BMJ Open

Association between medication adherence and non-drug healthcare utilisation and costs: a retrospective longitudinal cohort study among US women age 65 and older

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To cite: Ma S, Shepard DS, Ritter GA, *et al*. Association between medication adherence and non-drug healthcare utilisation and costs: a retrospective longitudinal cohort study among US women age 65 and older. *BMJ Open* 2021;**11**:e052146. doi:10.1136/bmjopen-2021-052146

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-052146).

Received 06 April 2021
Accepted 18 October 2021

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ABSTRACT

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

Design Retrospective longitudinal cohort study.

Setting The US 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 USA.

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 utilisation and healthcare costs for the first year of HT and each year, thereafter, for a total of 5 years.

Results 6045 eligible Medicare beneficiaries that met our selection criteria were included. We found that patients who were adherent to HT were associated with lower healthcare utilisation of all kinds (inpatient (0.35 vs 0.43, p<0.001), length of study during hospitalisation (4.19 vs 4.89, p<0.01), 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 the total medical cost reduction came from savings in hospitalisation 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 patients with breast cancer to improve their long-term oral medication adherence. Policymakers should consider adherence improvement strategies such as VBID plans, given that the costs likely will not surpass the total savings.

Strength and limitations of this study

- First of its kind to reveal the association between hormone therapy adherence and non-drug healthcare utilisation and costs among Medicare patients with breast cancer in the USA over the full course of 5-year treatment.
- Provided insights into the potential benefits of implementing value-based insurance design plans among patients with breast cancer to improve their long-term oral medication adherence.
- 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 US women, representing 30% of all new cancer cases in 2020.[1] With improved screening and treatment, the US 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 US$16.5 billion in 2010 to US$19.7 billion in 2018.[3]

Hormone receptor (HR)-positive breast cancer subtype accounts for over 80% of total breast cancer. Among HR-positive patients with breast cancer, adjuvant endocrine (or hormone) therapy has been incorporated as part of the treatment regime after surgical removal of the tumour.[4–7] There are several types of hormone therapy (HT) medications, including tamoxifen and aromatase inhibitors (AIs). AIs are a newer generation of adjuvant 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 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 hospitalised and 3.0% less likely to visit the emergency department (ED). In total, their total healthcare costs per year were US$5910 (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 dyslipidaemia) and found that medication adherence was associated with 1.18 (for dyslipidaemia) to 5.72 (for CHF) fewer days in inpatient stays, 0.01 to 0.04 reduction in ED visits and a corresponding US$1258 (for dyslipidaemia) to US$7823 (for CHF) reduction in total annual healthcare.[15] Boye *et al*[17] examined patients with type 2 diabetes and found that every 1% increase in medication adherence was associated with on average US$65 464 all-cause cost savings among 1000 patients, similarly driven by the lowered probability of hospitalisations and ED visits.

While a myriad of studies have found an inverse relationship between medication adherence and non-drug healthcare utilisation 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 utilisations and costs among patients with breast cancer. One 4-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 HT.[18] While this finding was informative, more research focusing on patients with breast cancer among a broader sample of Medicare beneficiaries are needed. In this study, we used a nationally representative sample of Medicare beneficiaries to examine the relationships between HT adherence and non-drug healthcare utilisation 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 utilisation and healthcare costs among patients with breast cancer? We hypothesise that the non-drug healthcare utilisation will be lower among patients with breast cancer who adhere to HT compared with 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 with non-adherent patients.

