIs long-term, which should be clinical useful.
3. Used advanced statistical methods to derive the most accurate estimates possible for the effects of type of Medicaid coverage on our two outcomes. These methods included propensity score methodology to minimize potential selection bias due to non-random assignment of the treatment group, and longitudinal hierarchical modeling to control for correlated data within patient.
4. The filled prescriptions does not necessarily equal the amount of medications patients took. In addition, our results do not reflect some cases where a patient may have supplementary insurance to cover their medication costs or a patient switched from aromatase inhibitor to other hormone therapy medications (i.e., tamoxifen).
5. The drug costs were calculated by using the gross drug costs (consisting of ingredient cost, dispensing fee, and total amount attributed to sales tax). However, Medicare usually receives rebates from pharmaceutical companies, which is confidential information. The actual Medicare payment amount for medications should be less than the total of gross drug costs. Therefore, it is likely that our study overestimated the pharmacy costs.

**Take-Away Points**

- Analysis of SEER-Medicare-linked database from 2007-2014 indicated that breast cancer patients who were adherent to hormone therapy were associated with lower healthcare utilization, significant reductions in many types of medical costs and neutral total healthcare costs despite the increased pharmacy costs.
- Potential success of implementing value-based insurance design (VBID) plans among breast cancer patients can improve their long-term oral medication adherence without increasing total healthcare costs.
- Policy makers should consider adherence improvement strategies such as VBID plans, given that the costs likely will not surpass the total savings.

## Introduction

Breast cancer is the most commonly diagnosed non-skin cancer among U.S. women, representing 30% of all new cancer cases in 2020.[1] With improved screening and treatment, breast cancer death rate has been decreasing by 1.8% each year over the past decade and the current 5-year survival rate is about 90% [2]. As more patients are living with breast cancer, the associated healthcare costs have also been increasing. Breast cancer accounts for the largest share of national expenditure for cancer care. It increased from $16.5 billion in 2010 to $19.7 billion in 2018 [3].

Hormone receptor (HR) positive breast cancer subtype accounts for over 80% of total breast cancer. Among HR positive breast cancer patients, adjuvant endocrine (or hormone) therapy has been incorporated as part of the treatment regime after surgical removal of the tumor[4-7]. There are several types of hormone therapy medications, including tamoxifen and aromatase inhibitors (AIs). AIs are a newer generation of adjuvant hormone therapy (HT) medications for postmenopausal women, including anastrozole, letrozole, and exemestane. Clinical evidence showed that AIs are more effective than tamoxifen in improving survival and reducing disease recurrence among postmenopausal women [8]. In order to achieve the most desired health benefits, the American Society of Clinical Oncology's (ASCO) recommended HT treatment for at least 5 years [9]. However, long-term HT adherence remains suboptimal. This is problematic, because failure to complete a full course of treatment compromises health benefits and often results in treatment failure[10-12].

Value-based insurance design (VBID) plans are designed to offer high-value healthcare at reduced out-of-pocket costs (OOPCs) to patients with certain diagnoses and/or socioeconomic status. Some Medicare Advantage plans adopted the VBID model for their beneficiaries to

manage the healthcare costs while maintaining healthcare quality. For example, Medicare Advantage patients can see reduced copayment for long term medications, if they have certain chronic diseases, and/or if they are dual eligible and covered by Medicaid as well. By reducing the copayments for these patients, VBID plans aim to improve their medication adherence. Previous studies found that improved medication adherence may associate with lower total healthcare costs, even though it may increase pharmacy costs. The increase in pharmacy costs due to medication adherence is often offset by savings in other non-drug medical costs, as overall health improves [13-15]. For example, in a four-state study of dual eligible beneficiaries with congestive heart failure (CHF), patients who were found to be adherent to their prescribed medication regimes were 4% less likely to be hospitalized and 3.0% less likely to visit the emergency department (ED). In total, their total healthcare costs per year were $5,910 (23%) lower than beneficiaries found to be non-adherent [16]. Roebuck *et al.* examined privately insured patients with four chronic conditions (CHF, hypertension, diabetes, and dyslipidemia) and found that medication adherence was associated with 1.18 (for dyslipidemia) to 5.72 (for CHF) fewer days in inpatient stays, 0.01 to 0.04 reduction in ED visits, and a corresponding $1,258 (for dyslipidemia) to $7,823 (for CHF) reduction in total annual healthcare [15]. Boye *et al*. examined type 2 diabetes patients and found that every 1% increase in medication adherence was associated with on average $65,464 all-cause cost savings among 1,000 patients, similarly driven by the lowered probability of hospitalizations and ED visits [17].

While a myriad of studies have found an inverse relationship between medication adherence and non-drug healthcare utilization and total healthcare costs, most of them focused on chronic cardiovascular diseases. Only a few studies explored the association between medication adherence and non-drug healthcare utilizations and costs among breast cancer

patients. One four-year longitudinal study of Medicaid beneficiaries with breast cancer from South Carolina found that HT adherence was associated with 31% decrease in medical costs, but no significant savings in total healthcare cost. The different results between medical and total healthcare costs could be due to adverse events associated with long-term use of hormone therapy [18]. While this finding was informative, more research focusing on breast cancer patients among a broader sample of Medicare beneficiaries is needed. In this study, we used a nationally representative sample of Medicare beneficiaries to examine the relationships between HT adherence and non-drug healthcare utilization and healthcare costs. The objective of our study is to explore the impact of HT adherence on non-drug healthcare utilization and healthcare costs among breast cancer patients. We hypothesize that the non-drug healthcare utilization will be lower among breast cancer patients who adhere to HT, as compared to those who do not. Furthermore, HT adherent patients will have higher prescription drug costs, but lower non-drug costs, and lower or neutral total healthcare costs compared to non-adherent patients.

## Method

### *Data Source*

We used SEER-Medicare linked database for the years of 2007 – 2014. The National Cancer Institute's SEER database is the only database that includes comprehensive population-based information on breast cancer patients' demographics, cancer diagnosis, time of diagnosis, and initial therapy (surgery and/or radiation). At the time of this study, SEER covered 34.6% of the U.S. population. The linked Medicare component includes beneficiaries' enrollment, prescription drug use and costs, and non-drug healthcare utilization and costs information [19].

*Study Sample*

Our study sample is women diagnosed with HR- positive early stage breast cancer in years 2007 to mid-2009 in the US. Other criteria for inclusion were: 1) 65 years or older, 2) no missing race value, 3) with only one breast cancer diagnosis within the study period, 4) initiated AI treatment within the first year of breast cancer diagnosis, 5) continuously enrolled in Medicare Part A and Part B and Part D from diagnosis data through five years after the first filled AI prescription or until dead, whichever came first (gaps of 45 days or less allowed), 6) did not spend a full year in an inpatient facility (i.e., hospital, or skilled nurse facility). The screening process for constructing our study cohort can be found in supplementary material.

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*Variables*

**Dependent variables**

We examined the non-drug healthcare utilization and healthcare costs for the patients' first year of AI treatment and each year thereafter for a total of five years (year 1 through year 5). Variables of non-drug healthcare utilization included any hospitalization, length of stay (LOS), and numbers of inpatient, outpatient, and physician office visits. Healthcare costs included all-cause non-drug medical costs (inpatient, outpatient and physician office visits costs), all-cause prescription costs, and the sum of the two as total healthcare costs. All costs were measured by the total amount paid by Medicare and standardized to 2014 dollars.

**Treatment variables**

A patient's adherence to AI treatment was based on the medication possession ratio (MPR),

calculated as the number of days of AI supplied divided by the number of days covered in a year. A patient's inpatient days were excluded from the denominator because AI medications may have come from another source during an inpatient stay and not be reflected in Medicare Part D data. If a patient died, he/she was excluded from the following years. MPR values in years when patients were alive but did not fill any AI prescriptions were set to 0. MPR as capped at 100% if numerator is greater than denominator due to early refills. As a sensitivity analysis, we also analyzed an 'adherence' indicator variable with value 1, if the patient's MPR for the year was 80% or more [20-24].

**Covariates**

Time invariant covariates used in our analyses included a patient's race/ethnicity, marital status, tumor stage, and certain treatment characteristics. Two time variant covariates were included in our analyses: patient's age at the start of each year (years 1 through year 5), and the patient's Hierarchical Condition Category [HCC] score. HCC score is a risk adjustment factor based on a patient's comorbidities. Our analyses also included variables representing calendar years to address the concurrent trends in healthcare utilization and costs. The descriptions of full list of our variables are shown in supplementary material.

*Data Analysis*

We first examined the distributions of all independent variables, including patients' MPR and adherence value and then calculated summary statistics on outcomes each year (year 1 through year 5): any hospitalization, ED visits, or outpatient visits, numbers of inpatient stays, outpatient clinic visits, or physician office visits, and mean LOS associated with hospitalization. We also calculated the average healthcare costs to Medicare including non-drug medical costs,

prescription drug costs and total healthcare costs.

Based on preliminary descriptive and bivariate analyses, we determined the appropriate statistical modeling methods and selected covariates to include as adjustors. Zero inflated negative binomial models was adopted to predict LOS and the numbers of hospitalization stays and outpatient visits, and negative binomial models was used to predict the number of physician office visits. For outpatient, non-drug medical, prescription drug, and total medical costs, we restricted our sample to positive observations and used generalized linear models (GLMs) with log link and gamma distribution for esitmation. For hospitalization costs, we adopted a two-part model, since only approximately 20% of our study sample had hospitalizations. In this model, the first part was a logistic regression model to predict the likelihood of having a nonzero hospitalization costs, and the second part of the model used GLM to estimate the nonzero hospitalization costs. All statistical analysis was conducted using SAS v9.3 [25] or Stata 14 [26] where applicable.

## Results

There were 6,045 eligible Medicare beneficiaries who met our sample selection criteria. The average age of our study cohort was 74.6 years old; 28.9% of them were in the '65-69' age group, 25.4% were in the '70-74' age group, 20.5% were in the '75-79' age group and 25.1% were in the '80+' age group. The majority identified as non-Hispanic White (84%), with the rest (16%) identifying as non-Hispanic Black, Hispanic, or Asian. Slightly more than half of the sample was unmarried (57.5%), had stage I breast cancer (54.5%), or received surgery and radiation (52.2%) as their main breast cancer treatment (Table 1).

Table 2 shows the summary statistics for treatment variables and outcome variables (including non-drug healthcare utilization and healthcare costs) over the 5-year course of treatment. The average MPR was the highest in the first year of treatment (79%) and lowest in the fifth year (54%) of treatment. The percentage of patients who were adherent in each of the 5 years (i.e., MPR>=80%) ranged from 39.4% to 64.2%. On average, about 20% of surviving patients each year had at least one hospitalization event, while about 90% had at least one outpatient visit, and approximately 99% had at least one physician office visit. Among those with at least one hospitalization in each year, the mean number of inpatient stays was 1.9-2.2 and mean LOS was 22.0-24.4 days. The mean annual total healthcare costs ranged from $12,970 to $21,431 over the 5 years of AI treatment, while medication costs accounted for 22% to 31% of the total healthcare costs each year ($2,875 - $6,664).

Table 3 presents the unadjusted annual non-drug healthcare utilization and costs in adherent and non-adherent Medicare beneficiaries across their 5 years of treatment. For year three through year five, a significantly lower percentage of adherent beneficiaries had at least one hospitalization compared to non-adherent beneficiaries. Among those with hospitalizations, however, neither number of stays nor mean LOS were statistically significant different in any year. Conversely, the percent of adherent beneficiaries who had any outpatient visits was higher than the percent of non-adherent beneficiaries in the fourth year and lower in the fifth year, while no statistically significant differences in the rest of the years. Across the five years, adherent patients had consistently fewer numbers of physician office visits than non-adherent patients. In general, adherent beneficiaries had lower medical costs, but higher medication costs than nonadherent beneficiaries, which led to slightly higher total healthcare costs among adherent beneficiaries compared to non-adherent beneficiaries.

Results of adjusted models predicting the association between MPR and non-drug healthcare utilization and costs are shown in Table 4. The results indicate that every 10% increase in MPR associates with a 0.009 decrease in the number of hospitalizations (P<0.001), a 0.088 shorter LOS (P<0.01), a 0.018 drop in the number of outpatient (P>0.05), and 0.111 fewer physician office visits (P<0.001). Every 10% increase in MPR also associates with an increase in medication costs ($365, P<0.001), and a decrease in total medical costs (-$281, P<0.001). The difference in total healthcare costs is not statistically significant. Table 5 shows results of adjusted models using the alternative indicator of adherence instead of the continuous MPR measure. Table 5 results indicate that healthcare utilization measures are always lower for adherent beneficiaries compared to nonadherent beneficiaries, adherent beneficiaries had fewer hospitalizations (0.35 vs 0.43, P<0.001) and fewer physician office visits (25.16 vs 26.17, P<0.001), and shorter LOS during hospitalization (4.19 vs 4.89, P<0.01). On average, Medicare paid $2,314 (P<0.001) more on medications for adherent beneficiaries, but $2,242 (P<0.001) less on total non-drug medical costs. This resulted in no statistically significant difference in total Medicare healthcare costs.

## Discussion

Our study explored the relationships between hormone therapy adherence and non-drug healthcare utilization and costs among breast cancer patients. To our knowledge, this is one of the first studies to examine the association of medication adherence and non-drug healthcare utilization and costs across the full five-year course of treatment and among a sample of patients as diverse as that provided by the SEER-Medicare database. We found that patients who were adherent to HT were associated with lower numbers of inpatient, outpatient and physician office visits. Consistent with previous studies[15,17,18], we also found that patients who were adherent to

HT were associated with significant reductions in many types of medical costs and their total. Half of total medical cost reduction came from savings in hospitalization costs. This makes sense, since staying on hormone therapy for at least 5 years, as clinical guidelines recommend, reduces the likelihood of breast cancer recurrence. Adherent patients are more likely to avoid a recurrence of breast cancer and the associated costs for related treatment. Our findings suggest that the added cost of hormone therapy adherence is all but offset by the reduced cost for other categories of medical care.

To determine the contingent effect of medication adherence on health care utilization and costs, we included unalterable patient level factors in our models such as age, race, and tumor stage at time of diagnosis. These factors are known to be strongly associated with adherence and through this also impact utilization and costs, but they are not factors, which clinicians and policy makers can directly change. However, earlier analyses have identified two manageable factors, which could improve adherence and by doing so, impact health care utilization and costs: care coordination for comorbid health conditions and financial help with medication copayments [27]. Systematic care coordination among health service providers to address comorbid health conditions is possible, but is usually considered costly to implement [27]. This study does indicate, however, that the additional cost would be limited to the care coordination itself. The added costs of medication due to higher adherence would be, for the most part, offset by lower non-drug medical costs.

The benefit of conducting our study with claims data is that the data contains real-world information on hormone therapy adherence and non-drug healthcare utilization and costs. However, there are also some limitations. First, we used Medicare Part D data to calculate MPR to reflect adherence. The filled prescriptions does not necessarily equal the amount of

medications patients took. In addition, our results do not reflect some cases where a patient may have supplementary insurance to cover their medication costs or a patient switched from aromatase inhibitor to other hormone therapy medications (i.e., tamoxifen). Secondly, the drug costs were calculated by using the gross drug costs (consisting of ingredient cost, dispensing fee, and total amount attributed to sales tax). However, Medicare usually receives rebates from pharmaceutical companies, which is confidential information. The actual Medicare payment amount for medications should be less than the total of gross drug costs. Therefore, it is likely that our study overestimated the pharmacy costs. Finally, we do not know if the reduced medical costs and healthcare utilization were solely associated with better adherence. It is possible that patients who were more adherent to hormone therapy treatment were more likely to be adherent to other non-drug treatments and/or have a healthier lifestyle, which could have biased the results away from the null. It would be meaningful for future studies to separate these effects from medication adherence.

## Conclusions

Our study is one of the first to analyze the association between hormone therapy adherence and non-drug healthcare utilization and costs among Medicare beneficiaries over the full course of treatment. Our results suggested that better adherence is associated with lower healthcare utilization of all kinds (inpatient, outpatient and physician office visits) and neutral total healthcare costs despite the increased pharmacy costs. Our study also provides insights into the potential benefits of implementing VBID plans among breast cancer patients to improve their long-term oral medication adherence. Policy makers should consider adherence improvement

strategies such as VBID plans given the potential health benefits, and that the costs likely will not surpass the total savings.

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## Tables

*Table 1. Baseline Characteristics of Eligible Medicare Beneficiaries with Hormone Receptor Positive Early Stage Breast Cancer Who Initiated Aromatase Inhibitor Treatment within the First Year of Diagnosis (n=6,045)*

| Characteristics | No. (%)[a] |
|---|---|
| **Median age, years (range)** | 74.6 (65 - 103) |
| **Age Group** | |
| 65-69 | 1,748 (28.9) |
| 70-74 | 1,537 (25.4) |
| 75-79 | 1,242 (20.6) |
| 80+ | 1,518 (25.1) |
| **Race/Ethnicity** | |
| White, non-Hispanic | 5,068 (83.8) |
| Black | 392 (6.5) |
| Hispanic | 334 (5.5) |
| Asian | 251 (4.2) |
| **Comorbidity (HCC score)** | |
| 0 | 2,098 (36.9) |
| 1 | 1,504 (26.5) |
| 2 | 918 (16.2) |
| 3+ | 1,161 (20.4) |
| **Marital Status** | |
| Married | 2,570 (42.5) |
| Unmarried | 3,475 (57.5) |
| **Tumor stage** | |
| I | 3,297 (54.5) |
| II | 2,124 (35.1) |
| III | 624 (10.3) |
| **Treatment** | |
| Surgery + radiation | 3,155 (52.2) |
| Surgery, no radiation | 2,709 (44.8) |
| No surgery | 181 (3.0) |

*Note: a. values are number (percentage) unless indicated otherwise*

*Table 2. Hormone Therapy Adherence, Healthcare Utilization and Costs over the Full Course of Aromatase Inhibitor Treatment among Medicare Beneficiaries with Breast Cancer*

| Variables | Year 1 (n=6,045) | Year 2 (n=5,847) | Year 3 (n=5,592) | Year 4 (n=5,322) | Year 5 (n=4,993) |
|---|---|---|---|---|---|
| *Treatment variables* | | | | | |
| MPR, mean (SD) | 0.79 (0.27) | 0.62 (0.39) | 0.61 (0.41) | 0.61 (0.43) | 0.54 (0.41) |
| Adherence (MPR>=80%), n (%) | 3,878 (64.2) | 2,855 (48.8) | 2,837 (50.7) | 2,848 (53.5) | 1,848 (39.4) |
| *Outcome variables* | | | | | |
| **Healthcare Utilization** | | | | | |
| Any hospitalization, n (%) | 1,166 (19.3) | 862 (14.7) | 873 (15.6) | 1,123 (21.1) | 1,174 (23.5) |
| No. of hospitalization (>0), mean (SD) | 2.0 (1.7) | 1.9 (1.5) | 2.0 (1.5) | 2.2 (1.9) | 2.2 (1.7) |
| No. of hospital days (>0), mean (SD) | 23.4 (47.2) | 22.9 (46.3) | 22.0 (38.5) | 24.3 (41.5) | 24.4 (41.8) |
| Any outpatient visits, n (%) | 5,636 (93.2) | 5,281 (90.3) | 4,969 (88.9) | 4,693 (88.2) | 4,395 (88.0) |
| No. of outpatient visits, mean (SD) | 7.7 (7.7) | 6.5 (7.4) | 6.1 (7.1) | 5.9 (6.8) | 6.0 (7.3) |
| Any physician office visits, n (%) | 6,041 (99.9) | 5,832 (99.7) | 5,567 (99.5) | 5,297 (99.5) | 4,956 (99.3) |
| No. of physician office visits, mean (SD) | 29.2 (17.6) | 25.4 (17.2) | 24.7 (17.6) | 24.3 (18.1) | 24.1 (18.4) |
| **Healthcare Costs** | | | | | |
| Medicare Payment Amount, $ mean (median) | | | | | |
| Total healthcare costs | 21,431 (14,508) | 15,204 (9,757) | 14,884 (8,657) | 15,362 (7,664) | 12,970 (5,438) |
| Total medical costs | 14,767 (7,586) | 9,630 (4,223) | 10,148 (4,047) | 11,611 (3,950) | 10,096 (2,894) |
| Hospitalization costs (>0) | 22,700 (12,654) | 22,084 (13,114) | 23,853 (15,309) | 25,461 (15,894) | 20,993 (11,515) |
| Outpatient costs | 3,708 (1,232) | 1,916 (671) | 1,976 (617) | 1,918 (571) | 1,556 (390) |
| Physician costs | 6,680 (3,942) | 4,458 (2,886) | 4,448 (2,767) | 4,319 (2,600) | 3,604 (1,926) |
| Total pharmacy costs | 6,664 (5,677) | 5,574 (4,623) | 4,735 (3,475) | 3,751 (2,371) | 2,875 (1,452) |

*Table 3. Unadjusted Annual Healthcare Utilization and Costs in Adherent and Nonadherent Medicare Beneficiaries with Breast Cancer over the Full Course of Treatment*

| Variables | Adherent | Non-Adherent | P |
|---|---|---|---|
| **Healthcare Utilization** | | | |
| Any hospitalization, n (%) | | | |
| Year 1 | 729 (18.8) | 437 (20.2) | NS |
| Year 2 | 395 (13.8) | 467 (15.6) | NS |
| Year 3 | 404 (14.2) | 469 (17.0) | ** |
| Year 4 | 521 (18.3) | 602 (24.3) | *** |
| Year 5 | 417 (21.2) | 757 (25.0) | ** |
| No. of hospitalization (>0), mean (SD) | | | |
| Year 1 | 2.0 (1.7) | 2.1 (1.7) | NS |
| Year 2 | 1.8 (1.4) | 2.0 (1.5) | NS |
| Year 3 | 2.0 (1.4) | 2.0 (1.5) | NS |
| Year 4 | 2.1 (1.8) | 2.2 (1.9) | NS |
| Year 5 | 2.1 (1.8) | 2.2 (1.7) | NS |
| No. of hospital days (>0), mean (SD) | | | |
| Year 1 | 25.5 (53.8) | 19.9 (33.0) | * |
| Year 2 | 22.3 (49.4) | 23.5 (43.5) | NS |
| Year 3 | 23.3 (41.8) | 20.8 (35.3) | NS |
| Year 4 | 24.8 (45.7) | 23.8 (37.6) | NS |
| Year 5 | 23.7 (38.0) | 24.8 (43.8) | NS |
| Any outpatient visits, n (%) | | | |
| Year 1 | 3,612 (93.1) | 2,024 (93.4) | NS |
| Year 2 | 2,600 (91.1) | 2,681 (89.6) | NS |
| Year 3 | 2,537 (89.4) | 2,432 (88.3) | NS |
| Year 4 | 2,564 (90.0) | 2,129 (86.1) | *** |
| Year 5 | 1,766 (89.8) | 2,629 (86.9) | ** |
| No. of outpatient visits, mean (SD) | | | |
| Year 1 | 7.7 (7.6) | 7.9 (7.9) | NS |
| Year 2 | 6.5 (7.4) | 6.4 (7.4) | NS |
| Year 3 | 6.2 (7.2) | 6.0 (7.0) | NS |
| Year 4 | 5.9 (6.8) | 5.9 (6.8) | NS |
| Year 5 | 6.1 (7.2) | 5.9 (7.4) | NS |
| No. of physician office visits, mean (SD) | | | |
| Year 1 | 28.5 (17.3) | 30.3 (18.1) | *** |