METHOD

Data source

We used SEER-Medicare linked database for the years 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 US population. The linked Medicare component includes beneficiaries'

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=6045)

Characteristics	Number (%)*
Median age, years (range)	74.6 (65–103)
Age group	
65–69	1748 (28.9)
70–74	1537 (25.4)
75–79	1242 (20.6)
80+	1518 (25.1)
Race/ethnicity	
White, non-Hispanic	5068 (83.8)
Black	392 (6.5)
Hispanic	334 (5.5)
Asian	251 (4.2)
Comorbidity (HCC score)	
0	2098 (36.9)
1	1504 (26.5)
2	918 (16.2)
3+	1161 (20.4)
Marital status	
Married	2570 (42.5)
Unmarried	3475 (57.5)
Tumour stage	
I	3297 (54.5)
II	2124 (35.1)
III	624 (10.3)
Treatment	
Surgery +radiation	3155 (52.2)
Surgery, no radiation	2709 (44.8)
No surgery	181 (3.0)

*Values are number (percentage) unless indicated otherwise.
HCC, Hierarchical Condition Category.

Table 2 Hormone therapy adherence, healthcare utilisation and costs over the full course of aromatase inhibitor treatment among Medicare beneficiaries with breast cancer

Variables	Year 1 (n=6045)	Year 2 (n=5847)	Year 3 (n=5592)	Year 4 (n=5322)	Year 5 (n=4993)
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 (%)	3878 (64.2)	2855 (48.8)	2837 (50.7)	2848 (53.5)	1848 (39.4)
Outcome variables					
Healthcare utilisation					
Any hospitalisation, n (%)	1166 (19.3)	862 (14.7)	873 (15.6)	1123 (21.1)	1174 (23.5)
Number of hospitalisation (>0), mean (SD)	2.0 (1.7)	1.9 (1.5)	2.0 (1.5)	2.2 (1.9)	2.2 (1.7)
Number 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 (%)	5636 (93.2)	5281 (90.3)	4969 (88.9)	4693 (88.2)	4395 (88.0)
Number 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 (%)	6041 (99.9)	5832 (99.7)	5567 (99.5)	5297 (99.5)	4956 (99.3)
Number 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, US$ 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)	9630 (4,223)	10 148 (4,047)	11 611 (3,950)	10 096 (2,894)
Hospitalisation costs (>0)	22 700 (12,654)	22 084 (13,114)	23 853 (15,309)	25 461 (15,894)	20 993 (11,515)
Outpatient costs	3708 (1,232)	1916 (671)	1976 (617)	1918 (571)	1556 (390)
Physician costs	6680 (3,942)	4458 (2,886)	4448 (2,767)	4319 (2,600)	3604 (1,926)
Total pharmacy costs	6664 (5,677)	5574 (4,623)	4735 (3,475)	3751 (2,371)	2875 (1,452)

MPR, medication possession ratio.

enrolment, prescription drug use and costs and non-drug healthcare utilisation and costs information.[19]

Study sample

Our study sample is women diagnosed with HR-positive early stage breast cancer in years from 2007 to mid-2009 in the USA. 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 5 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 (ie, hospital or skilled nurse facility). The screening process for constructing our study cohort is found in supplementary material (online supplemental appendix A).

Variables

Dependent variables

We examined the non-drug healthcare utilisation and healthcare costs for the patients' first year of AI treatment and each year, thereafter, for a total of 5 years (year 1 through year 5). Variables of non-drug healthcare utilisation included any hospitalisation, 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 standardised 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 an update to five MPRs: first year of AI treatment and each year, thereafter, for a total of 5 years (year 1 through year 5). If a patient died, he/she was excluded from the following years. MPR values in

Table 3 Unadjusted annual healthcare utilisation and costs in adherent and nonadherent Medicare beneficiaries with breast cancer over the full course of treatment

Variables	Adherent	Non-adherent	P
Healthcare utilisation			
Any hospitalisation, 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*
Number of hospitalisation (>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
Number 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	3612 (93.1)	2024 (93.4)	NS
Year 2	2600 (91.1)	2681 (89.6)	NS
Year 3	2537 (89.4)	2432 (88.3)	NS
Year 4	2564 (90.0)	2129 (86.1)	*<0.001*
Year 5	1766 (89.8)	2629 (86.9)	*<0.01*
Number 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
Number of physician office visits, mean (SD)			
Year 1	28.5 (17.3)	30.3 (18.1)	*<0.001*
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, US$ 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*