(continued the next page)

| Variables | Adherent | Non-Adherent | P |
|---|---|---|---|
| Year 2 | 25.2 (16.8) | 25.6 (17.5) | NS |
| Year 3 | 24.4 (16.5) | 25.0 (18.6) | NS |
| Year 4 | 23.9 (17.3) | 24.9 (18.9) | * |
| Year 5 | 23.8 (18.1) | 24.3 (18.5) | NS |
| | | | |
| **Healthcare Costs** | | | |
| Medicare Payment Amount | | | |
| Total healthcare costs, $ mean (median) | | | |
| Year 1 | 22,025 (15,502) | 20,370 (12,604) | ** |
| Year 2 | 16,624 (11,434) | 13,849 (8,072) | *** |
| Year 3 | 15,110 (9,865) | 14,651 (7,488) | NS |
| Year 4 | 14,563 (7,906) | 16,283 (7,347) | ** |
| Year 5 | 12,758 (5,837) | 13,109 (5,238) | NS |
| Total medical costs, $ mean (median) | | | |
| Year 1 | 14,306 (7,513) | 15,594 (7,775) | * |
| Year 2 | 9,090 (4,111) | 10,144 (4,324) | * |
| Year 3 | 9,025 (3,923) | 11,304 (4,209) | *** |
| Year 4 | 10,067 (3,688) | 13,389 (4,283) | *** |
| Year 5 | 9,103 (2,772) | 10,741 (2,981) | ** |
| Total hospitalization costs, $ mean (median) | | | |
| Year 1 | 22,176 (12,654) | 23,574 (12,775) | NS |
| Year 2 | 22,136 (12,462) | 22,040 (13,620) | NS |
| Year 3 | 23,036 (16,120) | 24,558 (14,584) | NS |
| Year 4 | 24,799 (15,880) | 26,035 (16,034) | NS |
| Year 5 | 20,213 (11,477) | 21,424 (11,569) | NS |
| Total outpatient costs, $ mean (median) | | | |
| Year 1 | 4,528 (2,035) | 5,151 (2,177) | NS |
| Year 2 | 3,380 (1,514) | 3,768 (1,481) | NS |
| Year 3 | 3,527 (1,549) | 4,316 (1,483) | NS |
| Year 4 | 3,485 (1,597) | 3,991 (1,420) | NS |
| Year 5 | 3,010 (943) | 2,925 (1,019) | NS |
| Total physician costs, $ mean (median) | | | |
| Year 1 | 9,602 (6,915) | 11,352 (8,175) | ** |
| Year 2 | 8,325 (6,093) | 8,323 (6,250) | NS |
| Year 3 | 8,289 (6,290) | 8,892 (6,128) | NS |

(continued the next page)

| Variables | Adherent | Non-Adherent | P |
|---|---|---|---|
| Year 4 | 7,639 (5,697) | 9,069 (6,308) | ** |
| Year 5 | 6,366 (4,588) | 6,810 (4,737) | NS |
| Total pharmacy costs, $ mean (median) | | | |
| Year 1 | 7,719 (6,561) | 4,776 (4,090) | *** |
| Year 2 | 7,534 (6,443) | 3,705 (3,150) | *** |
| Year 3 | 6,084 (5,032) | 3,347 (2,539) | *** |
| Year 4 | 4,495 (2,951) | 2,893 (1,847) | *** |
| Year 5 | 3,656 (1,954) | 2,367 (1,235) | *** |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*Table 4. Adjusted Healthcare Utilization and Costs among Medicare Beneficiaries with Breast Cancer over the Full Course of Treatment*

| **Variables** | MPR[/a] | P[/b] |
|---|---|---|
| **Healthcare Utilization** | | |
| No. of hospitalizations | -0.009 | *** |
| No. of hospital days | -0.088 | ** |
| No. of outpatient visits | -0.018 | NS |
| No. of physician office visits | -0.111 | *** |
| | | |
| **Healthcare Costs** | | |
| Medicare Payment Amount | | |
| Total healthcare costs | 51 | NS |
| Total medical costs | -281 | *** |
| Total hospitalization costs | -109 | *** |
| Total outpatient costs | -52 | *** |
| Total physician costs | -105 | *** |
| Total pharmacy costs | 365 | *** |

*Notes:*

a. *The prediction model controlled for other covariate, full results see Supplement Material.*
b. **statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

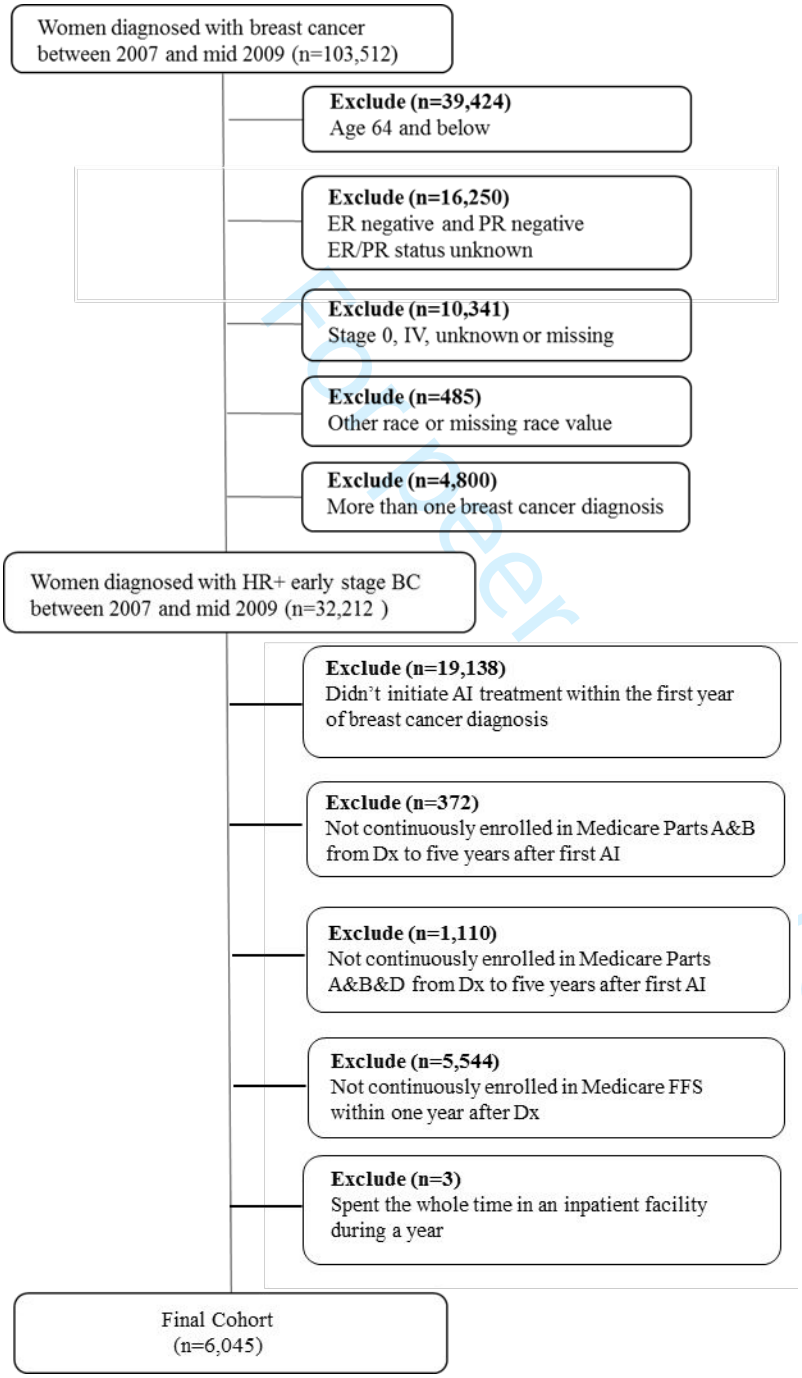
*Table 5. Adjusted Healthcare Utilization and Costs for Medicare Beneficiaries Adherent and Nonadherent to Hormone therapy over the Full Course of Treatment*

| Variables | Adherent[a] | Non-Adherent | Difference | P[b] |
|---|---|---|---|---|
| **Healthcare Utilization** | Margin (SE) | Margin (SE) | Margin (SE) | |
| No. of hospitalization | 0.35 (0.01) | 0.43 (0.01) | -0.08 (0.01) | *** |
| No. of hospital days | 4.19 (0.16) | 4.89 (0.18) | -0.70 (0.22) | ** |
| No. of outpatient visits | 6.45 (0.05) | 6.54 (0.06) | -0.09 (0.08) | NS |
| No. of physician office visits | 25.16 (0.13) | 26.17 (0.14) | -1.02 (0.20) | *** |
| **Healthcare Costs** | | | | |
| Medicare Payment Amount | | | | |
| Total healthcare costs | 16,246 (164) | 16,077 (200) | 169 (262) | NS |
| Medical costs | 10,310 (152) | 12,551 (195) | -2,242 (249) | *** |
| Hospitalization costs | 3,811 (115) | 4,840 (141) | -1,028 (183) | *** |
| Outpatient costs | 2,070 (37) | 2,484 (54) | -414 (65) | *** |
| Physician costs | 4,389 (47) | 5,190 (63) | -801 (77) | *** |
| Pharmacy costs | 5,891 (46) | 3,577 (37) | 2,314 (61) | *** |

*Notes:*

a. *The prediction model controlled for other covariate, full results see Supplement Material.*
b. **statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*Appendix A. Selection Criteria for Identifying Medicare Beneficiaries Diagnosed with Hormone Receptor-Positive Early Stage Breast Cancer from 2007 to Mid-2009*



*Appendix B. Descriptions of Variables*

| VARIABLE NAME | DEFINITION |
|---|---|
| **DEPENDENT VARIABLES** | |
| *Healthcare utilization* | |
| Any hospitalization | A dummy variable equal to 1 if at least one hospitalization |
| Inpatient visits | A continuous variable of number of hospitalizations |
| Length of stay | A continuous variable of number of days in hospital |
| Any outpatient visits | A dummy variable equal to 1 if at least one outpatient visits |
| Outpatient visits | A continuous variable of number of outpatient visits |
| *Healthcare costs* | |
| Total healthcare costs | A continuous variable measures the sum of non-drug medical costs and prescription drug costs |
| Non-drug medical costs | A continuous variable measures the sum of inpatient and outpatient costs |
| Inpatient costs | A subgroup of total medical costs |
| Outpatient costs | A subgroup of total medical costs |
| Prescription drug costs | A continuous variable |
| **TREATMENT VARIABLES** | |
| Adherence continuous | A continuous variable of MPR % |
| Adherence dummy | A dummy equal to 1 if MPR >=80% |
| **CONTROL VARIABLES** | |
| Race/Ethnicity | A dummy variable equal to 1 if White, non-Hispanic |
| Age continuous | A continuous variable, 65+ years old |
| Married | A dummy variable equal to 1 if married |
| Tumor Stage | A categorical variable where<br>1 Stage I<br>2 Stage II<br>3 Stage III |
| Initial Surgery/Radiation Treatment | A categorical variable where<br>1 No surgery<br>2 Surgery (breast-conserving surgery or mastectomy) + radiation<br>3 Surgery, no radiation |

| | |
|---|---|
| HCC Risk Score (see detailed construction description on NCI website: https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity.html) | A categorical variable where 1 0 2 1 3 2 4 3+ |

*Appendix C. Association between Medication Possession Ratio and Healthcare Utilization and Costs among Medicare Beneficiaries with Breast Cancer over the Full Course of Treatment, controlling for covariates*

## C-1. No. of Hospitalization

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | -0.083 | 0.013 | *** | -0.108 | -0.058 |
| Year | | | | | |
| 2 vs 1 | -0.132 | 0.018 | *** | -0.167 | -0.096 |
| 3 vs 1 | -0.108 | 0.019 | *** | -0.144 | -0.071 |
| 4 vs 1 | 0.033 | 0.021 | NS | -0.008 | 0.075 |
| 5 vs 1 | 0.066 | 0.022 | ** | 0.022 | 0.109 |
| HCC Score | | | | | |
| 1 vs 0 | 0.114 | 0.014 | *** | 0.088 | 0.141 |
| 2 vs 0 | 0.255 | 0.022 | *** | 0.211 | 0.299 |
| 3+ vs 0 | 0.599 | 0.033 | *** | 0.535 | 0.664 |
| Married | | | | | |
| Yes vs No | -0.098 | 0.013 | *** | -0.123 | -0.074 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 0.077 | 0.013 | *** | 0.052 | 0.102 |
| Surgery, no radiation vs Surgery + radiation | 0.304 | 0.056 | *** | 0.194 | 0.414 |
| Race | | | | | |
| Asian vs White | -0.182 | 0.023 | *** | -0.226 | -0.138 |
| Black vs White | 0.023 | 0.025 | NS | -0.026 | 0.073 |
| Hispanic vs White | -0.046 | 0.024 | NS | -0.094 | 0.001 |
| Stage | | | | | |
| II vs I | 0.059 | 0.013 | *** | 0.033 | 0.090 |
| III vs I | 0.152 | 0.024 | *** | 0.104 | 0.200 |
| Age | 0.010 | 0.001 | *** | 0.008 | 0.011 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-2. LOS*

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| MPR | -0.701 | 0.309 | * | -1.305 | -0.096 |
| Year | | | | | |
| 2 vs 1 | -1.403 | 0.328 | *** | -2.047 | -0.759 |
| 3 vs 1 | -0.882 | 0.370 | * | -1.607 | -0.157 |
| 4 vs 1 | 0.949 | 0.438 | * | 0.091 | 1.808 |
| 5 vs 1 | 0.724 | 0.383 | NS | -0.026 | 1.475 |
| HCC Score | | | | | |
| 1 vs 0 | 1.490 | 0.247 | *** | 1.006 | 1.974 |
| 2 vs 0 | 3.102 | 0.381 | *** | 2.354 | 3.849 |
| 3+ vs 0 | 8.179 | 0.628 | *** | 6.949 | 9.409 |
| Married | | | | | |
| Yes vs No | -2.036 | 0.215 | *** | -2.458 | -1.614 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 1.322 | 0.237 | *** | 0.858 | 1.787 |
| Surgery, no radiation vs Surgery + radiation | 4.842 | 1.198 | *** | 2.494 | 7.189 |
| Race | | | | | |
| Asian vs White | -2.255 | 0.390 | *** | -3.019 | -1.491 |
| Black vs White | 0.840 | 0.567 | NS | -0.271 | 1.951 |
| Hispanic vs White | -0.851 | 0.424 | * | -1.683 | -0.020 |
| Stage | | | | | |
| II vs I | 1.070 | 0.246 | *** | 0.588 | 1.552 |
| III vs I | 2.248 | 0.524 | *** | 1.221 | 3.275 |
| Age | 0.190 | 0.020 | *** | 0.151 | 0.229 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-3. No. of Outpatient Visits*

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| MPR | -0.230 | 0.103 | * | -0.431 | -0.029 |
| Year | | | | | |
| 2 vs 1 | -1.370 | 0.132 | *** | -1.628 | -1.112 |
| 3 vs 1 | -1.620 | 0.132 | *** | -1.878 | -1.361 |
| 4 vs 1 | -1.844 | 0.132 | *** | -2.103 | -1.585 |
| 5 vs 1 | -1.752 | 0.137 | *** | -2.020 | -1.485 |
| HCC Score | | | | | |
| 1 vs 0 | 0.757 | 0.093 | *** | 0.575 | 0.940 |
| 2 vs 0 | 1.651 | 0.143 | *** | 1.371 | 1.930 |
| 3+ vs 0 | 3.277 | 0.187 | *** | 2.911 | 3.643 |
| Married | | | | | |
| Yes vs No | -0.246 | 0.082 | ** | -0.406 | -0.085 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -0.463 | 0.082 | *** | -0.623 | -0.303 |
| Surgery, no radiation vs Surgery + radiation | -0.522 | 0.266 | NS | -1.044 | -0.001 |
| Race | | | | | |
| Asian vs White | -1.212 | 0.166 | *** | -1.537 | -0.886 |
| Black vs White | 1.080 | 0.195 | *** | 0.697 | 1.463 |
| Hispanic vs White | 0.216 | 0.180 | NS | -0.138 | 0.570 |
| Stage | | | | | |
| II vs I | 0.847 | 0.087 | *** | 0.676 | 1.018 |
| III vs I | 1.276 | 0.157 | *** | 0.968 | 1.583 |
| Age | -0.059 | 0.006 | *** | -0.072 | -0.046 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-4. No. of Physician Office Visits*

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| MPR | -1.233 | 0.257 | *** | -1.736 | -0.729 |
| Year | | | | | |
| 2 vs 1 | -4.469 | 0.327 | *** | -5.110 | -3.829 |
| 3 vs 1 | -5.454 | 0.326 | *** | -6.093 | -4.815 |
| 4 vs 1 | -5.773 | 0.329 | *** | -6.419 | -5.128 |
| 5 vs 1 | -6.128 | 0.337 | *** | -6.788 | -5.468 |
| HCC Score | | | | | |
| 1 vs 0 | 3.756 | 0.235 | *** | 3.294 | 4.217 |
| 2 vs 0 | 7.022 | 0.360 | *** | 6.316 | 7.728 |
| 3+ vs 0 | 14.854 | 0.487 | *** | 13.900 | 15.808 |
| Married | | | | | |
| Yes vs No | 0.040 | 0.207 | NS | -0.366 | 0.446 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -1.893 | 0.204 | *** | -2.293 | -1.493 |
| Surgery, no radiation vs Surgery + radiation | -1.230 | 0.680 | NS | -2.563 | 0.104 |
| Race | | | | | |
| Asian vs White | -2.075 | 0.448 | *** | -2.954 | -1.196 |
| Black vs White | -1.614 | 0.408 | *** | -2.415 | -0.814 |
| Hispanic vs White | -0.506 | 0.431 | NS | -1.352 | 0.339 |
| Stage | | | | | |
| II vs I | 0.654 | 0.215 | ** | 0.232 | 1.076 |
| III vs I | 0.334 | 0.356 | NS | -0.364 | 1.032 |
| Age | 0.014 | 0.016 | NS | -0.018 | 0.046 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

## C-5. Total Healthcare Costs

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| MPR | 579 | 358 | NS | -123 | 1,282 |
| Year | | | | | |
| 2 vs 1 | -6,919 | 365 | *** | -7,633 | -6,205 |
| 3 vs 1 | -7,389 | 400 | *** | -8,173 | -6,605 |
| 4 vs 1 | -7,127 | 428 | *** | -7,967 | -6,288 |
| 5 vs 1 | -9,523 | 432 | *** | -10,369 | -8,676 |
| HCC Score | | | | | |
| 1 vs 0 | 3,668 | 296 | *** | 3,087 | 4,249 |
| 2 vs 0 | 7,373 | 461 | *** | 6,469 | 8,277 |
| 3+ vs 0 | 17,036 | 748 | *** | 15,571 | 18,501 |
| Married | | | | | |
| Yes vs No | -1,637 | 264 | *** | -2,155 | -1,120 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 276 | 270 | NS | -253 | 804 |
| Surgery, no radiation vs Surgery + radiation | 2,108 | 906 | * | 333 | 3,884 |
| Race | | | | | |
| Asian vs White | -200 | 594 | NS | -1,364 | 965 |
| Black vs White | 1,837 | 636 | ** | 592 | 3,083 |
| Hispanic vs White | 1,588 | 592 | ** | 427 | 2,749 |
| Stage | | | | | |
| II vs I | 1,832 | 280 | *** | 1,283 | 2,380 |
| III vs I | 3,687 | 500 | *** | 2,707 | 4,667 |
| Age | 26 | 21 | NS | -15 | 68 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

## C-6. Total Non-drug Medical Costs

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| MPR | -2,716 | 322 | *** | -3,347 | -2,086 |
| Year | | | | | |
| 2 vs 1 | -6,404 | 362 | *** | -7,114 | -5,695 |
| 3 vs 1 | -5,964 | 391 | *** | -6,731 | -5,196 |
| 4 vs 1 | -4,681 | 420 | *** | -5,504 | -3,858 |
| 5 vs 1 | -6,363 | 418 | *** | -7,183 | -5,543 |
| HCC Score | | | | | |
| 1 vs 0 | 2,298 | 274 | *** | 1,761 | 2,836 |
| 2 vs 0 | 5,107 | 432 | *** | 4,260 | 5,955 |
| 3+ vs 0 | 13,098 | 708 | *** | 11,711 | 14,485 |
| Married | | | | | |
| Yes vs No | -1,115 | 245 | *** | -1,596 | -634 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -216 | 249 | NS | -703 | 272 |
| Surgery, no radiation vs Surgery + radiation | 2,306 | 869 | ** | 604 | 4,009 |
| Race | | | | | |
| Asian vs White | -1,633 | 553 | ** | -2,717 | -549 |
| Black vs White | 1,277 | 591 | * | 119 | 2,435 |
| Hispanic vs White | 1,328 | 568 | * | 215 | 2,441 |
| Stage | | | | | |
| II vs I | 1,489 | 258 | *** | 984 | 1,995 |
| III vs I | 3,670 | 477 | *** | 2,736 | 4,603 |
| Age | 51 | 20 | * | 12 | 89 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