Continued

Table 3 Continued

Variables	Adherent	Non-adherent	P
Year 5	12 758 (5,837)	13 109 (5,238)	NS
Total medical costs, US$ mean (median)			
Year 1	14 306 (7,513)	15 594 (7,775)	*<0.05*
Year 2	9090 (4,111)	10 144 (4,324)	*<0.05*
Year 3	9025 (3,923)	11 304 (4,209)	*<0.001*
Year 4	10 067 (3,688)	13 389 (4,283)	*<0.001*
Year 5	9103 (2,772)	10 741 (2,981)	*<0.01*
Total hospitalisation costs, US$ 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, US$ mean (median)			
Year 1	4528 (2,035)	5151 (2,177)	NS
Year 2	3380 (1,514)	3768 (1,481)	NS
Year 3	3527 (1,549)	4316 (1,483)	NS
Year 4	3485 (1,597)	3991 (1,420)	NS
Year 5	3010 (943)	2925 (1,019)	NS
Total physician costs, US$ mean (median)			
Year 1	9602 (6,915)	11 352 (8,175)	*<0.01*
Year 2	8325 (6,093)	8323 (6,250)	NS
Year 3	8289 (6,290)	8892 (6,128)	NS
Year 4	7639 (5,697)	9069 (6,308)	*<0.01*
Year 5	6366 (4,588)	6810 (4,737)	NS
Total pharmacy costs, US$ mean (median)			
Year 1	7719 (6,561)	4776 (4,090)	*<0.001*
Year 2	7534 (6,443)	3705 (3,150)	*<0.001*
Year 3	6084 (5,032)	3347 (2,539)	*<0.001*
Year 4	4495 (2,951)	2893 (1,847)	*<0.001*
Year 5	3656 (1,954)	2367 (1,235)	*<0.001*

Note: NS stands for not significant.

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 analysed 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, tumour 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 utilisation and costs. The descriptions of full list of our variables are shown in supplementary material (online supplemental 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 hospitalisation (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 hospitalisation. We also calculated the average healthcare costs to

Table 4 Adjusted healthcare utilisation and costs among Medicare beneficiaries with breast cancer over the full course of treatment

Variables	MPR*	P
Healthcare utilisation		
Number of hospitalisations†	−0.009	*<0.001*
Number of hospital days	−0.088	*<0.01*
Number of outpatient visits	−0.018	NS
Number 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 hospitalisation 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.
*The prediction model controlled for other covariate, full results see online supplemental material (online supplemental appendix C).
†An example for interpreting the finding: every 10% increase in MPR was associated with 0.009 less number of hospitalisations (p<0.001).
MPR, medication possession ratio.

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 modelling methods for each of our outcome measures as described in the following and selected covariates to include as adjustors. Zero-inflated negative binomial models were adopted to predict LOS and the numbers of hospitalisation stays and outpatient visits, and negative binomial models were 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 generalised linear models (GLMs) with log link and gamma distribution for estimation. For hospitalisation costs, we adopted a two-part model, since only approximately 20% of our study sample had hospitalisations. In this model, the first part was a logistic regression model to predict the likelihood of having a non-zero hospitalisation costs, and the second part of the model used GLM to estimate the non-zero hospitalisation costs. All statistical analyses were conducted using SAS V.9.3[25] or Stata V.14[26] where applicable.

Patient and public involvement statement

Patients and or public were not involved.

RESULTS

There were 6045 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 utilisation 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 (ie, MPR>=80%) ranged from 39.4% to 64.2%. On average, about 20% of surviving patients each year had at least one hospitalisation 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 hospitalisation 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 US$12 970 to US$21 431 over the 5 years of AI treatment (this translates to US$14 957 to US$24 714 in 2021 US dollars), while medication costs accounted for 22%–31% of the total healthcare costs each year (US$2875–US$6664).