## C-7. Medication Costs

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| MPR | 3,637 | 101 | *** | 3,440 | 3,834 |
| Year | | | | | |
| 2 vs 1 | -767 | 91 | *** | -946 | -589 |
| 3 vs 1 | -1,589 | 98 | *** | -1,782 | -1,396 |
| 4 vs 1 | -2,514 | 100 | *** | -2,711 | -2,317 |
| 5 vs 1 | -3,221 | 105 | *** | -3,427 | -3,016 |
| HCC Score | | | | | |
| 1 vs 0 | 1,476 | 81 | *** | 1,317 | 1,635 |
| 2 vs 0 | 2,428 | 128 | *** | 2,178 | 2,678 |
| 3+ vs 0 | 4,270 | 184 | *** | 3,909 | 4,631 |
| Married | | | | | |
| Yes vs No | -505 | 68 | *** | -639 | -371 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 553 | 74 | *** | 408 | 697 |
| Surgery, no radiation vs Surgery + radiation | -109 | 214 | NS | -528 | 310 |
| Race | | | | | |
| Asian vs White | 1,444 | 194 | *** | 1,063 | 1,825 |
| Black vs White | 378 | 141 | ** | 102 | 653 |
| Hispanic vs White | 286 | 124 | * | 44 | 528 |
| Stage | | | | | |
| II vs I | 209 | 73 | ** | 65 | 353 |
| III vs I | -84 | 117 | NS | -314 | 145 |
| Age | -28 | 5 | *** | -38 | -18 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*Appendix D. Association between Adherent and Nonadherent Breast Cancer Patients with Medicare Coverage and Healthcare Utilization and Costs over the Full Course of Treatment*

## D-1. No. of Hospitalization

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -0.083 | 0.013 | *** | -0.108 | -0.058 |
| Year | | | | | |
| 2 vs 1 | -0.131 | 0.018 | *** | -0.166 | -0.096 |
| 3 vs 1 | -0.105 | 0.019 | *** | -0.142 | -0.069 |
| 4 vs 1 | 0.034 | 0.021 | NS | -0.007 | 0.075 |
| 5 vs 1 | 0.062 | 0.022 | ** | 0.019 | 0.105 |
| HCC Score | | | | | |
| 1 vs 0 | 0.115 | 0.014 | *** | 0.089 | 0.142 |
| 2 vs 0 | 0.256 | 0.023 | *** | 0.212 | 0.301 |
| 3+ vs 0 | 0.583 | 0.033 | *** | 0.518 | 0.649 |
| Married | | | | | |
| Yes vs No | -0.096 | 0.013 | *** | -0.120 | -0.071 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 0.072 | 0.013 | *** | 0.047 | 0.097 |
| Surgery, no radiation vs Surgery + radiation | 0.284 | 0.056 | *** | 0.174 | 0.394 |
| Race | | | | | |
| Asian vs White | -0.167 | 0.022 | *** | -0.211 | -0.123 |
| Black vs White | 0.018 | 0.025 | NS | -0.030 | 0.067 |
| Hispanic vs White | -0.022 | 0.025 | NS | -0.072 | 0.027 |
| Stage | | | | | |
| II vs I | 0.063 | 0.013 | *** | 0.037 | 0.089 |
| III vs I | 0.133 | 0.024 | *** | 0.087 | 0.180 |
| Age | 0.009 | 0.001 | *** | 0.007 | 0.011 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-2. LOS*

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -0.607 | 0.215 | ** | -1.028 | -0.187 |
| Year | | | | | |
| 2 vs 1 | -1.378 | 0.294 | *** | -1.953 | -0.803 |
| 3 vs 1 | -0.841 | 0.316 | ** | -1.460 | -0.221 |
| 4 vs 1 | 1.018 | 0.376 | ** | 0.281 | 1.755 |
| 5 vs 1 | 0.751 | 0.362 | * | 0.042 | 1.460 |
| HCC Score | | | | | |
| 1 vs 0 | 1.495 | 0.214 | *** | 1.076 | 1.914 |
| 2 vs 0 | 3.109 | 0.368 | *** | 2.388 | 3.831 |
| 3+ vs 0 | 8.199 | 0.645 | *** | 6.936 | 9.463 |
| Married | | | | | |
| Yes vs No | -2.046 | 0.199 | *** | -2.436 | -1.656 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 1.331 | 0.211 | *** | 0.917 | 1.746 |
| Surgery, no radiation vs Surgery + radiation | 4.816 | 1.135 | *** | 2.591 | 7.040 |
| Race | | | | | |
| Asian vs White | -2.255 | 0.329 | *** | -2.899 | -1.611 |
| Black vs White | 0.848 | 0.495 | NS | -0.122 | 1.818 |
| Hispanic vs White | -0.846 | 0.369 | * | -1.570 | -0.123 |
| Stage | | | | | |
| II vs I | 1.067 | 0.228 | *** | 0.621 | 1.514 |
| III vs I | 2.253 | 0.451 | *** | 1.368 | 3.137 |
| Age | 0.191 | 0.019 | *** | 0.154 | 0.227 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-3. No. of Outpatient Visits*

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -0.141 | 0.080 | NS | -0.298 | 0.015 |
| Year | | | | | |
| 2 vs 1 | -1.351 | 0.130 | *** | -1.607 | -1.096 |
| 3 vs 1 | -1.599 | 0.130 | *** | -1.854 | -1.343 |
| 4 vs 1 | -1.825 | 0.130 | *** | -2.080 | -1.570 |
| 5 vs 1 | -1.733 | 0.135 | *** | -1.997 | -1.469 |
| HCC Score | | | | | |
| 1 vs 0 | 0.756 | 0.093 | *** | 0.573 | 0.939 |
| 2 vs 0 | 1.651 | 0.143 | *** | 1.371 | 1.932 |
| 3+ vs 0 | 3.271 | 0.187 | *** | 2.904 | 3.637 |
| Married | | | | | |
| Yes vs No | -0.252 | 0.082 | ** | -0.413 | -0.091 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -0.464 | 0.082 | *** | -0.624 | -0.304 |
| Surgery, no radiation vs Surgery + radiation | -0.538 | 0.265 | * | -1.058 | -0.018 |
| Race | | | | | |
| Asian vs White | -1.176 | 0.166 | *** | -1.500 | -0.851 |
| Black vs White | 1.079 | 0.195 | *** | 0.696 | 1.462 |
| Hispanic vs White | 0.204 | 0.181 | NS | -0.151 | 0.559 |
| Stage | | | | | |
| II vs I | 0.847 | 0.087 | *** | 0.677 | 1.018 |
| III vs I | 1.277 | 0.157 | *** | 0.969 | 1.584 |
| Age | -0.059 | 0.006 | *** | -0.071 | -0.046 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-4. No. of Physician Office Visits*

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -1.116 | 0.200 | *** | -1.507 | -0.724 |
| Year | | | | | |
| 2 vs 1 | -4.432 | 0.325 | *** | -5.068 | -3.795 |
| 3 vs 1 | -5.382 | 0.324 | *** | -6.016 | -4.748 |
| 4 vs 1 | -5.679 | 0.327 | *** | -6.319 | -5.039 |
| 5 vs 1 | -6.090 | 0.333 | *** | -6.743 | -5.436 |
| HCC Score | | | | | |
| 1 vs 0 | 3.762 | 0.235 | *** | 3.301 | 4.224 |
| 2 vs 0 | 7.038 | 0.360 | *** | 6.332 | 7.745 |
| 3+ vs 0 | 14.873 | 0.487 | *** | 13.918 | 15.827 |
| Married | | | | | |
| Yes vs No | 0.024 | 0.207 | NS | -0.383 | 0.430 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -1.884 | 0.204 | *** | -2.285 | -1.484 |
| Surgery, no radiation vs Surgery + radiation | -1.258 | 0.679 | NS | -2.589 | 0.074 |
| Race | | | | | |
| Asian vs White | -2.069 | 0.448 | *** | -2.947 | -1.190 |
| Black vs White | -1.605 | 0.408 | *** | -2.405 | -0.805 |
| Hispanic vs White | -0.488 | 0.432 | NS | -1.334 | 0.358 |
| Stage | | | | | |
| II vs I | 0.651 | 0.215 | ** | 0.229 | 1.072 |
| III vs I | 0.345 | 0.356 | NS | -0.354 | 1.044 |
| Age | 0.015 | 0.016 | NS | -0.017 | 0.046 |

## D-5. Total Healthcare Costs

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | 146 | 263 | NS | -369 | 661 |
| Year | | | | | |
| 2 vs 1 | -7,009 | 363 | *** | -7,720 | -6,298 |
| 3 vs 1 | -7,494 | 397 | *** | -8,271 | -6,717 |
| 4 vs 1 | -7,245 | 423 | *** | -8,074 | -6,416 |
| 5 vs 1 | -9,660 | 428 | *** | -10,499 | -8,821 |
| HCC Score | | | | | |
| 1 vs 0 | 3,672 | 296 | *** | 3,091 | 4,253 |
| 2 vs 0 | 7,388 | 462 | *** | 6,482 | 8,293 |
| 3+ vs 0 | 17,052 | 747 | *** | 15,588 | 18,517 |
| Married | | | | | |
| Yes vs No | -1,643 | 264 | *** | -2,160 | -1,126 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 269 | 269 | NS | -259 | 797 |
| Surgery, no radiation vs Surgery + radiation | 2,089 | 904 | * | 318 | 3,861 |
| Race | | | | | |
| Asian vs White | -158 | 597 | NS | -1,329 | 1,013 |
| Black vs White | 1,867 | 635 | ** | 621 | 3,112 |
| Hispanic vs White | 1,600 | 591 | ** | 441 | 2,759 |
| Stage | | | | | |
| II vs I | 1,846 | 279 | *** | 1,298 | 2,394 |
| III vs I | 3,677 | 499 | *** | 2,700 | 4,655 |
| Age | 25 | 21 | NS | -16 | 66 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

## D-6. Total Non-drug Medical Costs

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -2,243 | 250 | *** | -2,733 | -1,753 |
| Year | | | | | |
| 2 vs 1 | -6,257 | 355 | *** | -6,953 | -5,562 |
| 3 vs 1 | -5,760 | 383 | *** | -6,511 | -5,010 |
| 4 vs 1 | -4,448 | 410 | *** | -5,252 | -3,643 |
| 5 vs 1 | -6,171 | 413 | *** | -6,981 | -5,360 |
| HCC Score | | | | | |
| 1 vs 0 | 2,302 | 273 | *** | 1,768 | 2,837 |
| 2 vs 0 | 5,129 | 432 | *** | 4,283 | 5,976 |
| 3+ vs 0 | 13,102 | 707 | *** | 11,717 | 14,488 |
| Married | | | | | |
| Yes vs No | -1,128 | 245 | *** | -1,608 | -647 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -207 | 248 | NS | -693 | 279 |
| Surgery, no radiation vs Surgery + radiation | 2,232 | 865 | * | 536 | 3,928 |
| Race | | | | | |
| Asian vs White | -1,689 | 537 | ** | -2,741 | -637 |
| Black vs White | 1,308 | 590 | * | 151 | 2,465 |
| Hispanic vs White | 1,350 | 569 | * | 235 | 2,466 |
| Stage | | | | | |
| II vs I | 1,461 | 255 | *** | 960 | 1,961 |
| III vs I | 3,724 | 481 | *** | 2,781 | 4,666 |
| Age | 53 | 20 | ** | 15 | 91 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

## D-7. Medication Costs

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | 2,302 | 63 | *** | 2,179 | 2,426 |
| Year | | | | | |
| 2 vs 1 | -960 | 88 | *** | -1,133 | -786 |
| 3 vs 1 | -1,900 | 93 | *** | -2,082 | -1,718 |
| 4 vs 1 | -2,909 | 94 | *** | -3,093 | -2,724 |
| 5 vs 1 | -3,592 | 97 | *** | -3,783 | -3,402 |
| HCC Score | | | | | |
| 1 vs 0 | 1,413 | 80 | *** | 1,257 | 1,569 |
| 2 vs 0 | 2,376 | 127 | *** | 2,128 | 2,624 |
| 3+ vs 0 | 4,211 | 192 | *** | 3,835 | 4,588 |
| Married | | | | | |
| Yes vs No | -477 | 69 | *** | -612 | -342 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 502 | 73 | *** | 359 | 646 |
| Surgery, no radiation vs Surgery + radiation | -100 | 206 | NS | -503 | 303 |
| Race | | | | | |
| Asian vs White | 1,514 | 190 | *** | 1,142 | 1,886 |
| Black vs White | 430 | 140 | ** | 156 | 704 |
| Hispanic vs White | 299 | 124 | * | 57 | 541 |
| Stage | | | | | |
| II vs I | 304 | 77 | *** | 154 | 454 |
| III vs I | -64 | 112 | NS | -283 | 155 |
| Age | -32 | 5 | *** | -41 | -22 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | P2 | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | P2 |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | P3 | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | P5 | | |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | P5 | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | P6 | | |

| | | | | | |
|---|---|---|---|---|---|
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | P6 | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | P6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | P6-7 | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | P7 |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | P7 | | |

| | | | | | |
|---|---|---|---|---|---|
| Bias | 9 | Describe any efforts to address potential sources of bias | P11-12 | | |
| Study size | 10 | Explain how the study size was arrived at | P8 | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | Supplementary material: Appendix B | | |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | P7-8 | | |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. | P8 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | Supplement material: Appendix A | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | Table 1 | | |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure | Table 2, Table 3 | | |

| | | | | | |
|---|---|---|---|---|---|
| | | category, or summary measures of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 4, Table 5 | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | N/A | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | P10-11 | | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | P11-12 | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, | P10-12 | | |

| | | | | | |
|---|---|---|---|---|---|
| | | limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | P12 | | |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | P1 | | |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | P5 |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

# The Impact of Medication Adherence on Non-Drug Healthcare Utilization and Costs: A retrospective longitudinal cohort study among U.S. women age 65 and older

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**Title Page**

# The Impact of Medication Adherence on Non-Drug Healthcare Utilization and Costs: A retrospective longitudinal cohort study among U.S. women age 65 and older

Siyu Ma, Ph.D. , Donald S. Shepard, Ph.D. , Grant A Ritter, Ph.D. , Robert E Martell, MD , Cindy Parks Thomas, Ph.D.

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*Ethics approval statement*: the Brandeis Committee for Protection of Human Subjects, operating under Federal wide Assurance #FWA00004408, has deemed the protocol for this study (#18136) to be exempt from further IRB oversight in accordance with 45 CFR 46.101(b) (4).

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## Abstract

Word count: 252

**Objectives:** To explore the impact of hormone therapy (HT) adherence on non-drug healthcare utilization and healthcare costs among breast cancer patients.

**Design:** Retrospective longitudinal cohort study

**Setting:** The U.S. Medicare beneficiaries in the SEER-Medicare-linked database

**Participants:** Women aged >= 65 with hormone-receptor positive breast cancer from 2007 through mid-2009 in the U.S.

**Interventions**: We examined the relationship between HT and adherence and outcomes of our interests.

**Primary and secondary outcome measures**: our study cohort's HT adherence, non-drug healthcare utilization and healthcare costs for the first year of HT and each year thereafter for a total of five years.

**Results:** 6,045 eligible Medicare beneficiaries that met our selection criteria were included. We found that patients who were adherent to HT were associated with lower healthcare utilization of all kinds (inpatient [0.35 vs 0.43, P<0.001], length of study during hospitalization [4.19 vs 4.89, P<0.01] and physician office visits [25.16 vs 26.17, P<0.001]), and significant reductions in many types of medical costs and neutral total healthcare costs despite the increased pharmacy costs. Half of total medical cost reduction came from savings in hospitalization costs.

**Conclusions:** Our study suggests that the added cost of HT adherence was all but offset by the reduced cost for other medical care. Our study provides evidence on the potential success of

implementing value-based insurance design (VBID) plans among breast cancer patients to improve their long-term oral medication adherence. Policy makers should consider adherence improvement strategies such as VBID plans, given that the costs likely will not surpass the total savings.

**Strength and limitations**

1. First of its kind to reveal the impact of copayment reduction on HT adherence among the dual eligible breast cancer patients among Medicare patients in the US over the full course of five years treatment.
2. Used advanced statistical methods to derive the most accurate estimates possible for the effects of type of Medicaid coverage on our two outcomes (i.e., propensity score methodology to minimize potential selection bias due to non-random assignment of the treatment group, and longitudinal hierarchical modeling to control for correlated data within patients.)
3. Unable to precisely calculate the filled prescriptions or the drug costs due to data limitations.

## Introduction

Breast cancer is the most commonly diagnosed non-skin cancer among U.S. women, representing 30% of all new cancer cases in 2020.[1] With improved screening and treatment, the U.S. breast cancer death rate has been decreasing by 1.8% each year over the past decade and the current 5-year survival rate is about 90% [2]. As more patients are living with breast cancer, the associated healthcare costs have also been increasing. Breast cancer accounts for the largest share of national expenditure for cancer care. It increased from $16.5 billion in 2010 to $19.7 billion in 2018 [3].

Hormone receptor (HR) positive breast cancer subtype accounts for over 80% of total breast cancer. Among HR positive breast cancer patients, adjuvant endocrine (or hormone) therapy has been incorporated as part of the treatment regime after surgical removal of the tumor[4-7]. There are several types of hormone therapy medications, including tamoxifen and aromatase inhibitors (AIs). AIs are a newer generation of adjuvant hormone therapy (HT) medications for postmenopausal women, including anastrozole, letrozole, and exemestane. Clinical evidence showed that AIs are more effective than tamoxifen in improving survival and reducing disease recurrence among postmenopausal women [8]. In order to achieve the most desired health benefits, the American Society of Clinical Oncology (ASCO) recommended HT treatment for at least 5 years [9]. However, long-term HT adherence remains suboptimal. This is problematic, because failure to complete a full course of treatment compromises health benefits and often results in treatment failure[10-12].

Previous studies showed that improved medication adherence may associate with lower total healthcare costs, even though it may increase pharmacy costs. The increase in pharmacy

costs due to medication adherence is often offset by savings in other non-drug medical costs, as overall health improves [13-15]. For example, in a four-state study of dual eligible Medicare/Medicaid beneficiaries with congestive heart failure (CHF), patients who were found to be adherent to their prescribed medication regimes were 4% less likely to be hospitalized and 3.0% less likely to visit the emergency department (ED). In total, their total healthcare costs per year were $5,910 (23%) lower than beneficiaries found to be non-adherent [16]. Roebuck *et al.* examined privately insured patients with four chronic conditions (CHF, hypertension, diabetes, and dyslipidemia) and found that medication adherence was associated with 1.18 (for dyslipidemia) to 5.72 (for CHF) fewer days in inpatient stays, 0.01 to 0.04 reduction in ED visits, and a corresponding $1,258 (for dyslipidemia) to $7,823 (for CHF) reduction in total annual healthcare [15]. Boye *et al*. examined type 2 diabetes patients and found that every 1% increase in medication adherence was associated with on average $65,464 all-cause cost savings among 1,000 patients, similarly driven by the lowered probability of hospitalizations and ED visits [17].

While a myriad of studies have found an inverse relationship between medication adherence and non-drug healthcare utilization and total healthcare costs, most of them focused on chronic cardiovascular diseases. Only a few studies explored the association between medication adherence and non-drug healthcare utilizations and costs among breast cancer patients. One four-year longitudinal study of Medicaid beneficiaries with breast cancer from South Carolina found that HT adherence was associated with 31% decrease in medical costs, but no significant savings in total healthcare cost. The different results between medical and total healthcare costs could be due to adverse events associated with long-term use of hormone therapy [18]. While this finding was informative, more research focusing on breast cancer patients among a broader sample of Medicare beneficiaries is needed. In this study, we used a nationally

representative sample of Medicare beneficiaries to examine the relationships between HT adherence and non-drug healthcare utilization and healthcare costs. The objective of our study is to answer the research questions of what are the impacts of HT adherence on non-drug healthcare utilization and healthcare costs among breast cancer patients? We hypothesize that the non-drug healthcare utilization will be lower among breast cancer patients who adhere to HT compared to those who do not. Furthermore, HT adherent patients will have higher prescription drug costs, but lower non-drug costs, and lower or no difference in total healthcare costs compared to non-adherent patients.

## Method

### *Data Source*

We used SEER-Medicare linked database for the years of 2007 – 2014. The National Cancer Institute's SEER database is the only database that includes comprehensive population-based information on breast cancer patients' demographics, cancer diagnosis, time of diagnosis, and initial therapy (surgery and/or radiation). At the time of this study, SEER covered 34.6% of the U.S. population. The linked Medicare component includes beneficiaries' enrollment, prescription drug use and costs, and non-drug healthcare utilization and costs information [19].

### *Study Sample*

Our study sample is women diagnosed with HR- positive early stage breast cancer in years 2007 to mid-2009 in the US. Other criteria for inclusion were: 1) 65 years or older, 2) no missing race value, 3) with only one breast cancer diagnosis within the study period, 4) initiated AI treatment within the first year of breast cancer diagnosis, 5) continuously enrolled in Medicare

Part A and Part B and Part D from diagnosis data through five years after the first filled AI prescription or until dead, whichever came first (gaps of 45 days or less allowed), 6) did not spend a full year in an inpatient facility (i.e., hospital, or skilled nurse facility). The screening process for constructing our study cohort can be found in supplementary material (Appendix A).

*Variables*

**Dependent variables**

We examined the non-drug healthcare utilization and healthcare costs for the patients' first year of AI treatment and each year thereafter for a total of five years (year 1 through year 5). Variables of non-drug healthcare utilization included any hospitalization, length of stay (LOS), and numbers of inpatient, outpatient (including unplanned emergency room visits), and physician office visits. Healthcare costs included all-cause non-drug medical costs (inpatient, outpatient and physician office visits costs), all-cause prescription costs, and the sum of the two as total healthcare costs. All costs were measured by the total amount paid by Medicare and standardized to 2014 dollars using the medical care component of the consumer price index (https ://www.bls.gov/cpi/).

**Treatment variables**

A patient's adherence to AI treatment was based on the medication possession ratio (MPR), calculated as the number of days of AI supplied divided by the number of days covered in a year. A patient's inpatient days were excluded from the denominator because AI medications may have come from another source during an inpatient stay and not be reflected in Medicare Part D data. Each patient had update to 5 MPRs: first year of AI treatment and each year thereafter for a total of five years (year 1 through year 5). If a patient died, he/she was excluded from the

following years. MPR values in years when patients were alive but did not fill any AI prescriptions were set to 0. MPR as capped at 100% if numerator is greater than denominator due to early refills. As a sensitivity analysis, we also analyzed an 'adherence' indicator variable with value 1, if the patient's MPR for the year was 80% or more [20-24].

**Covariates**

Time invariant covariates used in our analyses included a patient's race/ethnicity, marital status, tumor stage, and certain treatment characteristics. Two time variant covariates were included in our analyses: patient's age at the start of each year (years 1 through year 5); and the patient's Hierarchical Condition Category [HCC] score. HCC score is a risk adjustment factor based on a patient's comorbidities. Our analyses also included variables representing calendar years to address the concurrent trends in healthcare utilization and costs. The descriptions of full list of our variables are shown in supplementary material (Appendix B).

*Data Analysis*

We first examined the distributions of all independent variables, including patients' MPR and adherence value and then calculated summary statistics on outcomes each year (year 1 through year 5): any hospitalization (yes or no), or outpatient visits (yes or no), numbers of inpatient stays, number of outpatient clinic visits, or number physician office visits, and mean LOS associated with hospitalization. We also calculated the average healthcare costs to Medicare including non-drug medical costs, prescription drug costs and total healthcare costs.

Based on preliminary descriptive and bivariate analyses, we determined the appropriate statistical modeling methods for each of our outcome measures as described in the following, and selected covariates to include as adjustors. Zero inflated negative binomial models was

adopted to predict LOS and the numbers of hospitalization stays and outpatient visits, and negative binomial models was used to predict the number of physician office visits. For outpatient, non-drug medical, prescription drug, and total medical costs, we restricted our sample to positive observations and used generalized linear models (GLMs) with log link and gamma distribution for estimation. For hospitalization costs, we adopted a two-part model, since only approximately 20% of our study sample had hospitalizations. In this model, the first part was a logistic regression model to predict the likelihood of having a nonzero hospitalization costs, and the second part of the model used GLM to estimate the nonzero hospitalization costs. All statistical analysis was conducted using SAS v9.3 [25] or Stata 14 [26] where applicable.

Patient and Public Involvement statement: patients and or public were not involved.

## Results

There were 6,045 eligible Medicare beneficiaries who met our sample selection criteria. The average age of our study cohort was 74.6 years old. The majority identified as non-Hispanic White (83.8%), with the rest (16.2%) identifying as non-Hispanic Black, Hispanic, or Asian (Table 1).

Table 2 shows the summary statistics for treatment variables and outcome variables (including non-drug healthcare utilization and healthcare costs) over the 5-year course of treatment. The average MPR was the highest in the first year of treatment (79%) and lowest in the fifth year (54%) of treatment. The percentage of patients who were adherent in each of the 5 years (i.e., MPR>=80%) ranged from 39.4% to 64.2%. On average, about 20% of surviving patients each year had at least one hospitalization event, while about 90% had at least one outpatient visit, and approximately 99% had at least one physician office visit. Among those with at least one

hospitalization in each year, the mean number of inpatient stays was 1.9-2.2 and mean LOS was 22.0-24.4 days. The mean annual total healthcare costs ranged from $12,970 to $21,431 over the 5 years of AI treatment (this translates to $14,957 to $24,714 in 2021 US dollars), while medication costs accounted for 22% to 31% of the total healthcare costs each year ($2,875 - $6,664).

Table 3 presents the unadjusted annual non-drug healthcare utilization and costs in adherent and non-adherent Medicare beneficiaries across their 5 years of treatment. For year three through year five, a significantly lower percentage of adherent beneficiaries had at least one hospitalization compared to non-adherent beneficiaries. Among those with hospitalizations, however, neither number of stays nor mean LOS were statistically significant different in any year. Conversely, the percent of adherent beneficiaries who had any outpatient visits was higher than the percent of non-adherent beneficiaries in the fourth year and lower in the fifth year, while no statistically significant differences in the rest of the years. Across the five years, adherent patients (MPR greater or equal to 80%) had consistently fewer physician office visits than non-adherent patients. In general, adherent beneficiaries had lower medical costs, but higher medication costs than nonadherent beneficiaries, which led to slightly higher total healthcare costs among adherent beneficiaries compared to non-adherent beneficiaries.

Results of adjusted models predicting the association between MPR and non-drug healthcare utilization and costs are shown in Table 4. The results showed that the increased MPR was statistically significantly associated with fewer hospitalizations, shorter LOS, and fewer outpatient visits (including emergency room visits), and fewer physician office visits. MPR was also positively associated with medication costs, and negatively associated with total medical costs. However, the difference in total healthcare costs is not statistically significant. Table 5 shows the results of adjusted models using the alternative indicator of adherence instead of the continuous

MPR measure. Table 5 results indicate that healthcare utilization measures are always lower for adherent beneficiaries compared to nonadherent beneficiaries. Adherent beneficiaries had fewer hospitalizations (0.35 vs 0.43, P<0.001) and fewer physician office visits (25.16 vs 26.17, P<0.001), and shorter LOS during hospitalization (4.19 vs 4.89, P<0.01). On average, Medicare paid $2,314 (P<0.001) more on medications for adherent beneficiaries, but $2,242 (P<0.001) less on total non-drug medical costs. This resulted in no statistically significant difference in total Medicare healthcare costs. Each line of results in Tables 4 and 5 were generated by an individual multivariant regression analysis as indicated in the method section. Full results could be found in supplementary material (Appendix C and Appendix D).

## Discussion

Our study explored the relationships between hormone therapy adherence and non-drug healthcare utilization and costs among breast cancer patients. To our knowledge, this is one of the first studies to examine the association of medication adherence and non-drug healthcare utilization and costs across the full five-year course of treatment and among a sample of patients as diverse as that provided by the SEER-Medicare database. We found that patients who were adherent to HT were associated with fewer inpatient, outpatient and physician office visits. Consistent with previous studies[15,17,18], we also found that patients who were adherent to HT were associated with significant reductions in many types of medical costs as well as total medical costs. Half of the reduction in total medical cost came from savings in hospitalizations. This is expected, since staying on hormone therapy for at least 5 years, as clinical guidelines recommend, reduces the likelihood of breast cancer recurrence. From this analysis, we find that adherent patients are more likely to avoid a recurrence of breast cancer and the associated costs

for related treatment. Our findings suggest that the added cost of hormone therapy adherence is all but offset by the reduced cost for other categories of medical care.

To determine the contingent effect of medication adherence on health care utilization and costs, we included unalterable patient level factors in our models such as age, race, and tumor stage at time of diagnosis. These factors are known to be strongly associated with adherence and thus also impact utilization and costs. However, they are not factors that clinicians and policy makers can directly change. Nevertheless, earlier analyses have identified two manageable factors that could improve adherence, and by doing so, impact health care utilization and costs: care coordination for comorbid health conditions; and financial help with medication copayments [27,28]. Systematic care coordination among health service providers to address comorbid health conditions is possible, but is usually considered costly to implement [27]. This study does indicate, however, that the additional cost would be limited to the care coordination itself. The added costs of medication due to higher adherence would be, for the most part, offset by lower non-drug medical costs.

Value-based insurance design (VBID) plans are designed to offer high-value healthcare at reduced out-of-pocket costs (OOPCs) to patients with certain diagnoses and/or socioeconomic status.[29] Some Medicare Advantage plans have adopted the VBID model to manage beneficiary healthcare costs while maintaining healthcare quality. For example, Medicare Advantage patients with certain chronic diseases may see reduced copayments for medications.[29] An study from 2020 found that lower OOPCs were associated with enhanced long-term medication treatment among Medicare beneficiaries with breast cancer. [28] The authors also showed that eliminating cost-sharing was associated with improved adherence among breast cancer patients who were Medicare/Medicaid dual eligibles.[30] By reducing the copayments for these patients, VBID plans

aim to improve medication adherence and avoid other costly medical services. The findings from our study further support this concept: improved medication adherence did not result in increased total healthcare use and costs, even though it drove up the pharmacy costs.

The benefit of conducting our study using claims data is that the data contains real-world information on hormone therapy adherence and non-drug healthcare utilization and costs. However, there are also some limitations. First, we used Medicare Part D data to calculate MPR to indicate adherence. Filled prescriptions do not necessarily mean that all were consumed by the patient. In addition, our results do not reflect some cases where a patient may have supplementary insurance to cover their medication costs or in the event that a patient switched from aromatase inhibitor to other hormone therapy medications (i.e., tamoxifen). Secondly, the drug costs were calculated by using the gross drug costs (consisting of ingredient cost, dispensing fee, and total amount attributed to sales tax). However, Medicare drug plans may receive rebates from pharmaceutical companies for these medications, which is confidential information. The actual Medicare payment amount for medications may be less than the total of gross drug costs reported. Therefore, it is likely that our study overestimated the pharmacy costs. Thirdly, the costs of breast cancer management may be different throughout years due to advances in the prevention, screening, and treatment of breast cancer. We were unable to capture all the impacts of these advances throughout years, however, we included variables representing calendar years to address these concurrent trends. Finally, we do not know if the reduced medical costs and healthcare utilization were solely associated with better adherence. It is possible that patients who were more adherent to hormone therapy treatment were more likely to be adherent to other non-drug treatments and/or have a healthier lifestyle, which could have biased the results

away from the null. It would be meaningful for future studies to separate these effects from medication adherence.

**Conclusions**

Our study is one of the first to analyze the association between hormone therapy adherence and non-drug healthcare utilization and costs among Medicare beneficiaries over the full course of treatment. Our results suggested that better adherence is associated with lower healthcare utilization of all kinds (inpatient, outpatient and physician office visits) and no change in total healthcare costs despite the increased pharmacy costs. Our study also provides insights into the potential benefits of implementing VBID plans among breast cancer patients to improve their long-term oral medication adherence. Policy makers should consider adherence improvement strategies such as VBID plans given the potential health benefits, and that the costs likely will not surpass the total savings.

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# Tables

*Table 1. Baseline Characteristics of Eligible Medicare Beneficiaries with Hormone Receptor Positive Early Stage Breast Cancer Who Initiated Aromatase Inhibitor Treatment within the First Year of Diagnosis (n=6,045)*

| Characteristics | No. (%)[a] |
|---|---|
| **Median age, years (range)** | 74.6 (65 - 103) |
| **Age Group** | |
| 65-69 | 1,748 (28.9) |
| 70-74 | 1,537 (25.4) |
| 75-79 | 1,242 (20.6) |
| 80+ | 1,518 (25.1) |
| **Race/Ethnicity** | |
| White, non-Hispanic | 5,068 (83.8) |
| Black | 392 (6.5) |
| Hispanic | 334 (5.5) |
| Asian | 251 (4.2) |
| **Comorbidity (HCC score)** | |
| 0 | 2,098 (36.9) |
| 1 | 1,504 (26.5) |
| 2 | 918 (16.2) |
| 3+ | 1,161 (20.4) |
| **Marital Status** | |
| Married | 2,570 (42.5) |
| Unmarried | 3,475 (57.5) |
| **Tumor stage** | |
| I | 3,297 (54.5) |
| II | 2,124 (35.1) |
| III | 624 (10.3) |
| **Treatment** | |
| Surgery + radiation | 3,155 (52.2) |
| Surgery, no radiation | 2,709 (44.8) |
| No surgery | 181 (3.0) |

*Note: a. values are number (percentage) unless indicated otherwise*

*Table 2. Hormone Therapy Adherence, Healthcare Utilization and Costs over the Full Course of Aromatase Inhibitor Treatment among Medicare Beneficiaries with Breast Cancer*

| Variables | Year 1 (n=6,045) | Year 2 (n=5,847) | Year 3 (n=5,592) | Year 4 (n=5,322) | Year 5 (n=4,993) |
|---|---|---|---|---|---|
| *Treatment variables* | | | | | |
| MPR, mean (SD) | 0.79 (0.27) | 0.62 (0.39) | 0.61 (0.41) | 0.61 (0.43) | 0.54 (0.41) |
| Adherence (MPR>=80%), n (%) | 3,878 (64.2) | 2,855 (48.8) | 2,837 (50.7) | 2,848 (53.5) | 1,848 (39.4) |
| *Outcome variables* | | | | | |
| **Healthcare Utilization** | | | | | |
| Any hospitalization, n (%) | 1,166 (19.3) | 862 (14.7) | 873 (15.6) | 1,123 (21.1) | 1,174 (23.5) |
| No. of hospitalization (>0), mean (SD) | 2.0 (1.7) | 1.9 (1.5) | 2.0 (1.5) | 2.2 (1.9) | 2.2 (1.7) |
| No. of hospital days (>0), mean (SD) | 23.4 (47.2) | 22.9 (46.3) | 22.0 (38.5) | 24.3 (41.5) | 24.4 (41.8) |
| Any outpatient visits, n (%) | 5,636 (93.2) | 5,281 (90.3) | 4,969 (88.9) | 4,693 (88.2) | 4,395 (88.0) |
| No. of outpatient visits, mean (SD) | 7.7 (7.7) | 6.5 (7.4) | 6.1 (7.1) | 5.9 (6.8) | 6.0 (7.3) |
| Any physician office visits, n (%) | 6,041 (99.9) | 5,832 (99.7) | 5,567 (99.5) | 5,297 (99.5) | 4,956 (99.3) |
| No. of physician office visits, mean (SD) | 29.2 (17.6) | 25.4 (17.2) | 24.7 (17.6) | 24.3 (18.1) | 24.1 (18.4) |
| **Healthcare Costs** | | | | | |
| Medicare Payment Amount, $ mean (median) | | | | | |
| Total healthcare costs | 21,431 (14,508) | 15,204 (9,757) | 14,884 (8,657) | 15,362 (7,664) | 12,970 (5,438) |
| Total medical costs | 14,767 (7,586) | 9,630 (4,223) | 10,148 (4,047) | 11,611 (3,950) | 10,096 (2,894) |
| Hospitalization costs (>0) | 22,700 (12,654) | 22,084 (13,114) | 23,853 (15,309) | 25,461 (15,894) | 20,993 (11,515) |
| Outpatient costs | 3,708 (1,232) | 1,916 (671) | 1,976 (617) | 1,918 (571) | 1,556 (390) |
| Physician costs | 6,680 (3,942) | 4,458 (2,886) | 4,448 (2,767) | 4,319 (2,600) | 3,604 (1,926) |
| Total pharmacy costs | 6,664 (5,677) | 5,574 (4,623) | 4,735 (3,475) | 3,751 (2,371) | 2,875 (1,452) |

3

*Table 3. Unadjusted Annual Healthcare Utilization and Costs in Adherent and Nonadherent Medicare Beneficiaries with Breast Cancer over the Full Course of Treatment*

| Variables | Adherent | Non-Adherent | P |
|---|---|---|---|
| **Healthcare Utilization** | | | |
| Any hospitalization, n (%) | | | |
| Year 1 | 729 (18.8) | 437 (20.2) | NS |
| Year 2 | 395 (13.8) | 467 (15.6) | NS |
| Year 3 | 404 (14.2) | 469 (17.0) | *<0.01* |
| Year 4 | 521 (18.3) | 602 (24.3) | *<0.001* |
| Year 5 | 417 (21.2) | 757 (25.0) | *<0.01* |
| No. of hospitalization (>0), mean (SD) | | | |
| Year 1 | 2.0 (1.7) | 2.1 (1.7) | NS |
| Year 2 | 1.8 (1.4) | 2.0 (1.5) | NS |
| Year 3 | 2.0 (1.4) | 2.0 (1.5) | NS |
| Year 4 | 2.1 (1.8) | 2.2 (1.9) | NS |
| Year 5 | 2.1 (1.8) | 2.2 (1.7) | NS |
| No. of hospital days (>0), mean (SD) | | | |
| Year 1 | 25.5 (53.8) | 19.9 (33.0) | *<0.05* |
| Year 2 | 22.3 (49.4) | 23.5 (43.5) | NS |
| Year 3 | 23.3 (41.8) | 20.8 (35.3) | NS |
| Year 4 | 24.8 (45.7) | 23.8 (37.6) | NS |
| Year 5 | 23.7 (38.0) | 24.8 (43.8) | NS |
| Any outpatient visits, n (%) | | | |
| Year 1 | 3,612 (93.1) | 2,024 (93.4) | NS |
| Year 2 | 2,600 (91.1) | 2,681 (89.6) | NS |
| Year 3 | 2,537 (89.4) | 2,432 (88.3) | NS |
| Year 4 | 2,564 (90.0) | 2,129 (86.1) | *<0.001* |
| Year 5 | 1,766 (89.8) | 2,629 (86.9) | *<0.01* |
| No. of outpatient visits, mean (SD) | | | |
| Year 1 | 7.7 (7.6) | 7.9 (7.9) | NS |
| Year 2 | 6.5 (7.4) | 6.4 (7.4) | NS |
| Year 3 | 6.2 (7.2) | 6.0 (7.0) | NS |
| Year 4 | 5.9 (6.8) | 5.9 (6.8) | NS |
| Year 5 | 6.1 (7.2) | 5.9 (7.4) | NS |
| No. of physician office visits, mean (SD) | | | |
| Year 1 | 28.5 (17.3) | 30.3 (18.1) | *<0.001* |

(continued the next page)

| Variables | Adherent | Non-Adherent | P |
|---|---|---|---|
| Year 2 | 25.2 (16.8) | 25.6 (17.5) | NS |
| Year 3 | 24.4 (16.5) | 25.0 (18.6) | NS |
| Year 4 | 23.9 (17.3) | 24.9 (18.9) | *<0.05* |
| Year 5 | 23.8 (18.1) | 24.3 (18.5) | NS |
| **Healthcare Costs** | | | |
| Medicare Payment Amount | | | |
| Total healthcare costs, $ mean (median) | | | |
| Year 1 | 22,025 (15,502) | 20,370 (12,604) | *<0.01* |
| Year 2 | 16,624 (11,434) | 13,849 (8,072) | *<0.001* |
| Year 3 | 15,110 (9,865) | 14,651 (7,488) | NS |
| Year 4 | 14,563 (7,906) | 16,283 (7,347) | *<0.01* |
| Year 5 | 12,758 (5,837) | 13,109 (5,238) | NS |
| Total medical costs, $ mean (median) | | | |
| Year 1 | 14,306 (7,513) | 15,594 (7,775) | *<0.05* |
| Year 2 | 9,090 (4,111) | 10,144 (4,324) | *<0.05* |
| Year 3 | 9,025 (3,923) | 11,304 (4,209) | *<0.001* |
| Year 4 | 10,067 (3,688) | 13,389 (4,283) | *<0.001* |
| Year 5 | 9,103 (2,772) | 10,741 (2,981) | *<0.01* |
| Total hospitalization costs, $ mean (median) | | | |
| Year 1 | 22,176 (12,654) | 23,574 (12,775) | NS |
| Year 2 | 22,136 (12,462) | 22,040 (13,620) | NS |
| Year 3 | 23,036 (16,120) | 24,558 (14,584) | NS |
| Year 4 | 24,799 (15,880) | 26,035 (16,034) | NS |
| Year 5 | 20,213 (11,477) | 21,424 (11,569) | NS |
| Total outpatient costs, $ mean (median) | | | |
| Year 1 | 4,528 (2,035) | 5,151 (2,177) | NS |
| Year 2 | 3,380 (1,514) | 3,768 (1,481) | NS |
| Year 3 | 3,527 (1,549) | 4,316 (1,483) | NS |
| Year 4 | 3,485 (1,597) | 3,991 (1,420) | NS |
| Year 5 | 3,010 (943) | 2,925 (1,019) | NS |
| Total physician costs, $ mean (median) | | | |
| Year 1 | 9,602 (6,915) | 11,352 (8,175) | *<0.01* |
| Year 2 | 8,325 (6,093) | 8,323 (6,250) | NS |
| Year 3 | 8,289 (6,290) | 8,892 (6,128) | NS |

(continued the next page)

| Variables | Adherent | Non-Adherent | P |
|---|---|---|---|
| Year 4 | 7,639 (5,697) | 9,069 (6,308) | *<0.01* |
| Year 5 | 6,366 (4,588) | 6,810 (4,737) | NS |
| Total pharmacy costs, $ mean (median) | | | |
| Year 1 | 7,719 (6,561) | 4,776 (4,090) | *<0.001* |
| Year 2 | 7,534 (6,443) | 3,705 (3,150) | *<0.001* |
| Year 3 | 6,084 (5,032) | 3,347 (2,539) | *<0.001* |
| Year 4 | 4,495 (2,951) | 2,893 (1,847) | *<0.001* |
| Year 5 | 3,656 (1,954) | 2,367 (1,235) | *<0.001* |

*Note: NS stands for not significant*

*Table 4. Adjusted Healthcare Utilization and Costs among Medicare Beneficiaries with Breast Cancer over the Full Course of Treatment*

| Variables | MPR[a] | P |
|---|---|---|
| **Healthcare Utilization** | | |
| No. of hospitalizations[b] | -0.009 | *<0.001* |
| No. of hospital days | -0.088 | *<0.01* |
| No. of outpatient visits | -0.018 | NS |
| No. of physician office visits | -0.111 | *<0.001* |
| **Healthcare Costs** | | |
| Medicare Payment Amount | | |
| Total healthcare costs | 51 | NS |
| Total medical costs | -281 | *<0.001* |
| Total hospitalization costs | -109 | *<0.001* |
| Total outpatient costs | -52 | *<0.001* |
| Total physician costs | -105 | *<0.001* |
| Total pharmacy costs | 365 | *<0.001* |

*Notes: NS stands for not significant*

a. *The prediction model controlled for other covariate, full results see Supplementary Material (Appendix C).*
b. *An example for interpreting the finding: every 10% increase in MPR was associated with 0.009 less number of hospitalizations (p<0.001)*