Table 3 presents the unadjusted annual non-drug healthcare utilisation and costs in adherent and non-adherent Medicare beneficiaries across their 5 years of treatment. For year 3 through year 5, a significantly lower percentage of adherent beneficiaries had at least one hospitalisation compared with non-adherent beneficiaries. Among those with hospitalisations, however, neither number of stays nor mean LOS were statistically significant different in any year. Conversely, the per cent of adherent beneficiaries who had any outpatient visits was higher than the per cent 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 5 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 non-adherent beneficiaries, which led to slightly higher total healthcare costs among adherent beneficiaries compared with non-adherent beneficiaries.

Results of adjusted models predicting the association between MPR and non-drug healthcare utilisation and costs are shown in table 4. The results showed that the increased MPR was statistically significantly associated with fewer hospitalisations, shorter LOS, 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 utilisation measures are always lower for adherent beneficiaries compared with non-adherent beneficiaries. Adherent beneficiaries had fewer hospitalisations (0.35

Table 5 Adjusted healthcare utilisation and costs for Medicare beneficiaries' adherent and non-adherent to hormone therapy over the full course of treatment

Variables	Adherent*	Non-adherent	Difference	P†
Healthcare utilisation	Margin (SE)	Margin (SE)	Margin (SE)	
Number of hospitalisation	0.35 (0.01)	0.43 (0.01)	−0.08 (0.01)	*<0.001*
Number of hospital days	4.19 (0.16)	4.89 (0.18)	−0.70 (0.22)	*<0.01*
Number of outpatient visits	6.45 (0.05)	6.54 (0.06)	−0.09 (0.08)	NS
Number 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	16246 (164)	16077 (200)	169 (262)	NS
Medical costs	10310 (152)	12551 (195)	−2,242 (249)	*<0.001*
Hospitalisation costs	3811 (115)	4840 (141)	−1,028 (183)	*<0.001*
Outpatient costs	2070 (37)	2484 (54)	−414 (65)	*<0.001*
Physician costs	4389 (47)	5190 (63)	−801 (77)	*<0.001*
Pharmacy costs	5891 (46)	3577 (37)	2314 (61)	*<0.001*

*The prediction model controlled for other covariate, full results see Supplementary Material (online supplemental appendix D).
†NS stands for not significant.

vs 0.43, p<0.001) and fewer physician office visits (25.16 vs 26.17, p<0.001) and shorter LOS during hospitalisation (4.19 vs 4.89, p<0.01). On average, Medicare paid US$2314 (p<0.001) more on medications for adherent beneficiaries, but US$2242 (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 was generated by an individual multivariant regression analysis as indicated in the method section. Full results are found in supplementary material (online supplemental appendices C and D).

DISCUSSION

Our study explored the relationships between HT adherence and non-drug healthcare utilisation and costs among patients with breast cancer. To our knowledge, this is one of the first studies to examine the association of medication adherence and non-drug healthcare utilisation and costs across the full 5-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 hospitalisations. This is expected, since staying on HT 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 HT adherence is all but offset by the reduced cost for other categories of medical care.

To determine the contingent effect of medication adherence on healthcare utilisation and costs, we included unalterable patient level factors in our models such as age, race and tumour stage at time of diagnosis. These factors are known to be strongly associated with adherence and, thus, also impact utilisation and costs. However, they are not factors that clinicians and policymakers can directly change. Nevertheless, earlier analyses have identified two manageable factors that could improve adherence, and by doing so, impact healthcare utilisation 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 patients with breast cancer 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 contain real-world information on HT adherence and non-drug healthcare utilisation 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 AI to other HT medications (ie, tamoxifen). Second, 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. Third, 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 utilisation were solely associated with better adherence. It is possible that patients who were more adherent to HT 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 analyse the association between HT adherence and non-drug healthcare utilisation and costs among Medicare beneficiaries over the full course of treatment. Our results suggested that better adherence is associated with lower healthcare utilisation 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 patients with breast cancer to improve their long-term oral medication adherence. Policymakers 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.