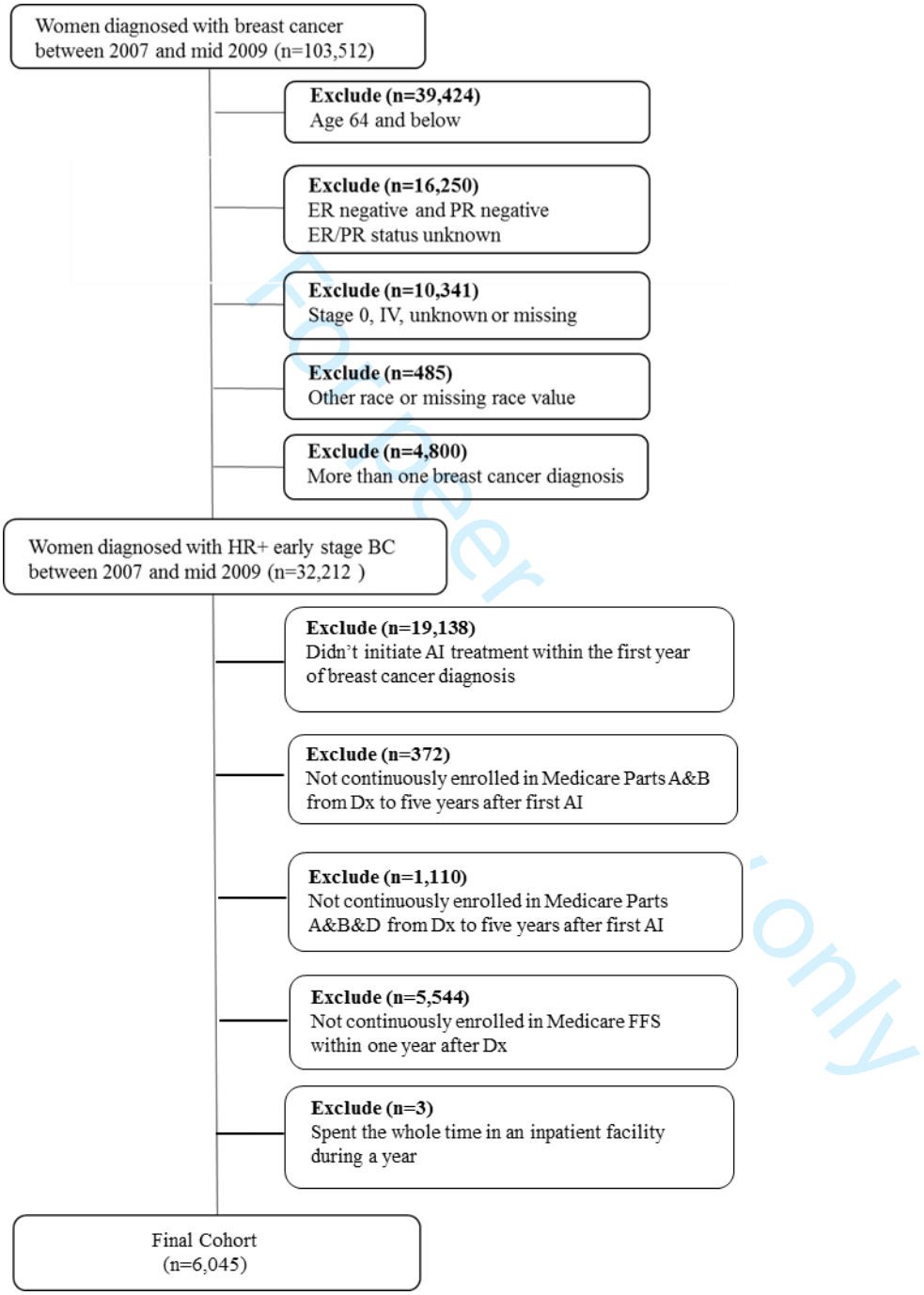
*Table 5. Adjusted Healthcare Utilization and Costs for Medicare Beneficiaries Adherent and Nonadherent to Hormone therapy over the Full Course of Treatment*

| **Variables** | **Adherent[a]** | **Non-Adherent** | **Difference** | **P[b]** |
|---|---|---|---|---|
| **Healthcare Utilization** | Margin (SE) | Margin (SE) | Margin (SE) | |
| No. of hospitalization | 0.35 (0.01) | 0.43 (0.01) | -0.08 (0.01) | *<0.001* |
| No. of hospital days | 4.19 (0.16) | 4.89 (0.18) | -0.70 (0.22) | *<0.01* |
| No. of outpatient visits | 6.45 (0.05) | 6.54 (0.06) | -0.09 (0.08) | NS |
| No. of physician office visits | 25.16 (0.13) | 26.17 (0.14) | -1.02 (0.20) | *<0.001* |
| **Healthcare Costs** | | | | |
| Medicare Payment Amount | | | | |
| Total healthcare costs | 16,246 (164) | 16,077 (200) | 169 (262) | NS |
| Medical costs | 10,310 (152) | 12,551 (195) | -2,242 (249) | *<0.001* |
| Hospitalization costs | 3,811 (115) | 4,840 (141) | -1,028 (183) | *<0.001* |
| Outpatient costs | 2,070 (37) | 2,484 (54) | -414 (65) | *<0.001* |
| Physician costs | 4,389 (47) | 5,190 (63) | -801 (77) | *<0.001* |
| Pharmacy costs | 5,891 (46) | 3,577 (37) | 2,314 (61) | *<0.001* |

*Notes:*

a. *The prediction model controlled for other covariate, full results see Supplementary Material (Appendix D).*
b. *NS stands for not significant*

*Appendix A. Selection Criteria for Identifying Medicare Beneficiaries Diagnosed with Hormone Receptor-Positive Early Stage Breast Cancer from 2007 to Mid-2009*



*Appendix B. Descriptions of Variables*

| VARIABLE NAME | DEFINITION |
|---|---|
| **DEPENDENT VARIABLES** | |
| *Healthcare utilization* | |
| Any hospitalization | A dummy variable equal to 1 if at least one hospitalization |
| Inpatient visits | A continuous variable of number of hospitalizations |
| Length of stay | A continuous variable of number of days in hospital |
| Any outpatient visits | A dummy variable equal to 1 if at least one outpatient visits |
| Outpatient visits | A continuous variable of number of outpatient visits |
| *Healthcare costs* | |
| Total healthcare costs | A continuous variable measures the sum of non-drug medical costs and prescription drug costs |
| Non-drug medical costs | A continuous variable measures the sum of inpatient and outpatient costs |
| Inpatient costs | A subgroup of total medical costs |
| Outpatient costs | A subgroup of total medical costs |
| Prescription drug costs | A continuous variable |
| **TREATMENT VARIABLES** | |
| Adherence continuous | A continuous variable of MPR % |
| Adherence dummy | A dummy equal to 1 if MPR >=80% |
| **CONTROL VARIABLES** | |
| Race/Ethnicity | A dummy variable equal to 1 if White, non-Hispanic |
| Age continuous | A continuous variable, 65+ years old |
| Married | A dummy variable equal to 1 if married |
| Tumor Stage | A categorical variable where<br>1 Stage I<br>2 Stage II<br>3 Stage III |
| Initial Surgery/Radiation Treatment | A categorical variable where<br>1 No surgery<br>2 Surgery (breast-conserving surgery or mastectomy) + radiation<br>3 Surgery, no radiation |

| | |
|---|---|
| HCC Risk Score (see detailed construction description on NCI website: https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity.html) | A categorical variable where<br>1 0<br>2 1<br>3 2<br>4 3+ |

*Appendix C. Association between Medication Possession Ratio and Healthcare Utilization and Costs among Medicare Beneficiaries with Breast Cancer over the Full Course of Treatment, controlling for covariates*

*C-1. No. of Hospitalization*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | -0.083 | 0.013 | *** | -0.108 | -0.058 |
| Year | | | | | |
| 2 vs 1 | -0.132 | 0.018 | *** | -0.167 | -0.096 |
| 3 vs 1 | -0.108 | 0.019 | *** | -0.144 | -0.071 |
| 4 vs 1 | 0.033 | 0.021 | NS | -0.008 | 0.075 |
| 5 vs 1 | 0.066 | 0.022 | ** | 0.022 | 0.109 |
| HCC Score | | | | | |
| 1 vs 0 | 0.114 | 0.014 | *** | 0.088 | 0.141 |
| 2 vs 0 | 0.255 | 0.022 | *** | 0.211 | 0.299 |
| 3+ vs 0 | 0.599 | 0.033 | *** | 0.535 | 0.664 |
| Married | | | | | |
| Yes vs No | -0.098 | 0.013 | *** | -0.123 | -0.074 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 0.077 | 0.013 | *** | 0.052 | 0.102 |
| Surgery, no radiation vs Surgery + radiation | 0.304 | 0.056 | *** | 0.194 | 0.414 |
| Race | | | | | |
| Asian vs White | -0.182 | 0.023 | *** | -0.226 | -0.138 |
| Black vs White | 0.023 | 0.025 | NS | -0.026 | 0.073 |
| Hispanic vs White | -0.046 | 0.024 | NS | -0.094 | 0.001 |
| Stage | | | | | |
| II vs I | 0.059 | 0.013 | *** | 0.033 | 0.090 |
| III vs I | 0.152 | 0.024 | *** | 0.104 | 0.200 |
| Age | 0.010 | 0.001 | *** | 0.008 | 0.011 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-2. LOS*

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| MPR | -0.701 | 0.309 | * | -1.305 | -0.096 |
| Year | | | | | |
| 2 vs 1 | -1.403 | 0.328 | *** | -2.047 | -0.759 |
| 3 vs 1 | -0.882 | 0.370 | * | -1.607 | -0.157 |
| 4 vs 1 | 0.949 | 0.438 | * | 0.091 | 1.808 |
| 5 vs 1 | 0.724 | 0.383 | NS | -0.026 | 1.475 |
| HCC Score | | | | | |
| 1 vs 0 | 1.490 | 0.247 | *** | 1.006 | 1.974 |
| 2 vs 0 | 3.102 | 0.381 | *** | 2.354 | 3.849 |
| 3+ vs 0 | 8.179 | 0.628 | *** | 6.949 | 9.409 |
| Married | | | | | |
| Yes vs No | -2.036 | 0.215 | *** | -2.458 | -1.614 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 1.322 | 0.237 | *** | 0.858 | 1.787 |
| Surgery, no radiation vs Surgery + radiation | 4.842 | 1.198 | *** | 2.494 | 7.189 |
| Race | | | | | |
| Asian vs White | -2.255 | 0.390 | *** | -3.019 | -1.491 |
| Black vs White | 0.840 | 0.567 | NS | -0.271 | 1.951 |
| Hispanic vs White | -0.851 | 0.424 | * | -1.683 | -0.020 |
| Stage | | | | | |
| II vs I | 1.070 | 0.246 | *** | 0.588 | 1.552 |
| III vs I | 2.248 | 0.524 | *** | 1.221 | 3.275 |
| Age | 0.190 | 0.020 | *** | 0.151 | 0.229 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-3. No. of Outpatient Visits*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | -0.230 | 0.103 | * | -0.431 | -0.029 |
| Year | | | | | |
| 2 vs 1 | -1.370 | 0.132 | *** | -1.628 | -1.112 |
| 3 vs 1 | -1.620 | 0.132 | *** | -1.878 | -1.361 |
| 4 vs 1 | -1.844 | 0.132 | *** | -2.103 | -1.585 |
| 5 vs 1 | -1.752 | 0.137 | *** | -2.020 | -1.485 |
| HCC Score | | | | | |
| 1 vs 0 | 0.757 | 0.093 | *** | 0.575 | 0.940 |
| 2 vs 0 | 1.651 | 0.143 | *** | 1.371 | 1.930 |
| 3+ vs 0 | 3.277 | 0.187 | *** | 2.911 | 3.643 |
| Married | | | | | |
| Yes vs No | -0.246 | 0.082 | ** | -0.406 | -0.085 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -0.463 | 0.082 | *** | -0.623 | -0.303 |
| Surgery, no radiation vs Surgery + radiation | -0.522 | 0.266 | NS | -1.044 | -0.001 |
| Race | | | | | |
| Asian vs White | -1.212 | 0.166 | *** | -1.537 | -0.886 |
| Black vs White | 1.080 | 0.195 | *** | 0.697 | 1.463 |
| Hispanic vs White | 0.216 | 0.180 | NS | -0.138 | 0.570 |
| Stage | | | | | |
| II vs I | 0.847 | 0.087 | *** | 0.676 | 1.018 |
| III vs I | 1.276 | 0.157 | *** | 0.968 | 1.583 |
| Age | -0.059 | 0.006 | *** | -0.072 | -0.046 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-4. No. of Physician Office Visits*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | -1.233 | 0.257 | *** | -1.736 | -0.729 |
| Year | | | | | |
| 2 vs 1 | -4.469 | 0.327 | *** | -5.110 | -3.829 |
| 3 vs 1 | -5.454 | 0.326 | *** | -6.093 | -4.815 |
| 4 vs 1 | -5.773 | 0.329 | *** | -6.419 | -5.128 |
| 5 vs 1 | -6.128 | 0.337 | *** | -6.788 | -5.468 |
| HCC Score | | | | | |
| 1 vs 0 | 3.756 | 0.235 | *** | 3.294 | 4.217 |
| 2 vs 0 | 7.022 | 0.360 | *** | 6.316 | 7.728 |
| 3+ vs 0 | 14.854 | 0.487 | *** | 13.900 | 15.808 |
| Married | | | | | |
| Yes vs No | 0.040 | 0.207 | NS | -0.366 | 0.446 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -1.893 | 0.204 | *** | -2.293 | -1.493 |
| Surgery, no radiation vs Surgery + radiation | -1.230 | 0.680 | NS | -2.563 | 0.104 |
| Race | | | | | |
| Asian vs White | -2.075 | 0.448 | *** | -2.954 | -1.196 |
| Black vs White | -1.614 | 0.408 | *** | -2.415 | -0.814 |
| Hispanic vs White | -0.506 | 0.431 | NS | -1.352 | 0.339 |
| Stage | | | | | |
| II vs I | 0.654 | 0.215 | ** | 0.232 | 1.076 |
| III vs I | 0.334 | 0.356 | NS | -0.364 | 1.032 |
| Age | 0.014 | 0.016 | NS | -0.018 | 0.046 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-5. Total Healthcare Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | 579 | 358 | NS | -123 | 1,282 |
| Year | | | | | |
| 2 vs 1 | -6,919 | 365 | *** | -7,633 | -6,205 |
| 3 vs 1 | -7,389 | 400 | *** | -8,173 | -6,605 |
| 4 vs 1 | -7,127 | 428 | *** | -7,967 | -6,288 |
| 5 vs 1 | -9,523 | 432 | *** | -10,369 | -8,676 |
| HCC Score | | | | | |
| 1 vs 0 | 3,668 | 296 | *** | 3,087 | 4,249 |
| 2 vs 0 | 7,373 | 461 | *** | 6,469 | 8,277 |
| 3+ vs 0 | 17,036 | 748 | *** | 15,571 | 18,501 |
| Married | | | | | |
| Yes vs No | -1,637 | 264 | *** | -2,155 | -1,120 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 276 | 270 | NS | -253 | 804 |
| Surgery, no radiation vs Surgery + radiation | 2,108 | 906 | * | 333 | 3,884 |
| Race | | | | | |
| Asian vs White | -200 | 594 | NS | -1,364 | 965 |
| Black vs White | 1,837 | 636 | ** | 592 | 3,083 |
| Hispanic vs White | 1,588 | 592 | ** | 427 | 2,749 |
| Stage | | | | | |
| II vs I | 1,832 | 280 | *** | 1,283 | 2,380 |
| III vs I | 3,687 | 500 | *** | 2,707 | 4,667 |
| Age | 26 | 21 | NS | -15 | 68 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-6. Total Non-drug Medical Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | -2,716 | 322 | *** | -3,347 | -2,086 |
| Year | | | | | |
| 2 vs 1 | -6,404 | 362 | *** | -7,114 | -5,695 |
| 3 vs 1 | -5,964 | 391 | *** | -6,731 | -5,196 |
| 4 vs 1 | -4,681 | 420 | *** | -5,504 | -3,858 |
| 5 vs 1 | -6,363 | 418 | *** | -7,183 | -5,543 |
| HCC Score | | | | | |
| 1 vs 0 | 2,298 | 274 | *** | 1,761 | 2,836 |
| 2 vs 0 | 5,107 | 432 | *** | 4,260 | 5,955 |
| 3+ vs 0 | 13,098 | 708 | *** | 11,711 | 14,485 |
| Married | | | | | |
| Yes vs No | -1,115 | 245 | *** | -1,596 | -634 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -216 | 249 | NS | -703 | 272 |
| Surgery, no radiation vs Surgery + radiation | 2,306 | 869 | ** | 604 | 4,009 |
| Race | | | | | |
| Asian vs White | -1,633 | 553 | ** | -2,717 | -549 |
| Black vs White | 1,277 | 591 | * | 119 | 2,435 |
| Hispanic vs White | 1,328 | 568 | * | 215 | 2,441 |
| Stage | | | | | |
| II vs I | 1,489 | 258 | *** | 984 | 1,995 |
| III vs I | 3,670 | 477 | *** | 2,736 | 4,603 |
| Age | 51 | 20 | * | 12 | 89 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-7. Medication Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | 3,637 | 101 | *** | 3,440 | 3,834 |
| Year | | | | | |
| 2 vs 1 | -767 | 91 | *** | -946 | -589 |
| 3 vs 1 | -1,589 | 98 | *** | -1,782 | -1,396 |
| 4 vs 1 | -2,514 | 100 | *** | -2,711 | -2,317 |
| 5 vs 1 | -3,221 | 105 | *** | -3,427 | -3,016 |
| HCC Score | | | | | |
| 1 vs 0 | 1,476 | 81 | *** | 1,317 | 1,635 |
| 2 vs 0 | 2,428 | 128 | *** | 2,178 | 2,678 |
| 3+ vs 0 | 4,270 | 184 | *** | 3,909 | 4,631 |
| Married | | | | | |
| Yes vs No | -505 | 68 | *** | -639 | -371 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 553 | 74 | *** | 408 | 697 |
| Surgery, no radiation vs Surgery + radiation | -109 | 214 | NS | -528 | 310 |
| Race | | | | | |
| Asian vs White | 1,444 | 194 | *** | 1,063 | 1,825 |
| Black vs White | 378 | 141 | ** | 102 | 653 |
| Hispanic vs White | 286 | 124 | * | 44 | 528 |
| Stage | | | | | |
| II vs I | 209 | 73 | ** | 65 | 353 |
| III vs I | -84 | 117 | NS | -314 | 145 |
| Age | -28 | 5 | *** | -38 | -18 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*Appendix D. Association between Adherent and Nonadherent Breast Cancer Patients with Medicare Coverage and Healthcare Utilization and Costs over the Full Course of Treatment*

*D-1. No. of Hospitalization*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -0.083 | 0.013 | *** | -0.108 | -0.058 |
| Year | | | | | |
| 2 vs 1 | -0.131 | 0.018 | *** | -0.166 | -0.096 |
| 3 vs 1 | -0.105 | 0.019 | *** | -0.142 | -0.069 |
| 4 vs 1 | 0.034 | 0.021 | NS | -0.007 | 0.075 |
| 5 vs 1 | 0.062 | 0.022 | ** | 0.019 | 0.105 |
| HCC Score | | | | | |
| 1 vs 0 | 0.115 | 0.014 | *** | 0.089 | 0.142 |
| 2 vs 0 | 0.256 | 0.023 | *** | 0.212 | 0.301 |
| 3+ vs 0 | 0.583 | 0.033 | *** | 0.518 | 0.649 |
| Married | | | | | |
| Yes vs No | -0.096 | 0.013 | *** | -0.120 | -0.071 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 0.072 | 0.013 | *** | 0.047 | 0.097 |
| Surgery, no radiation vs Surgery + radiation | 0.284 | 0.056 | *** | 0.174 | 0.394 |
| Race | | | | | |
| Asian vs White | -0.167 | 0.022 | *** | -0.211 | -0.123 |
| Black vs White | 0.018 | 0.025 | NS | -0.030 | 0.067 |
| Hispanic vs White | -0.022 | 0.025 | NS | -0.072 | 0.027 |
| Stage | | | | | |
| II vs I | 0.063 | 0.013 | *** | 0.037 | 0.089 |
| III vs I | 0.133 | 0.024 | *** | 0.087 | 0.180 |
| Age | 0.009 | 0.001 | *** | 0.007 | 0.011 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-2. LOS*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -0.607 | 0.215 | ** | -1.028 | -0.187 |
| Year | | | | | |
| 2 vs 1 | -1.378 | 0.294 | *** | -1.953 | -0.803 |
| 3 vs 1 | -0.841 | 0.316 | ** | -1.460 | -0.221 |
| 4 vs 1 | 1.018 | 0.376 | ** | 0.281 | 1.755 |
| 5 vs 1 | 0.751 | 0.362 | * | 0.042 | 1.460 |
| HCC Score | | | | | |
| 1 vs 0 | 1.495 | 0.214 | *** | 1.076 | 1.914 |
| 2 vs 0 | 3.109 | 0.368 | *** | 2.388 | 3.831 |
| 3+ vs 0 | 8.199 | 0.645 | *** | 6.936 | 9.463 |
| Married | | | | | |
| Yes vs No | -2.046 | 0.199 | *** | -2.436 | -1.656 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 1.331 | 0.211 | *** | 0.917 | 1.746 |
| Surgery, no radiation vs Surgery + radiation | 4.816 | 1.135 | *** | 2.591 | 7.040 |
| Race | | | | | |
| Asian vs White | -2.255 | 0.329 | *** | -2.899 | -1.611 |
| Black vs White | 0.848 | 0.495 | NS | -0.122 | 1.818 |
| Hispanic vs White | -0.846 | 0.369 | * | -1.570 | -0.123 |
| Stage | | | | | |
| II vs I | 1.067 | 0.228 | *** | 0.621 | 1.514 |
| III vs I | 2.253 | 0.451 | *** | 1.368 | 3.137 |
| Age | 0.191 | 0.019 | *** | 0.154 | 0.227 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-3. No. of Outpatient Visits*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -0.141 | 0.080 | NS | -0.298 | 0.015 |
| Year | | | | | |
| 2 vs 1 | -1.351 | 0.130 | *** | -1.607 | -1.096 |
| 3 vs 1 | -1.599 | 0.130 | *** | -1.854 | -1.343 |
| 4 vs 1 | -1.825 | 0.130 | *** | -2.080 | -1.570 |
| 5 vs 1 | -1.733 | 0.135 | *** | -1.997 | -1.469 |
| HCC Score | | | | | |
| 1 vs 0 | 0.756 | 0.093 | *** | 0.573 | 0.939 |
| 2 vs 0 | 1.651 | 0.143 | *** | 1.371 | 1.932 |
| 3+ vs 0 | 3.271 | 0.187 | *** | 2.904 | 3.637 |
| Married | | | | | |
| Yes vs No | -0.252 | 0.082 | ** | -0.413 | -0.091 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -0.464 | 0.082 | *** | -0.624 | -0.304 |
| Surgery, no radiation vs Surgery + radiation | -0.538 | 0.265 | * | -1.058 | -0.018 |
| Race | | | | | |
| Asian vs White | -1.176 | 0.166 | *** | -1.500 | -0.851 |
| Black vs White | 1.079 | 0.195 | *** | 0.696 | 1.462 |
| Hispanic vs White | 0.204 | 0.181 | NS | -0.151 | 0.559 |
| Stage | | | | | |
| II vs I | 0.847 | 0.087 | *** | 0.677 | 1.018 |
| III vs I | 1.277 | 0.157 | *** | 0.969 | 1.584 |
| Age | -0.059 | 0.006 | *** | -0.071 | -0.046 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-4. No. of Physician Office Visits*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -1.116 | 0.200 | *** | -1.507 | -0.724 |
| Year | | | | | |
| 2 vs 1 | -4.432 | 0.325 | *** | -5.068 | -3.795 |
| 3 vs 1 | -5.382 | 0.324 | *** | -6.016 | -4.748 |
| 4 vs 1 | -5.679 | 0.327 | *** | -6.319 | -5.039 |
| 5 vs 1 | -6.090 | 0.333 | *** | -6.743 | -5.436 |
| HCC Score | | | | | |
| 1 vs 0 | 3.762 | 0.235 | *** | 3.301 | 4.224 |
| 2 vs 0 | 7.038 | 0.360 | *** | 6.332 | 7.745 |
| 3+ vs 0 | 14.873 | 0.487 | *** | 13.918 | 15.827 |
| Married | | | | | |
| Yes vs No | 0.024 | 0.207 | NS | -0.383 | 0.430 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -1.884 | 0.204 | *** | -2.285 | -1.484 |
| Surgery, no radiation vs Surgery + radiation | -1.258 | 0.679 | NS | -2.589 | 0.074 |
| Race | | | | | |
| Asian vs White | -2.069 | 0.448 | *** | -2.947 | -1.190 |
| Black vs White | -1.605 | 0.408 | *** | -2.405 | -0.805 |
| Hispanic vs White | -0.488 | 0.432 | NS | -1.334 | 0.358 |
| Stage | | | | | |
| II vs I | 0.651 | 0.215 | ** | 0.229 | 1.072 |
| III vs I | 0.345 | 0.356 | NS | -0.354 | 1.044 |
| Age | 0.015 | 0.016 | NS | -0.017 | 0.046 |

*D-5. Total Healthcare Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | 146 | 263 | NS | -369 | 661 |
| Year | | | | | |
| 2 vs 1 | -7,009 | 363 | *** | -7,720 | -6,298 |
| 3 vs 1 | -7,494 | 397 | *** | -8,271 | -6,717 |
| 4 vs 1 | -7,245 | 423 | *** | -8,074 | -6,416 |
| 5 vs 1 | -9,660 | 428 | *** | -10,499 | -8,821 |
| HCC Score | | | | | |
| 1 vs 0 | 3,672 | 296 | *** | 3,091 | 4,253 |
| 2 vs 0 | 7,388 | 462 | *** | 6,482 | 8,293 |
| 3+ vs 0 | 17,052 | 747 | *** | 15,588 | 18,517 |
| Married | | | | | |
| Yes vs No | -1,643 | 264 | *** | -2,160 | -1,126 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 269 | 269 | NS | -259 | 797 |
| Surgery, no radiation vs Surgery + radiation | 2,089 | 904 | * | 318 | 3,861 |
| Race | | | | | |
| Asian vs White | -158 | 597 | NS | -1,329 | 1,013 |
| Black vs White | 1,867 | 635 | ** | 621 | 3,112 |
| Hispanic vs White | 1,600 | 591 | ** | 441 | 2,759 |
| Stage | | | | | |
| II vs I | 1,846 | 279 | *** | 1,298 | 2,394 |
| III vs I | 3,677 | 499 | *** | 2,700 | 4,655 |
| Age | 25 | 21 | NS | -16 | 66 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-6. Total Non-drug Medical Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -2,243 | 250 | *** | -2,733 | -1,753 |
| Year | | | | | |
| 2 vs 1 | -6,257 | 355 | *** | -6,953 | -5,562 |
| 3 vs 1 | -5,760 | 383 | *** | -6,511 | -5,010 |
| 4 vs 1 | -4,448 | 410 | *** | -5,252 | -3,643 |
| 5 vs 1 | -6,171 | 413 | *** | -6,981 | -5,360 |
| HCC Score | | | | | |
| 1 vs 0 | 2,302 | 273 | *** | 1,768 | 2,837 |
| 2 vs 0 | 5,129 | 432 | *** | 4,283 | 5,976 |
| 3+ vs 0 | 13,102 | 707 | *** | 11,717 | 14,488 |
| Married | | | | | |
| Yes vs No | -1,128 | 245 | *** | -1,608 | -647 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -207 | 248 | NS | -693 | 279 |
| Surgery, no radiation vs Surgery + radiation | 2,232 | 865 | * | 536 | 3,928 |
| Race | | | | | |
| Asian vs White | -1,689 | 537 | ** | -2,741 | -637 |
| Black vs White | 1,308 | 590 | * | 151 | 2,465 |
| Hispanic vs White | 1,350 | 569 | * | 235 | 2,466 |
| Stage | | | | | |
| II vs I | 1,461 | 255 | *** | 960 | 1,961 |
| III vs I | 3,724 | 481 | *** | 2,781 | 4,666 |
| Age | 53 | 20 | ** | 15 | 91 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-7. Medication Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | 2,302 | 63 | *** | 2,179 | 2,426 |
| Year | | | | | |
| 2 vs 1 | -960 | 88 | *** | -1,133 | -786 |
| 3 vs 1 | -1,900 | 93 | *** | -2,082 | -1,718 |
| 4 vs 1 | -2,909 | 94 | *** | -3,093 | -2,724 |
| 5 vs 1 | -3,592 | 97 | *** | -3,783 | -3,402 |
| HCC Score | | | | | |
| 1 vs 0 | 1,413 | 80 | *** | 1,257 | 1,569 |
| 2 vs 0 | 2,376 | 127 | *** | 2,128 | 2,624 |
| 3+ vs 0 | 4,211 | 192 | *** | 3,835 | 4,588 |
| Married | | | | | |
| Yes vs No | -477 | 69 | *** | -612 | -342 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 502 | 73 | *** | 359 | 646 |
| Surgery, no radiation vs Surgery + radiation | -100 | 206 | NS | -503 | 303 |
| Race | | | | | |
| Asian vs White | 1,514 | 190 | *** | 1,142 | 1,886 |
| Black vs White | 430 | 140 | ** | 156 | 704 |
| Hispanic vs White | 299 | 124 | * | 57 | 541 |
| Stage | | | | | |
| II vs I | 304 | 77 | *** | 154 | 454 |
| III vs I | -64 | 112 | NS | -283 | 155 |
| Age | -32 | 5 | *** | -41 | -22 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | P2 | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | P2 |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | P3 | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | P5 | | |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | P5 | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | P6 | | |

| | | | | | |
|---|---|---|---|---|---|
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | P6 | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | P6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | P6-7 | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | P7 |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | P7 | | |

| | | | | | |
|---|---|---|---|---|---|
| Bias | 9 | Describe any efforts to address potential sources of bias | P11-12 | | |
| Study size | 10 | Explain how the study size was arrived at | P8 | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | Supplementary material: Appendix B | | |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | P7-8 | | |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. | P8 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | Supplement material: Appendix A | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | Table 1 | | |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure | Table 2, Table 3 | | |

| | | | | | |
|---|---|---|---|---|---|
| | | category, or summary measures of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 4, Table 5 | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | N/A | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | P10-11 | | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | P11-12 | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, | P10-12 | | |

| | | | | | |
|---|---|---|---|---|---|
| | | limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | P12 | | |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | P1 | | |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | P5 |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

# The Association between Medication Adherence and Non-Drug Healthcare Utilization and Costs: A retrospective longitudinal cohort study among U.S. women age 65 and older



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# Title Page

**The Association between Medication Adherence and Non-Drug Healthcare Utilization and Costs: A retrospective longitudinal cohort study among U.S. women age 65 and older**

Siyu Ma, Ph.D. , Donald S. Shepard, Ph.D. , Grant A Ritter, Ph.D. , Robert E Martell, MD , Cindy Parks Thomas, Ph.D.

RUNNING TITLE: MEDICATION ADHERENCE AND HEALTHCARE UTILITZATION AND COSTS

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*Data availability statement*:
All data relevant to the study are included in the article or uploaded as supplementary information.

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## Abstract

Word count: 252

**Objectives:** To explore the association between hormone therapy (HT) adherence and non-drug healthcare utilization and healthcare costs among breast cancer patients.

**Design:** Retrospective longitudinal cohort study

**Setting:** The U.S. Medicare beneficiaries in the SEER-Medicare-linked database

**Participants:** Women aged >= 65 with hormone-receptor positive breast cancer from 2007 through mid-2009 in the U.S.

**Interventions**: We examined the relationship between HT and adherence and outcomes of our interests.

**Primary and secondary outcome measures**: our study cohort's HT adherence, non-drug healthcare utilization and healthcare costs for the first year of HT and each year thereafter for a total of five years.

**Results:** 6,045 eligible Medicare beneficiaries that met our selection criteria were included. We found that patients who were adherent to HT were associated with lower healthcare utilization of all kinds (inpatient [0.35 vs 0.43, P<0.001], length of study during hospitalization [4.19 vs 4.89, P<0.01] and physician office visits [25.16 vs 26.17, P<0.001]), and significant reductions in many types of medical costs and neutral total healthcare costs despite the increased pharmacy costs. Half of total medical cost reduction came from savings in hospitalization costs.

**Conclusions:** Our study suggests that the added cost of HT adherence was all but offset by the reduced cost for other medical care. Our study provides evidence on the potential success of

implementing value-based insurance design (VBID) plans among breast cancer patients to improve their long-term oral medication adherence. Policy makers should consider adherence improvement strategies such as VBID plans, given that the costs likely will not surpass the total savings.

**Strength and limitations**

1. First of its kind to reveal the association between HT adherence and non-drug healthcare utilization and costs among Medicare patients with breast cancer in the US over the full course of five years treatment.
2. Provided insights into the potential benefits of implementing VBID plans among breast cancer patients to improve their long-term oral medication adherence.
3. Unable to precisely calculate the filled prescriptions or the drug costs due to data limitations.

## Introduction

Breast cancer is the most commonly diagnosed non-skin cancer among U.S. women, representing 30% of all new cancer cases in 2020.[1] With improved screening and treatment, the U.S. breast cancer death rate has been decreasing by 1.8% each year over the past decade and the current 5-year survival rate is about 90% [2]. As more patients are living with breast cancer, the associated healthcare costs have also been increasing. Breast cancer accounts for the largest share of national expenditure for cancer care. It increased from $16.5 billion in 2010 to $19.7 billion in 2018 [3].

Hormone receptor (HR) positive breast cancer subtype accounts for over 80% of total breast cancer. Among HR positive breast cancer patients, adjuvant endocrine (or hormone) therapy has been incorporated as part of the treatment regime after surgical removal of the tumor[4-7]. There are several types of hormone therapy medications, including tamoxifen and aromatase inhibitors (AIs). AIs are a newer generation of adjuvant hormone therapy (HT) medications for postmenopausal women, including anastrozole, letrozole, and exemestane. Clinical evidence showed that AIs are more effective than tamoxifen in improving survival and reducing disease recurrence among postmenopausal women [8]. In order to achieve the most desired health benefits, the American Society of Clinical Oncology (ASCO) recommended HT treatment for at least 5 years [9]. However, long-term HT adherence remains suboptimal. This is problematic, because failure to complete a full course of treatment compromises health benefits and often results in treatment failure[10-12].

Previous studies showed that improved medication adherence may associate with lower total healthcare costs, even though it may increase pharmacy costs. The increase in pharmacy

costs due to medication adherence is often offset by savings in other non-drug medical costs, as overall health improves [13-15]. For example, in a four-state study of dual eligible Medicare/Medicaid beneficiaries with congestive heart failure (CHF), patients who were found to be adherent to their prescribed medication regimes were 4% less likely to be hospitalized and 3.0% less likely to visit the emergency department (ED). In total, their total healthcare costs per year were $5,910 (23%) lower than beneficiaries found to be non-adherent [16]. Roebuck *et al.* examined privately insured patients with four chronic conditions (CHF, hypertension, diabetes, and dyslipidemia) and found that medication adherence was associated with 1.18 (for dyslipidemia) to 5.72 (for CHF) fewer days in inpatient stays, 0.01 to 0.04 reduction in ED visits, and a corresponding $1,258 (for dyslipidemia) to $7,823 (for CHF) reduction in total annual healthcare [15]. Boye *et al*. examined type 2 diabetes patients and found that every 1% increase in medication adherence was associated with on average $65,464 all-cause cost savings among 1,000 patients, similarly driven by the lowered probability of hospitalizations and ED visits [17].

While a myriad of studies have found an inverse relationship between medication adherence and non-drug healthcare utilization and total healthcare costs, most of them focused on chronic cardiovascular diseases. Only a few studies explored the association between medication adherence and non-drug healthcare utilizations and costs among breast cancer patients. One four-year longitudinal study of Medicaid beneficiaries with breast cancer from South Carolina found that HT adherence was associated with 31% decrease in medical costs, but no significant savings in total healthcare cost. The different results between medical and total healthcare costs could be due to adverse events associated with long-term use of hormone therapy [18]. While this finding was informative, more research focusing on breast cancer patients among a broader sample of Medicare beneficiaries is needed. In this study, we used a nationally

representative sample of Medicare beneficiaries to examine the relationships between HT adherence and non-drug healthcare utilization and healthcare costs. The objective of our study is to answer the research questions of what are the association between HT adherence and non-drug healthcare utilization and healthcare costs among breast cancer patients? We hypothesize that the non-drug healthcare utilization will be lower among breast cancer patients who adhere to HT compared to those who do not. Furthermore, HT adherent patients will have higher prescription drug costs, but lower non-drug costs, and lower or no difference in total healthcare costs compared to non-adherent patients.

## Method

### *Data Source*

We used SEER-Medicare linked database for the years of 2007 – 2014. The National Cancer Institute's SEER database is the only database that includes comprehensive population-based information on breast cancer patients' demographics, cancer diagnosis, time of diagnosis, and initial therapy (surgery and/or radiation). At the time of this study, SEER covered 34.6% of the U.S. population. The linked Medicare component includes beneficiaries' enrollment, prescription drug use and costs, and non-drug healthcare utilization and costs information [19].

### *Study Sample*

Our study sample is women diagnosed with HR- positive early stage breast cancer in years 2007 to mid-2009 in the US. Other criteria for inclusion were: 1) 65 years or older, 2) no missing race value, 3) with only one breast cancer diagnosis within the study period, 4) initiated AI treatment within the first year of breast cancer diagnosis, 5) continuously enrolled in Medicare

Part A and Part B and Part D from diagnosis data through five years after the first filled AI prescription or until dead, whichever came first (gaps of 45 days or less allowed), 6) did not spend a full year in an inpatient facility (i.e., hospital, or skilled nurse facility). The screening process for constructing our study cohort can be found in supplementary material (Appendix A).

*Variables*

**Dependent variables**

We examined the non-drug healthcare utilization and healthcare costs for the patients' first year of AI treatment and each year thereafter for a total of five years (year 1 through year 5). Variables of non-drug healthcare utilization included any hospitalization, length of stay (LOS), and numbers of inpatient, outpatient (including unplanned emergency room visits), and physician office visits. Healthcare costs included all-cause non-drug medical costs (inpatient, outpatient and physician office visits costs), all-cause prescription costs, and the sum of the two as total healthcare costs. All costs were measured by the total amount paid by Medicare and standardized to 2014 dollars using the medical care component of the consumer price index (https ://www.bls.gov/cpi/).

**Treatment variables**

A patient's adherence to AI treatment was based on the medication possession ratio (MPR), calculated as the number of days of AI supplied divided by the number of days covered in a year. A patient's inpatient days were excluded from the denominator because AI medications may have come from another source during an inpatient stay and not be reflected in Medicare Part D data. Each patient had update to 5 MPRs: first year of AI treatment and each year thereafter for a total of five years (year 1 through year 5). If a patient died, he/she was excluded from the

following years. MPR values in years when patients were alive but did not fill any AI prescriptions were set to 0. MPR as capped at 100% if numerator is greater than denominator due to early refills. As a sensitivity analysis, we also analyzed an 'adherence' indicator variable with value 1, if the patient's MPR for the year was 80% or more [20-24].

**Covariates**

Time invariant covariates used in our analyses included a patient's race/ethnicity, marital status, tumor stage, and certain treatment characteristics. Two time variant covariates were included in our analyses: patient's age at the start of each year (years 1 through year 5); and the patient's Hierarchical Condition Category [HCC] score. HCC score is a risk adjustment factor based on a patient's comorbidities. Our analyses also included variables representing calendar years to address the concurrent trends in healthcare utilization and costs. The descriptions of full list of our variables are shown in supplementary material (Appendix B).

*Data Analysis*

We first examined the distributions of all independent variables, including patients' MPR and adherence value and then calculated summary statistics on outcomes each year (year 1 through year 5): any hospitalization (yes or no), or outpatient visits (yes or no), numbers of inpatient stays, number of outpatient clinic visits, or number physician office visits, and mean LOS associated with hospitalization. We also calculated the average healthcare costs to Medicare including non-drug medical costs, prescription drug costs and total healthcare costs.

Based on preliminary descriptive and bivariate analyses, we determined the appropriate statistical modeling methods for each of our outcome measures as described in the following, and selected covariates to include as adjustors. Zero inflated negative binomial models was

adopted to predict LOS and the numbers of hospitalization stays and outpatient visits, and negative binomial models was used to predict the number of physician office visits. For outpatient, non-drug medical, prescription drug, and total medical costs, we restricted our sample to positive observations and used generalized linear models (GLMs) with log link and gamma distribution for estimation. For hospitalization costs, we adopted a two-part model, since only approximately 20% of our study sample had hospitalizations. In this model, the first part was a logistic regression model to predict the likelihood of having a nonzero hospitalization costs, and the second part of the model used GLM to estimate the nonzero hospitalization costs. All statistical analysis was conducted using SAS v9.3 [25] or Stata 14 [26] where applicable.

*Patient and Public Involvement statement*

Patients and or public were not involved.

## Results

There were 6,045 eligible Medicare beneficiaries who met our sample selection criteria. The average age of our study cohort was 74.6 years old. The majority identified as non-Hispanic White (83.8%), with the rest (16.2%) identifying as non-Hispanic Black, Hispanic, or Asian (Table 1).

Table 2 shows the summary statistics for treatment variables and outcome variables (including non-drug healthcare utilization and healthcare costs) over the 5-year course of treatment. The average MPR was the highest in the first year of treatment (79%) and lowest in the fifth year (54%) of treatment. The percentage of patients who were adherent in each of the 5 years (i.e., MPR>=80%) ranged from 39.4% to 64.2%. On average, about 20% of surviving patients each year

had at least one hospitalization event, while about 90% had at least one outpatient visit, and approximately 99% had at least one physician office visit. Among those with at least one hospitalization in each year, the mean number of inpatient stays was 1.9-2.2 and mean LOS was 22.0-24.4 days. The mean annual total healthcare costs ranged from $12,970 to $21,431 over the 5 years of AI treatment (this translates to $14,957 to $24,714 in 2021 US dollars), while medication costs accounted for 22% to 31% of the total healthcare costs each year ($2,875 - $6,664).

Table 3 presents the unadjusted annual non-drug healthcare utilization and costs in adherent and non-adherent Medicare beneficiaries across their 5 years of treatment. For year three through year five, a significantly lower percentage of adherent beneficiaries had at least one hospitalization compared to non-adherent beneficiaries. Among those with hospitalizations, however, neither number of stays nor mean LOS were statistically significant different in any year. Conversely, the percent of adherent beneficiaries who had any outpatient visits was higher than the percent of non-adherent beneficiaries in the fourth year and lower in the fifth year, while no statistically significant differences in the rest of the years. Across the five years, adherent patients (MPR greater or equal to 80%) had consistently fewer physician office visits than non-adherent patients. In general, adherent beneficiaries had lower medical costs, but higher medication costs than nonadherent beneficiaries, which led to slightly higher total healthcare costs among adherent beneficiaries compared to non-adherent beneficiaries.

Results of adjusted models predicting the association between MPR and non-drug healthcare utilization and costs are shown in Table 4. The results showed that the increased MPR was statistically significantly associated with fewer hospitalizations, shorter LOS, and fewer outpatient visits (including emergency room visits), and fewer physician office visits. MPR was also positively associated with medication costs, and negatively associated with total medical costs.

However, the difference in total healthcare costs is not statistically significant. Table 5 shows the results of adjusted models using the alternative indicator of adherence instead of the continuous MPR measure. Table 5 results indicate that healthcare utilization measures are always lower for adherent beneficiaries compared to nonadherent beneficiaries. Adherent beneficiaries had fewer hospitalizations (0.35 vs 0.43, P<0.001) and fewer physician office visits (25.16 vs 26.17, P<0.001), and shorter LOS during hospitalization (4.19 vs 4.89, P<0.01). On average, Medicare paid $2,314 (P<0.001) more on medications for adherent beneficiaries, but $2,242 (P<0.001) less on total non-drug medical costs. This resulted in no statistically significant difference in total Medicare healthcare costs. Each line of results in Tables 4 and 5 were generated by an individual multivariant regression analysis as indicated in the method section. Full results could be found in supplementary material (Appendix C and Appendix D).

## Discussion

Our study explored the relationships between hormone therapy adherence and non-drug healthcare utilization and costs among breast cancer patients. To our knowledge, this is one of the first studies to examine the association of medication adherence and non-drug healthcare utilization and costs across the full five-year course of treatment and among a sample of patients as diverse as that provided by the SEER-Medicare database. We found that patients who were adherent to HT were associated with fewer inpatient, outpatient and physician office visits. Consistent with previous studies[15,17,18], we also found that patients who were adherent to HT were associated with significant reductions in many types of medical costs as well as total medical costs. Half of the reduction in total medical cost came from savings in hospitalizations. This is expected, since staying on hormone therapy for at least 5 years, as clinical guidelines

recommend, reduces the likelihood of breast cancer recurrence. From this analysis, we find that adherent patients are more likely to avoid a recurrence of breast cancer and the associated costs for related treatment. Our findings suggest that the added cost of hormone therapy adherence is all but offset by the reduced cost for other categories of medical care.

To determine the contingent effect of medication adherence on health care utilization and costs, we included unalterable patient level factors in our models such as age, race, and tumor stage at time of diagnosis. These factors are known to be strongly associated with adherence and thus also impact utilization and costs. However, they are not factors that clinicians and policy makers can directly change. Nevertheless, earlier analyses have identified two manageable factors that could improve adherence, and by doing so, impact health care utilization and costs: care coordination for comorbid health conditions; and financial help with medication copayments [27,28]. Systematic care coordination among health service providers to address comorbid health conditions is possible, but is usually considered costly to implement [27]. This study does indicate, however, that the additional cost would be limited to the care coordination itself. The added costs of medication due to higher adherence would be, for the most part, offset by lower non-drug medical costs.

Value-based insurance design (VBID) plans are designed to offer high-value healthcare at reduced out-of-pocket costs (OOPCs) to patients with certain diagnoses and/or socioeconomic status.[29] Some Medicare Advantage plans have adopted the VBID model to manage beneficiary healthcare costs while maintaining healthcare quality. For example, Medicare Advantage patients with certain chronic diseases may see reduced copayments for medications.[29] An study from 2020 found that lower OOPCs were associated with enhanced long-term medication treatment among Medicare beneficiaries with breast cancer. [28] The authors also showed that eliminating

cost-sharing was associated with improved adherence among breast cancer patients who were Medicare/Medicaid dual eligibles.[30] By reducing the copayments for these patients, VBID plans aim to improve medication adherence and avoid other costly medical services. The findings from our study further support this concept: improved medication adherence did not result in increased total healthcare use and costs, even though it drove up the pharmacy costs.