Contributors Study concepts: SM, CT, REM. Study design: SM, GAR. Data acquisition: SM, CT. Data analysis and interpretation: SM, GAR, CT, DSS. Statistical analysis: SM, GR. Manuscript preparation: SM, CT, GAR, DSS. Manuscript editing: SM, CT, DSS, REM, GAR. Manuscript review: SM, CT, DSS, REM, GAR. SM acts as the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

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

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. N/A.

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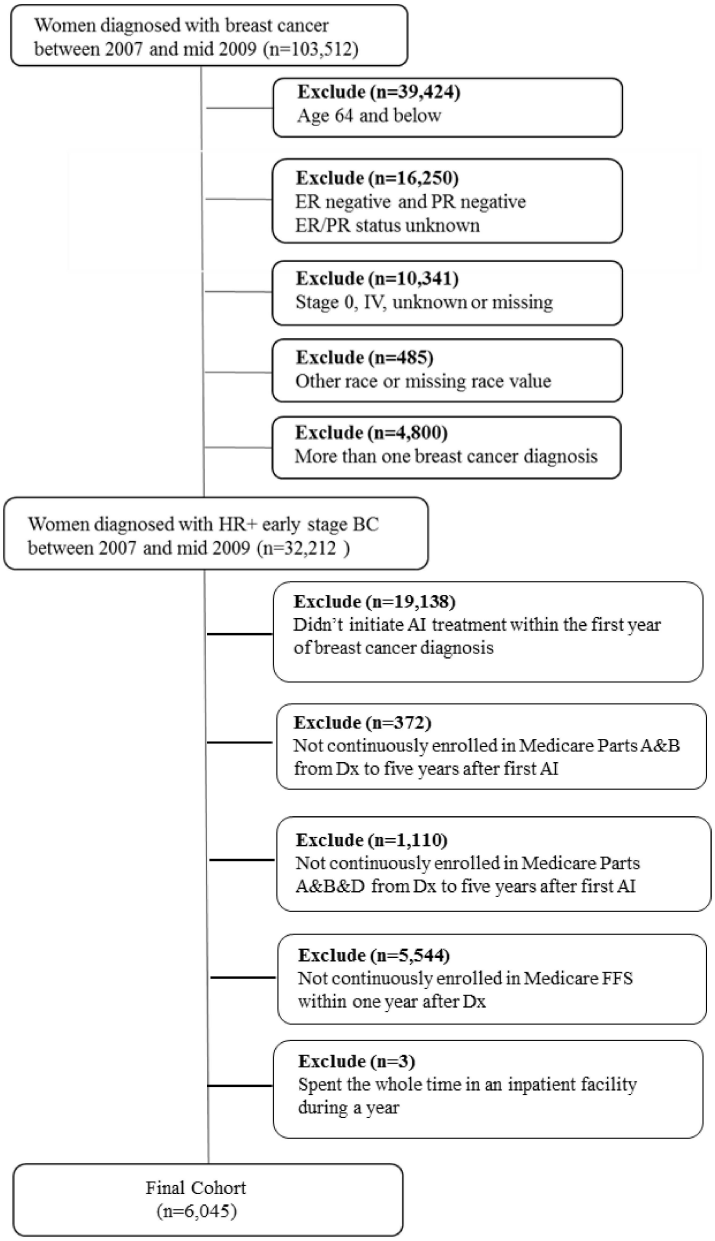
Appendix A. Selection Criteria for Identifying Medicare Beneficiaries Diagnosed with Hormone Receptor-Positive Early Stage Breast Cancer from 2007 to Mid-2009



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 1 Stage I 2 Stage II 3 Stage III
Initial Surgery/Radiation Treatment	A categorical variable where 1 No surgery 2 Surgery (breast-conserving surgery or mastectomy) + radiation 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*