The benefit of conducting our study using claims data is that the data contains real-world information on hormone therapy adherence and non-drug healthcare utilization and costs. However, there are also some limitations. First, we used Medicare Part D data to calculate MPR to indicate adherence. Filled prescriptions do not necessarily mean that all were consumed by the patient. In addition, our results do not reflect some cases where a patient may have supplementary insurance to cover their medication costs or in the event that a patient switched from aromatase inhibitor to other hormone therapy medications (i.e., tamoxifen). Secondly, the drug costs were calculated by using the gross drug costs (consisting of ingredient cost, dispensing fee, and total amount attributed to sales tax). However, Medicare drug plans may receive rebates from pharmaceutical companies for these medications, which is confidential information. The actual Medicare payment amount for medications may be less than the total of gross drug costs reported. Therefore, it is likely that our study overestimated the pharmacy costs. Thirdly, the costs of breast cancer management may be different throughout years due to advances in the prevention, screening, and treatment of breast cancer. We were unable to capture all the impacts of these advances throughout years, however, we included variables representing calendar years to address these concurrent trends. Finally, we do not know if the reduced medical costs and healthcare utilization were solely associated with better adherence. It is possible that patients who were more adherent to hormone therapy treatment were more likely to be adherent

to other non-drug treatments and/or have a healthier lifestyle, which could have biased the results away from the null. It would be meaningful for future studies to separate these effects from medication adherence.

**Conclusions**

Our study is one of the first to analyze the association between hormone therapy adherence and non-drug healthcare utilization and costs among Medicare beneficiaries over the full course of treatment. Our results suggested that better adherence is associated with lower healthcare utilization of all kinds (inpatient, outpatient and physician office visits) and no change in total healthcare costs despite the increased pharmacy costs. Our study also provides insights into the potential benefits of implementing VBID plans among breast cancer patients to improve their long-term oral medication adherence. Policy makers should consider adherence improvement strategies such as VBID plans given the potential health benefits, and that the costs likely will not surpass the total savings.

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# Tables

*Table 1. Baseline Characteristics of Eligible Medicare Beneficiaries with Hormone Receptor Positive Early Stage Breast Cancer Who Initiated Aromatase Inhibitor Treatment within the First Year of Diagnosis (n=6,045)*

| Characteristics | No. (%)[a] |
|---|---|
| **Median age, years (range)** | 74.6 (65 - 103) |
| **Age Group** | |
| 65-69 | 1,748 (28.9) |
| 70-74 | 1,537 (25.4) |
| 75-79 | 1,242 (20.6) |
| 80+ | 1,518 (25.1) |
| **Race/Ethnicity** | |
| White, non-Hispanic | 5,068 (83.8) |
| Black | 392 (6.5) |
| Hispanic | 334 (5.5) |
| Asian | 251 (4.2) |
| **Comorbidity (HCC score)** | |
| 0 | 2,098 (36.9) |
| 1 | 1,504 (26.5) |
| 2 | 918 (16.2) |
| 3+ | 1,161 (20.4) |
| **Marital Status** | |
| Married | 2,570 (42.5) |
| Unmarried | 3,475 (57.5) |
| **Tumor stage** | |
| I | 3,297 (54.5) |
| II | 2,124 (35.1) |
| III | 624 (10.3) |
| **Treatment** | |
| Surgery + radiation | 3,155 (52.2) |
| Surgery, no radiation | 2,709 (44.8) |
| No surgery | 181 (3.0) |

*Note: a. values are number (percentage) unless indicated otherwise*

*Table 2. Hormone Therapy Adherence, Healthcare Utilization and Costs over the Full Course of Aromatase Inhibitor Treatment among Medicare Beneficiaries with Breast Cancer*

| Variables | Year 1 (n=6,045) | Year 2 (n=5,847) | Year 3 (n=5,592) | Year 4 (n=5,322) | Year 5 (n=4,993) |
|---|---|---|---|---|---|
| *Treatment variables* | | | | | |
| MPR, mean (SD) | 0.79 (0.27) | 0.62 (0.39) | 0.61 (0.41) | 0.61 (0.43) | 0.54 (0.41) |
| Adherence (MPR>=80%), n (%) | 3,878 (64.2) | 2,855 (48.8) | 2,837 (50.7) | 2,848 (53.5) | 1,848 (39.4) |
| *Outcome variables* | | | | | |
| **Healthcare Utilization** | | | | | |
| Any hospitalization, n (%) | 1,166 (19.3) | 862 (14.7) | 873 (15.6) | 1,123 (21.1) | 1,174 (23.5) |
| No. of hospitalization (>0), mean (SD) | 2.0 (1.7) | 1.9 (1.5) | 2.0 (1.5) | 2.2 (1.9) | 2.2 (1.7) |
| No. of hospital days (>0), mean (SD) | 23.4 (47.2) | 22.9 (46.3) | 22.0 (38.5) | 24.3 (41.5) | 24.4 (41.8) |
| Any outpatient visits, n (%) | 5,636 (93.2) | 5,281 (90.3) | 4,969 (88.9) | 4,693 (88.2) | 4,395 (88.0) |
| No. of outpatient visits, mean (SD) | 7.7 (7.7) | 6.5 (7.4) | 6.1 (7.1) | 5.9 (6.8) | 6.0 (7.3) |
| Any physician office visits, n (%) | 6,041 (99.9) | 5,832 (99.7) | 5,567 (99.5) | 5,297 (99.5) | 4,956 (99.3) |
| No. of physician office visits, mean (SD) | 29.2 (17.6) | 25.4 (17.2) | 24.7 (17.6) | 24.3 (18.1) | 24.1 (18.4) |
| **Healthcare Costs** | | | | | |
| Medicare Payment Amount, $ mean (median) | | | | | |
| Total healthcare costs | 21,431 (14,508) | 15,204 (9,757) | 14,884 (8,657) | 15,362 (7,664) | 12,970 (5,438) |
| Total medical costs | 14,767 (7,586) | 9,630 (4,223) | 10,148 (4,047) | 11,611 (3,950) | 10,096 (2,894) |
| Hospitalization costs (>0) | 22,700 (12,654) | 22,084 (13,114) | 23,853 (15,309) | 25,461 (15,894) | 20,993 (11,515) |
| Outpatient costs | 3,708 (1,232) | 1,916 (671) | 1,976 (617) | 1,918 (571) | 1,556 (390) |
| Physician costs | 6,680 (3,942) | 4,458 (2,886) | 4,448 (2,767) | 4,319 (2,600) | 3,604 (1,926) |
| Total pharmacy costs | 6,664 (5,677) | 5,574 (4,623) | 4,735 (3,475) | 3,751 (2,371) | 2,875 (1,452) |

3

*Table 3. Unadjusted Annual Healthcare Utilization and Costs in Adherent and Nonadherent Medicare Beneficiaries with Breast Cancer over the Full Course of Treatment*

| Variables | Adherent | Non-Adherent | P |
|---|---|---|---|
| **Healthcare Utilization** | | | |
| Any hospitalization, n (%) | | | |
| Year 1 | 729 (18.8) | 437 (20.2) | NS |
| Year 2 | 395 (13.8) | 467 (15.6) | NS |
| Year 3 | 404 (14.2) | 469 (17.0) | *<0.01* |
| Year 4 | 521 (18.3) | 602 (24.3) | *<0.001* |
| Year 5 | 417 (21.2) | 757 (25.0) | *<0.01* |
| No. of hospitalization (>0), mean (SD) | | | |
| Year 1 | 2.0 (1.7) | 2.1 (1.7) | NS |
| Year 2 | 1.8 (1.4) | 2.0 (1.5) | NS |
| Year 3 | 2.0 (1.4) | 2.0 (1.5) | NS |
| Year 4 | 2.1 (1.8) | 2.2 (1.9) | NS |
| Year 5 | 2.1 (1.8) | 2.2 (1.7) | NS |
| No. of hospital days (>0), mean (SD) | | | |
| Year 1 | 25.5 (53.8) | 19.9 (33.0) | *<0.05* |
| Year 2 | 22.3 (49.4) | 23.5 (43.5) | NS |
| Year 3 | 23.3 (41.8) | 20.8 (35.3) | NS |
| Year 4 | 24.8 (45.7) | 23.8 (37.6) | NS |
| Year 5 | 23.7 (38.0) | 24.8 (43.8) | NS |
| Any outpatient visits, n (%) | | | |
| Year 1 | 3,612 (93.1) | 2,024 (93.4) | NS |
| Year 2 | 2,600 (91.1) | 2,681 (89.6) | NS |
| Year 3 | 2,537 (89.4) | 2,432 (88.3) | NS |
| Year 4 | 2,564 (90.0) | 2,129 (86.1) | *<0.001* |
| Year 5 | 1,766 (89.8) | 2,629 (86.9) | *<0.01* |
| No. of outpatient visits, mean (SD) | | | |
| Year 1 | 7.7 (7.6) | 7.9 (7.9) | NS |
| Year 2 | 6.5 (7.4) | 6.4 (7.4) | NS |
| Year 3 | 6.2 (7.2) | 6.0 (7.0) | NS |
| Year 4 | 5.9 (6.8) | 5.9 (6.8) | NS |
| Year 5 | 6.1 (7.2) | 5.9 (7.4) | NS |
| No. of physician office visits, mean (SD) | | | |
| Year 1 | 28.5 (17.3) | 30.3 (18.1) | *<0.001* |

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| Variables | Adherent | Non-Adherent | P |
|---|---|---|---|
| Year 2 | 25.2 (16.8) | 25.6 (17.5) | NS |
| Year 3 | 24.4 (16.5) | 25.0 (18.6) | NS |
| Year 4 | 23.9 (17.3) | 24.9 (18.9) | *<0.05* |
| Year 5 | 23.8 (18.1) | 24.3 (18.5) | NS |
| **Healthcare Costs** | | | |
| Medicare Payment Amount | | | |
| Total healthcare costs, $ mean (median) | | | |
| Year 1 | 22,025 (15,502) | 20,370 (12,604) | *<0.01* |
| Year 2 | 16,624 (11,434) | 13,849 (8,072) | *<0.001* |
| Year 3 | 15,110 (9,865) | 14,651 (7,488) | NS |
| Year 4 | 14,563 (7,906) | 16,283 (7,347) | *<0.01* |
| Year 5 | 12,758 (5,837) | 13,109 (5,238) | NS |
| Total medical costs, $ mean (median) | | | |
| Year 1 | 14,306 (7,513) | 15,594 (7,775) | *<0.05* |
| Year 2 | 9,090 (4,111) | 10,144 (4,324) | *<0.05* |
| Year 3 | 9,025 (3,923) | 11,304 (4,209) | *<0.001* |
| Year 4 | 10,067 (3,688) | 13,389 (4,283) | *<0.001* |
| Year 5 | 9,103 (2,772) | 10,741 (2,981) | *<0.01* |
| Total hospitalization costs, $ mean (median) | | | |
| Year 1 | 22,176 (12,654) | 23,574 (12,775) | NS |
| Year 2 | 22,136 (12,462) | 22,040 (13,620) | NS |
| Year 3 | 23,036 (16,120) | 24,558 (14,584) | NS |
| Year 4 | 24,799 (15,880) | 26,035 (16,034) | NS |
| Year 5 | 20,213 (11,477) | 21,424 (11,569) | NS |
| Total outpatient costs, $ mean (median) | | | |
| Year 1 | 4,528 (2,035) | 5,151 (2,177) | NS |
| Year 2 | 3,380 (1,514) | 3,768 (1,481) | NS |
| Year 3 | 3,527 (1,549) | 4,316 (1,483) | NS |
| Year 4 | 3,485 (1,597) | 3,991 (1,420) | NS |
| Year 5 | 3,010 (943) | 2,925 (1,019) | NS |
| Total physician costs, $ mean (median) | | | |
| Year 1 | 9,602 (6,915) | 11,352 (8,175) | *<0.01* |
| Year 2 | 8,325 (6,093) | 8,323 (6,250) | NS |
| Year 3 | 8,289 (6,290) | 8,892 (6,128) | NS |

(continued the next page)

| Variables | Adherent | Non-Adherent | P |
|---|---|---|---|
| Year 4 | 7,639 (5,697) | 9,069 (6,308) | *<0.01* |
| Year 5 | 6,366 (4,588) | 6,810 (4,737) | NS |
| Total pharmacy costs, $ mean (median) | | | |
| Year 1 | 7,719 (6,561) | 4,776 (4,090) | *<0.001* |
| Year 2 | 7,534 (6,443) | 3,705 (3,150) | *<0.001* |
| Year 3 | 6,084 (5,032) | 3,347 (2,539) | *<0.001* |
| Year 4 | 4,495 (2,951) | 2,893 (1,847) | *<0.001* |
| Year 5 | 3,656 (1,954) | 2,367 (1,235) | *<0.001* |

*Note: NS stands for not significant*

*Table 4. Adjusted Healthcare Utilization and Costs among Medicare Beneficiaries with Breast Cancer over the Full Course of Treatment*

| Variables | MPR[a] | P |
|---|---|---|
| **Healthcare Utilization** | | |
| No. of hospitalizations[b] | -0.009 | *<0.001* |
| No. of hospital days | -0.088 | *<0.01* |
| No. of outpatient visits | -0.018 | NS |
| No. of physician office visits | -0.111 | *<0.001* |
| **Healthcare Costs** | | |
| Medicare Payment Amount | | |
| Total healthcare costs | 51 | NS |
| Total medical costs | -281 | *<0.001* |
| Total hospitalization costs | -109 | *<0.001* |
| Total outpatient costs | -52 | *<0.001* |
| Total physician costs | -105 | *<0.001* |
| Total pharmacy costs | 365 | *<0.001* |

*Notes: NS stands for not significant*

a. *The prediction model controlled for other covariate, full results see Supplementary Material (Appendix C).*
b. *An example for interpreting the finding: every 10% increase in MPR was associated with 0.009 less number of hospitalizations (p<0.001)*

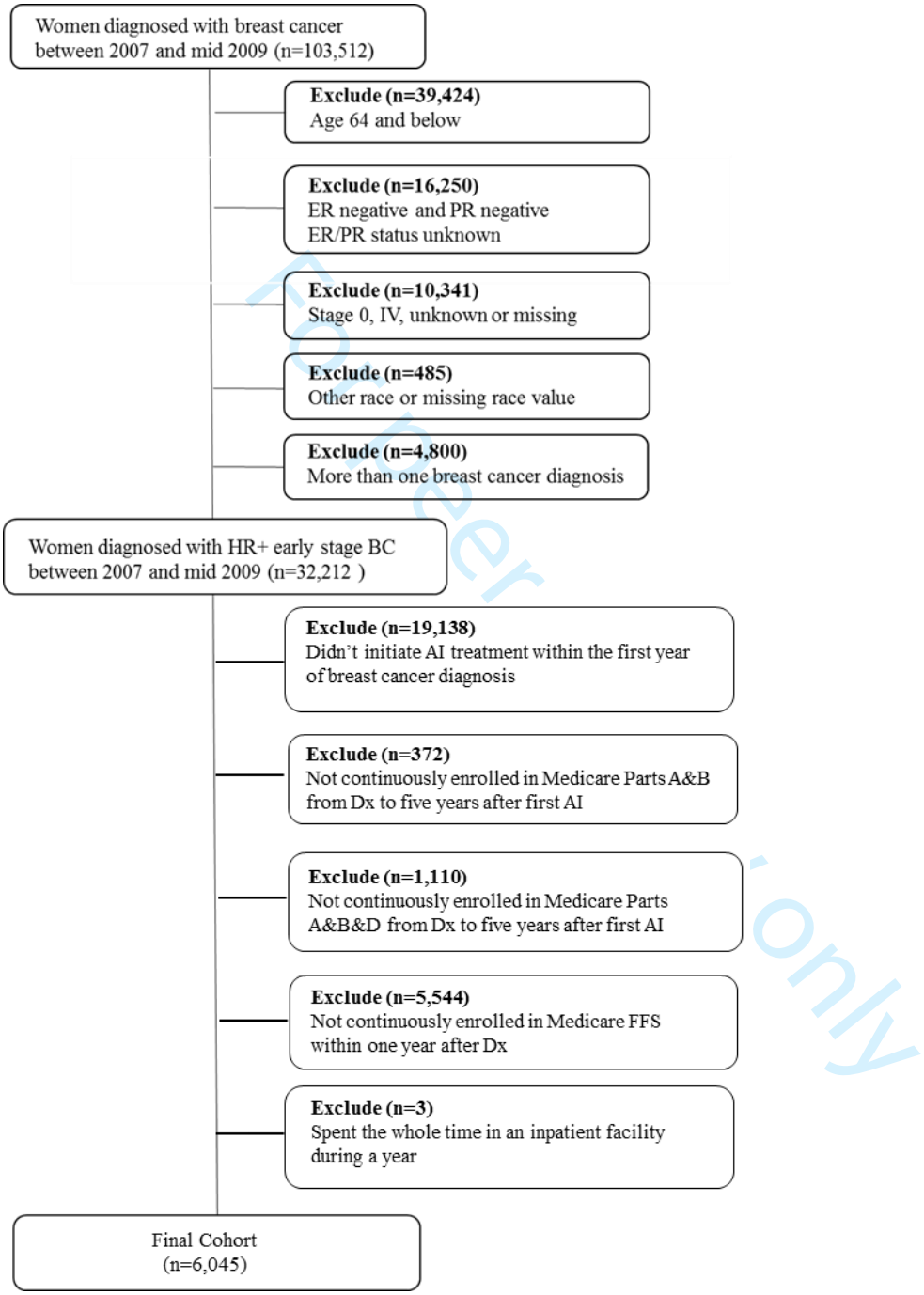
*Table 5. Adjusted Healthcare Utilization and Costs for Medicare Beneficiaries Adherent and Nonadherent to Hormone therapy over the Full Course of Treatment*

| **Variables** | **Adherent[a]** | **Non-Adherent** | **Difference** | **P[b]** |
|---|---|---|---|---|
| **Healthcare Utilization** | Margin (SE) | Margin (SE) | Margin (SE) | |
| No. of hospitalization | 0.35 (0.01) | 0.43 (0.01) | -0.08 (0.01) | *<0.001* |
| No. of hospital days | 4.19 (0.16) | 4.89 (0.18) | -0.70 (0.22) | *<0.01* |
| No. of outpatient visits | 6.45 (0.05) | 6.54 (0.06) | -0.09 (0.08) | NS |
| No. of physician office visits | 25.16 (0.13) | 26.17 (0.14) | -1.02 (0.20) | *<0.001* |
| **Healthcare Costs** | | | | |
| Medicare Payment Amount | | | | |
| Total healthcare costs | 16,246 (164) | 16,077 (200) | 169 (262) | NS |
| Medical costs | 10,310 (152) | 12,551 (195) | -2,242 (249) | *<0.001* |
| Hospitalization costs | 3,811 (115) | 4,840 (141) | -1,028 (183) | *<0.001* |
| Outpatient costs | 2,070 (37) | 2,484 (54) | -414 (65) | *<0.001* |
| Physician costs | 4,389 (47) | 5,190 (63) | -801 (77) | *<0.001* |
| Pharmacy costs | 5,891 (46) | 3,577 (37) | 2,314 (61) | *<0.001* |

*Notes:*

a. *The prediction model controlled for other covariate, full results see Supplementary Material (Appendix D).*
b. *NS stands for not significant*

*Appendix A. Selection Criteria for Identifying Medicare Beneficiaries Diagnosed with Hormone Receptor-Positive Early Stage Breast Cancer from 2007 to Mid-2009*



*Appendix B. Descriptions of Variables*

| VARIABLE NAME | DEFINITION |
|---|---|
| **DEPENDENT VARIABLES** | |
| *Healthcare utilization* | |
| Any hospitalization | A dummy variable equal to 1 if at least one hospitalization |
| Inpatient visits | A continuous variable of number of hospitalizations |
| Length of stay | A continuous variable of number of days in hospital |
| Any outpatient visits | A dummy variable equal to 1 if at least one outpatient visits |
| Outpatient visits | A continuous variable of number of outpatient visits |
| *Healthcare costs* | |
| Total healthcare costs | A continuous variable measures the sum of non-drug medical costs and prescription drug costs |
| Non-drug medical costs | A continuous variable measures the sum of inpatient and outpatient costs |
| Inpatient costs | A subgroup of total medical costs |
| Outpatient costs | A subgroup of total medical costs |
| Prescription drug costs | A continuous variable |
| **TREATMENT VARIABLES** | |
| Adherence continuous | A continuous variable of MPR % |
| Adherence dummy | A dummy equal to 1 if MPR >=80% |
| **CONTROL VARIABLES** | |
| Race/Ethnicity | A dummy variable equal to 1 if White, non-Hispanic |
| Age continuous | A continuous variable, 65+ years old |
| Married | A dummy variable equal to 1 if married |
| Tumor Stage | A categorical variable where<br>1 Stage I<br>2 Stage II<br>3 Stage III |
| Initial Surgery/Radiation Treatment | A categorical variable where<br>1 No surgery<br>2 Surgery (breast-conserving surgery or mastectomy) + radiation<br>3 Surgery, no radiation |

| | |
|---|---|
| HCC Risk Score (see detailed construction description on NCI website: https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity.html) | A categorical variable where<br>1 0<br>2 1<br>3 2<br>4 3+ |

*Appendix C. Association between Medication Possession Ratio and Healthcare Utilization and Costs among Medicare Beneficiaries with Breast Cancer over the Full Course of Treatment, controlling for covariates*

*C-1. No. of Hospitalization*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | -0.083 | 0.013 | *** | -0.108 | -0.058 |
| Year | | | | | |
| 2 vs 1 | -0.132 | 0.018 | *** | -0.167 | -0.096 |
| 3 vs 1 | -0.108 | 0.019 | *** | -0.144 | -0.071 |
| 4 vs 1 | 0.033 | 0.021 | NS | -0.008 | 0.075 |
| 5 vs 1 | 0.066 | 0.022 | ** | 0.022 | 0.109 |
| HCC Score | | | | | |
| 1 vs 0 | 0.114 | 0.014 | *** | 0.088 | 0.141 |
| 2 vs 0 | 0.255 | 0.022 | *** | 0.211 | 0.299 |
| 3+ vs 0 | 0.599 | 0.033 | *** | 0.535 | 0.664 |
| Married | | | | | |
| Yes vs No | -0.098 | 0.013 | *** | -0.123 | -0.074 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 0.077 | 0.013 | *** | 0.052 | 0.102 |
| Surgery, no radiation vs Surgery + radiation | 0.304 | 0.056 | *** | 0.194 | 0.414 |
| Race | | | | | |
| Asian vs White | -0.182 | 0.023 | *** | -0.226 | -0.138 |
| Black vs White | 0.023 | 0.025 | NS | -0.026 | 0.073 |
| Hispanic vs White | -0.046 | 0.024 | NS | -0.094 | 0.001 |
| Stage | | | | | |
| II vs I | 0.059 | 0.013 | *** | 0.033 | 0.090 |
| III vs I | 0.152 | 0.024 | *** | 0.104 | 0.200 |
| Age | 0.010 | 0.001 | *** | 0.008 | 0.011 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-2. LOS*

| Variables | Estimates | SE | P | | 95% CI |
|---|---|---|---|---|---|
| MPR | -0.701 | 0.309 | * | -1.305 | -0.096 |
| Year | | | | | |
| 2 vs 1 | -1.403 | 0.328 | *** | -2.047 | -0.759 |
| 3 vs 1 | -0.882 | 0.370 | * | -1.607 | -0.157 |
| 4 vs 1 | 0.949 | 0.438 | * | 0.091 | 1.808 |
| 5 vs 1 | 0.724 | 0.383 | NS | -0.026 | 1.475 |
| HCC Score | | | | | |
| 1 vs 0 | 1.490 | 0.247 | *** | 1.006 | 1.974 |
| 2 vs 0 | 3.102 | 0.381 | *** | 2.354 | 3.849 |
| 3+ vs 0 | 8.179 | 0.628 | *** | 6.949 | 9.409 |
| Married | | | | | |
| Yes vs No | -2.036 | 0.215 | *** | -2.458 | -1.614 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 1.322 | 0.237 | *** | 0.858 | 1.787 |
| Surgery, no radiation vs Surgery + radiation | 4.842 | 1.198 | *** | 2.494 | 7.189 |
| Race | | | | | |
| Asian vs White | -2.255 | 0.390 | *** | -3.019 | -1.491 |
| Black vs White | 0.840 | 0.567 | NS | -0.271 | 1.951 |
| Hispanic vs White | -0.851 | 0.424 | * | -1.683 | -0.020 |
| Stage | | | | | |
| II vs I | 1.070 | 0.246 | *** | 0.588 | 1.552 |
| III vs I | 2.248 | 0.524 | *** | 1.221 | 3.275 |
| Age | 0.190 | 0.020 | *** | 0.151 | 0.229 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-3. No. of Outpatient Visits*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | -0.230 | 0.103 | * | -0.431 | -0.029 |
| Year | | | | | |
| 2 vs 1 | -1.370 | 0.132 | *** | -1.628 | -1.112 |
| 3 vs 1 | -1.620 | 0.132 | *** | -1.878 | -1.361 |
| 4 vs 1 | -1.844 | 0.132 | *** | -2.103 | -1.585 |
| 5 vs 1 | -1.752 | 0.137 | *** | -2.020 | -1.485 |
| HCC Score | | | | | |
| 1 vs 0 | 0.757 | 0.093 | *** | 0.575 | 0.940 |
| 2 vs 0 | 1.651 | 0.143 | *** | 1.371 | 1.930 |
| 3+ vs 0 | 3.277 | 0.187 | *** | 2.911 | 3.643 |
| Married | | | | | |
| Yes vs No | -0.246 | 0.082 | ** | -0.406 | -0.085 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -0.463 | 0.082 | *** | -0.623 | -0.303 |
| Surgery, no radiation vs Surgery + radiation | -0.522 | 0.266 | NS | -1.044 | -0.001 |
| Race | | | | | |
| Asian vs White | -1.212 | 0.166 | *** | -1.537 | -0.886 |
| Black vs White | 1.080 | 0.195 | *** | 0.697 | 1.463 |
| Hispanic vs White | 0.216 | 0.180 | NS | -0.138 | 0.570 |
| Stage | | | | | |
| II vs I | 0.847 | 0.087 | *** | 0.676 | 1.018 |
| III vs I | 1.276 | 0.157 | *** | 0.968 | 1.583 |
| Age | -0.059 | 0.006 | *** | -0.072 | -0.046 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-4. No. of Physician Office Visits*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | -1.233 | 0.257 | *** | -1.736 | -0.729 |
| Year | | | | | |
| 2 vs 1 | -4.469 | 0.327 | *** | -5.110 | -3.829 |
| 3 vs 1 | -5.454 | 0.326 | *** | -6.093 | -4.815 |
| 4 vs 1 | -5.773 | 0.329 | *** | -6.419 | -5.128 |
| 5 vs 1 | -6.128 | 0.337 | *** | -6.788 | -5.468 |
| HCC Score | | | | | |
| 1 vs 0 | 3.756 | 0.235 | *** | 3.294 | 4.217 |
| 2 vs 0 | 7.022 | 0.360 | *** | 6.316 | 7.728 |
| 3+ vs 0 | 14.854 | 0.487 | *** | 13.900 | 15.808 |
| Married | | | | | |
| Yes vs No | 0.040 | 0.207 | NS | -0.366 | 0.446 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -1.893 | 0.204 | *** | -2.293 | -1.493 |
| Surgery, no radiation vs Surgery + radiation | -1.230 | 0.680 | NS | -2.563 | 0.104 |
| Race | | | | | |
| Asian vs White | -2.075 | 0.448 | *** | -2.954 | -1.196 |
| Black vs White | -1.614 | 0.408 | *** | -2.415 | -0.814 |
| Hispanic vs White | -0.506 | 0.431 | NS | -1.352 | 0.339 |
| Stage | | | | | |
| II vs I | 0.654 | 0.215 | ** | 0.232 | 1.076 |
| III vs I | 0.334 | 0.356 | NS | -0.364 | 1.032 |
| Age | 0.014 | 0.016 | NS | -0.018 | 0.046 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-5. Total Healthcare Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | 579 | 358 | NS | -123 | 1,282 |
| Year | | | | | |
| 2 vs 1 | -6,919 | 365 | *** | -7,633 | -6,205 |
| 3 vs 1 | -7,389 | 400 | *** | -8,173 | -6,605 |
| 4 vs 1 | -7,127 | 428 | *** | -7,967 | -6,288 |
| 5 vs 1 | -9,523 | 432 | *** | -10,369 | -8,676 |
| HCC Score | | | | | |
| 1 vs 0 | 3,668 | 296 | *** | 3,087 | 4,249 |
| 2 vs 0 | 7,373 | 461 | *** | 6,469 | 8,277 |
| 3+ vs 0 | 17,036 | 748 | *** | 15,571 | 18,501 |
| Married | | | | | |
| Yes vs No | -1,637 | 264 | *** | -2,155 | -1,120 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 276 | 270 | NS | -253 | 804 |
| Surgery, no radiation vs Surgery + radiation | 2,108 | 906 | * | 333 | 3,884 |
| Race | | | | | |
| Asian vs White | -200 | 594 | NS | -1,364 | 965 |
| Black vs White | 1,837 | 636 | ** | 592 | 3,083 |
| Hispanic vs White | 1,588 | 592 | ** | 427 | 2,749 |
| Stage | | | | | |
| II vs I | 1,832 | 280 | *** | 1,283 | 2,380 |
| III vs I | 3,687 | 500 | *** | 2,707 | 4,667 |
| Age | 26 | 21 | NS | -15 | 68 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-6. Total Non-drug Medical Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | -2,716 | 322 | *** | -3,347 | -2,086 |
| Year | | | | | |
| 2 vs 1 | -6,404 | 362 | *** | -7,114 | -5,695 |
| 3 vs 1 | -5,964 | 391 | *** | -6,731 | -5,196 |
| 4 vs 1 | -4,681 | 420 | *** | -5,504 | -3,858 |
| 5 vs 1 | -6,363 | 418 | *** | -7,183 | -5,543 |
| HCC Score | | | | | |
| 1 vs 0 | 2,298 | 274 | *** | 1,761 | 2,836 |
| 2 vs 0 | 5,107 | 432 | *** | 4,260 | 5,955 |
| 3+ vs 0 | 13,098 | 708 | *** | 11,711 | 14,485 |
| Married | | | | | |
| Yes vs No | -1,115 | 245 | *** | -1,596 | -634 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -216 | 249 | NS | -703 | 272 |
| Surgery, no radiation vs Surgery + radiation | 2,306 | 869 | ** | 604 | 4,009 |
| Race | | | | | |
| Asian vs White | -1,633 | 553 | ** | -2,717 | -549 |
| Black vs White | 1,277 | 591 | * | 119 | 2,435 |
| Hispanic vs White | 1,328 | 568 | * | 215 | 2,441 |
| Stage | | | | | |
| II vs I | 1,489 | 258 | *** | 984 | 1,995 |
| III vs I | 3,670 | 477 | *** | 2,736 | 4,603 |
| Age | 51 | 20 | * | 12 | 89 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*C-7. Medication Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| MPR | 3,637 | 101 | *** | 3,440 | 3,834 |
| Year | | | | | |
| 2 vs 1 | -767 | 91 | *** | -946 | -589 |
| 3 vs 1 | -1,589 | 98 | *** | -1,782 | -1,396 |
| 4 vs 1 | -2,514 | 100 | *** | -2,711 | -2,317 |
| 5 vs 1 | -3,221 | 105 | *** | -3,427 | -3,016 |
| HCC Score | | | | | |
| 1 vs 0 | 1,476 | 81 | *** | 1,317 | 1,635 |
| 2 vs 0 | 2,428 | 128 | *** | 2,178 | 2,678 |
| 3+ vs 0 | 4,270 | 184 | *** | 3,909 | 4,631 |
| Married | | | | | |
| Yes vs No | -505 | 68 | *** | -639 | -371 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 553 | 74 | *** | 408 | 697 |
| Surgery, no radiation vs Surgery + radiation | -109 | 214 | NS | -528 | 310 |
| Race | | | | | |
| Asian vs White | 1,444 | 194 | *** | 1,063 | 1,825 |
| Black vs White | 378 | 141 | ** | 102 | 653 |
| Hispanic vs White | 286 | 124 | * | 44 | 528 |
| Stage | | | | | |
| II vs I | 209 | 73 | ** | 65 | 353 |
| III vs I | -84 | 117 | NS | -314 | 145 |
| Age | -28 | 5 | *** | -38 | -18 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*Appendix D. Association between Adherent and Nonadherent Breast Cancer Patients with Medicare Coverage and Healthcare Utilization and Costs over the Full Course of Treatment*

*D-1. No. of Hospitalization*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -0.083 | 0.013 | *** | -0.108 | -0.058 |
| Year | | | | | |
| 2 vs 1 | -0.131 | 0.018 | *** | -0.166 | -0.096 |
| 3 vs 1 | -0.105 | 0.019 | *** | -0.142 | -0.069 |
| 4 vs 1 | 0.034 | 0.021 | NS | -0.007 | 0.075 |
| 5 vs 1 | 0.062 | 0.022 | ** | 0.019 | 0.105 |
| HCC Score | | | | | |
| 1 vs 0 | 0.115 | 0.014 | *** | 0.089 | 0.142 |
| 2 vs 0 | 0.256 | 0.023 | *** | 0.212 | 0.301 |
| 3+ vs 0 | 0.583 | 0.033 | *** | 0.518 | 0.649 |
| Married | | | | | |
| Yes vs No | -0.096 | 0.013 | *** | -0.120 | -0.071 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 0.072 | 0.013 | *** | 0.047 | 0.097 |
| Surgery, no radiation vs Surgery + radiation | 0.284 | 0.056 | *** | 0.174 | 0.394 |
| Race | | | | | |
| Asian vs White | -0.167 | 0.022 | *** | -0.211 | -0.123 |
| Black vs White | 0.018 | 0.025 | NS | -0.030 | 0.067 |
| Hispanic vs White | -0.022 | 0.025 | NS | -0.072 | 0.027 |
| Stage | | | | | |
| II vs I | 0.063 | 0.013 | *** | 0.037 | 0.089 |
| III vs I | 0.133 | 0.024 | *** | 0.087 | 0.180 |
| Age | 0.009 | 0.001 | *** | 0.007 | 0.011 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-2. LOS*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -0.607 | 0.215 | ** | -1.028 | -0.187 |
| Year | | | | | |
| 2 vs 1 | -1.378 | 0.294 | *** | -1.953 | -0.803 |
| 3 vs 1 | -0.841 | 0.316 | ** | -1.460 | -0.221 |
| 4 vs 1 | 1.018 | 0.376 | ** | 0.281 | 1.755 |
| 5 vs 1 | 0.751 | 0.362 | * | 0.042 | 1.460 |
| HCC Score | | | | | |
| 1 vs 0 | 1.495 | 0.214 | *** | 1.076 | 1.914 |
| 2 vs 0 | 3.109 | 0.368 | *** | 2.388 | 3.831 |
| 3+ vs 0 | 8.199 | 0.645 | *** | 6.936 | 9.463 |
| Married | | | | | |
| Yes vs No | -2.046 | 0.199 | *** | -2.436 | -1.656 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 1.331 | 0.211 | *** | 0.917 | 1.746 |
| Surgery, no radiation vs Surgery + radiation | 4.816 | 1.135 | *** | 2.591 | 7.040 |
| Race | | | | | |
| Asian vs White | -2.255 | 0.329 | *** | -2.899 | -1.611 |
| Black vs White | 0.848 | 0.495 | NS | -0.122 | 1.818 |
| Hispanic vs White | -0.846 | 0.369 | * | -1.570 | -0.123 |
| Stage | | | | | |
| II vs I | 1.067 | 0.228 | *** | 0.621 | 1.514 |
| III vs I | 2.253 | 0.451 | *** | 1.368 | 3.137 |
| Age | 0.191 | 0.019 | *** | 0.154 | 0.227 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-3. No. of Outpatient Visits*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -0.141 | 0.080 | NS | -0.298 | 0.015 |
| Year | | | | | |
| 2 vs 1 | -1.351 | 0.130 | *** | -1.607 | -1.096 |
| 3 vs 1 | -1.599 | 0.130 | *** | -1.854 | -1.343 |
| 4 vs 1 | -1.825 | 0.130 | *** | -2.080 | -1.570 |
| 5 vs 1 | -1.733 | 0.135 | *** | -1.997 | -1.469 |
| HCC Score | | | | | |
| 1 vs 0 | 0.756 | 0.093 | *** | 0.573 | 0.939 |
| 2 vs 0 | 1.651 | 0.143 | *** | 1.371 | 1.932 |
| 3+ vs 0 | 3.271 | 0.187 | *** | 2.904 | 3.637 |
| Married | | | | | |
| Yes vs No | -0.252 | 0.082 | ** | -0.413 | -0.091 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -0.464 | 0.082 | *** | -0.624 | -0.304 |
| Surgery, no radiation vs Surgery + radiation | -0.538 | 0.265 | * | -1.058 | -0.018 |
| Race | | | | | |
| Asian vs White | -1.176 | 0.166 | *** | -1.500 | -0.851 |
| Black vs White | 1.079 | 0.195 | *** | 0.696 | 1.462 |
| Hispanic vs White | 0.204 | 0.181 | NS | -0.151 | 0.559 |
| Stage | | | | | |
| II vs I | 0.847 | 0.087 | *** | 0.677 | 1.018 |
| III vs I | 1.277 | 0.157 | *** | 0.969 | 1.584 |
| Age | -0.059 | 0.006 | *** | -0.071 | -0.046 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-4. No. of Physician Office Visits*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -1.116 | 0.200 | *** | -1.507 | -0.724 |
| Year | | | | | |
| 2 vs 1 | -4.432 | 0.325 | *** | -5.068 | -3.795 |
| 3 vs 1 | -5.382 | 0.324 | *** | -6.016 | -4.748 |
| 4 vs 1 | -5.679 | 0.327 | *** | -6.319 | -5.039 |
| 5 vs 1 | -6.090 | 0.333 | *** | -6.743 | -5.436 |
| HCC Score | | | | | |
| 1 vs 0 | 3.762 | 0.235 | *** | 3.301 | 4.224 |
| 2 vs 0 | 7.038 | 0.360 | *** | 6.332 | 7.745 |
| 3+ vs 0 | 14.873 | 0.487 | *** | 13.918 | 15.827 |
| Married | | | | | |
| Yes vs No | 0.024 | 0.207 | NS | -0.383 | 0.430 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -1.884 | 0.204 | *** | -2.285 | -1.484 |
| Surgery, no radiation vs Surgery + radiation | -1.258 | 0.679 | NS | -2.589 | 0.074 |
| Race | | | | | |
| Asian vs White | -2.069 | 0.448 | *** | -2.947 | -1.190 |
| Black vs White | -1.605 | 0.408 | *** | -2.405 | -0.805 |
| Hispanic vs White | -0.488 | 0.432 | NS | -1.334 | 0.358 |
| Stage | | | | | |
| II vs I | 0.651 | 0.215 | ** | 0.229 | 1.072 |
| III vs I | 0.345 | 0.356 | NS | -0.354 | 1.044 |
| Age | 0.015 | 0.016 | NS | -0.017 | 0.046 |

*D-5. Total Healthcare Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | 146 | 263 | NS | -369 | 661 |
| Year | | | | | |
| 2 vs 1 | -7,009 | 363 | *** | -7,720 | -6,298 |
| 3 vs 1 | -7,494 | 397 | *** | -8,271 | -6,717 |
| 4 vs 1 | -7,245 | 423 | *** | -8,074 | -6,416 |
| 5 vs 1 | -9,660 | 428 | *** | -10,499 | -8,821 |
| HCC Score | | | | | |
| 1 vs 0 | 3,672 | 296 | *** | 3,091 | 4,253 |
| 2 vs 0 | 7,388 | 462 | *** | 6,482 | 8,293 |
| 3+ vs 0 | 17,052 | 747 | *** | 15,588 | 18,517 |
| Married | | | | | |
| Yes vs No | -1,643 | 264 | *** | -2,160 | -1,126 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 269 | 269 | NS | -259 | 797 |
| Surgery, no radiation vs Surgery + radiation | 2,089 | 904 | * | 318 | 3,861 |
| Race | | | | | |
| Asian vs White | -158 | 597 | NS | -1,329 | 1,013 |
| Black vs White | 1,867 | 635 | ** | 621 | 3,112 |
| Hispanic vs White | 1,600 | 591 | ** | 441 | 2,759 |
| Stage | | | | | |
| II vs I | 1,846 | 279 | *** | 1,298 | 2,394 |
| III vs I | 3,677 | 499 | *** | 2,700 | 4,655 |
| Age | 25 | 21 | NS | -16 | 66 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-6. Total Non-drug Medical Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | -2,243 | 250 | *** | -2,733 | -1,753 |
| Year | | | | | |
| 2 vs 1 | -6,257 | 355 | *** | -6,953 | -5,562 |
| 3 vs 1 | -5,760 | 383 | *** | -6,511 | -5,010 |
| 4 vs 1 | -4,448 | 410 | *** | -5,252 | -3,643 |
| 5 vs 1 | -6,171 | 413 | *** | -6,981 | -5,360 |
| HCC Score | | | | | |
| 1 vs 0 | 2,302 | 273 | *** | 1,768 | 2,837 |
| 2 vs 0 | 5,129 | 432 | *** | 4,283 | 5,976 |
| 3+ vs 0 | 13,102 | 707 | *** | 11,717 | 14,488 |
| Married | | | | | |
| Yes vs No | -1,128 | 245 | *** | -1,608 | -647 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | -207 | 248 | NS | -693 | 279 |
| Surgery, no radiation vs Surgery + radiation | 2,232 | 865 | * | 536 | 3,928 |
| Race | | | | | |
| Asian vs White | -1,689 | 537 | ** | -2,741 | -637 |
| Black vs White | 1,308 | 590 | * | 151 | 2,465 |
| Hispanic vs White | 1,350 | 569 | * | 235 | 2,466 |
| Stage | | | | | |
| II vs I | 1,461 | 255 | *** | 960 | 1,961 |
| III vs I | 3,724 | 481 | *** | 2,781 | 4,666 |
| Age | 53 | 20 | ** | 15 | 91 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

*D-7. Medication Costs*

| Variables | Estimates | SE | P | 95% CI | |
|---|---|---|---|---|---|
| Adherent (Yes vs No) | 2,302 | 63 | *** | 2,179 | 2,426 |
| Year | | | | | |
| 2 vs 1 | -960 | 88 | *** | -1,133 | -786 |
| 3 vs 1 | -1,900 | 93 | *** | -2,082 | -1,718 |
| 4 vs 1 | -2,909 | 94 | *** | -3,093 | -2,724 |
| 5 vs 1 | -3,592 | 97 | *** | -3,783 | -3,402 |
| HCC Score | | | | | |
| 1 vs 0 | 1,413 | 80 | *** | 1,257 | 1,569 |
| 2 vs 0 | 2,376 | 127 | *** | 2,128 | 2,624 |
| 3+ vs 0 | 4,211 | 192 | *** | 3,835 | 4,588 |
| Married | | | | | |
| Yes vs No | -477 | 69 | *** | -612 | -342 |
| Treatment | | | | | |
| No surgery vs Surgery + radiation | 502 | 73 | *** | 359 | 646 |
| Surgery, no radiation vs Surgery + radiation | -100 | 206 | NS | -503 | 303 |
| Race | | | | | |
| Asian vs White | 1,514 | 190 | *** | 1,142 | 1,886 |
| Black vs White | 430 | 140 | ** | 156 | 704 |
| Hispanic vs White | 299 | 124 | * | 57 | 541 |
| Stage | | | | | |
| II vs I | 304 | 77 | *** | 154 | 454 |
| III vs I | -64 | 112 | NS | -283 | 155 |
| Age | -32 | 5 | *** | -41 | -22 |

*Note: *statistically significant at P<0.05 level, ** at P<0.01 level, *** at P<0.001 level; NS stands for not significant*

**The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.**

| | Item No. | STROBE items | Location in manuscript where items are reported | RECORD items | Location in manuscript where items are reported |
|---|---|---|---|---|---|
| **Title and abstract** | | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | P2 | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.<br><br>RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.<br><br>RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | P2 |
| **Introduction** | | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | P3 | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | P5 | | |
| **Methods** | | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | P5 | | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | P6 | | |

| | | | | | |
|---|---|---|---|---|---|
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | P6 | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.<br><br>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | P6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | P6-7 | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | P7 |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement).<br>Describe comparability of assessment methods if there is more than one group | P7 | | |

| | | | | | |
|---|---|---|---|---|---|
| Bias | 9 | Describe any efforts to address potential sources of bias | P11-12 | | |
| Study size | 10 | Explain how the study size was arrived at | P8 | | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | Supplementary material: Appendix B | | |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | P7-8 | | |
| Data access and cleaning methods | | .. | | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. | P8 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | |
| Linkage | | .. | | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | Supplement material: Appendix A | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram. | |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | Table 1 | | |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure | Table 2, Table 3 | | |

| | | | | | |
|---|---|---|---|---|---|
| | | category, or summary measures of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | | |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 4, Table 5 | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | N/A | | |
| **Discussion** | | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | P10-11 | | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | P11-12 | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, | P10-12 | | |

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| | | limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | P12 | | |
| **Other Information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | P1 | | |
| Accessibility of protocol, raw data, and programming code | | .. | | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | P5 |

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.