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Association Between Out-Of-Pocket Costs, Race/Ethnicity, and Adjuvant Endocrine Therapy Adherence Among Medicare Patients With Breast Cancer

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ABSTRACT

Purpose

Previous studies suggest that adherence to adjuvant endocrine therapy (AET) for patients with breast cancer is suboptimal, especially among minorities, and is associated with out-of-pocket medication costs. This study aimed to determine whether there are racial/ethnic differences in 1-year adherence to AET and whether out-of-pocket costs explain the racial/ethnic disparities in adherence.

Methods

This retrospective cohort study used the SEER-Medicare linked database to identify patients ≥ 65 years of age with hormone receptor–positive breast cancer who were enrolled in Medicare Part D from 2007 to 2009. The cohort included non-Hispanic whites, blacks, Hispanics, and Asians. Out-of-pocket costs for AET medications were standardized for a 30-day supply. Adherence to tamoxifen, aromatase inhibitors (AIs), and overall AET (tamoxifen or AIs) was assessed using the medication possession ratio (≥ 80%) during the 12-month period.

Results

Of 8,688 patients, 3,197 (36.8%) were nonadherent to AET. Out-of-pocket costs for AET medication were associated with lower adjusted odds of adherence for all four cost categories compared with the lowest category of ≤ $2.65 ($P < .01$). In the univariable analysis, Hispanics had higher odds of adherence to any AET at initiation (OR, 1.30; 95% CI, 1.07 to 1.57), and blacks had higher odds of adherence to AIs at initiation (OR, 1.27; 95% CI, 1.04 to 1.54) compared with non-Hispanic whites. After adjusting for copayments, poverty status, and comorbidities, the association was no longer significant for Hispanics (OR, 0.95; 95% CI, 0.78 to 1.17) or blacks (OR, 0.96; 95% CI, 0.77 to 1.19). Blacks had significantly lower adjusted odds of adherence than non-Hispanic whites when they initiated AET therapy with tamoxifen (OR, 0.54; 95% CI, 0.31 to 0.93) after adjusting for socio-economic, clinic, and prognostic factors.

Conclusion

Racial/ethnic disparities in AET adherence were largely explained by women's differences in socioeconomic status and out-of-pocket medication costs.

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INTRODUCTION

Black and Hispanic women experience an increased risk of breast cancer death compared with non-Hispanic white women.[1-4] These racial/ethnic disparities in mortality have been attributed to late stage at diagnosis,[2,3] socioeconomic status,[4] tumor subtypes,[5,6] and the initiation and timing of effective, recommended treatment of breast cancer.[2,4] One way to significantly reduce breast cancer mortality is to improve adherence to recommended treatment.[7] Adherence to guidelines for systemic adjuvant endocrine therapy (AET) is associated with improved disease-free survival for women with early-stage breast cancer.[8-12] Treatment with tamoxifen can reduce 5-year mortality by up to 26%.[8,10,13]

AET treatment includes tamoxifen and the aromatase inhibitors (AIs) exemestane, anastrozole, and letrozole. The National Comprehensive Cancer Network recommends that postmenopausal women diagnosed with early breast cancer receive either AI as initial adjuvant therapy for 5 years, or tamoxifen for 2 to 3 years followed by an AI to complete 5 years, or tamoxifen alone for 5 years

for women who have contraindications to AIs.[14] In general, the drugs are taken orally every day.[14] There is no clear indication whether tamoxifen or AIs should be the first line of adjuvant endocrine treatment for older postmenopausal women. Understanding adherence during the first 12 months of treatment following breast cancer diagnosis may provide evidence for the effective use of one drug over the other.

Despite the effectiveness of AET in improving survival and decreasing cancer recurrence, adherence rates remain low. In studies of treatment adherence, in which adherence is defined as possessing ≥ 80% of the prescribed medication over a 1-year period, 55% to 75% of patients with breast cancer are adherent.[16] Low adherence is associated with the number of other medications prescribed for comorbidities,[17] demographic characteristics such as age,[18,19] and AET adverse effects.[16,20-24] Previous studies have examined lower adherence rates for nonwhite women, a finding that may contribute to the disparity in breast cancer mortality observed between minorities and white women.[18,25,26] A study by Hershman et al[25] found that household net worth partially explains the racial disparity in AET adherence. However, the study examined overall AET medication but not the AIs or tamoxifen separately. This is important because we recently found that Hispanic and black women were more likely to initiate AET with AIs than were non-Hispanic white women.[27] It is important to examine differences in the type of AET medication because the out-of-pocket costs for AIs and tamoxifen vary, and higher copayments are inversely associated with AET adherence.[28,29] A review by Ursem et al[26] underscored the importance of drug costs on the impact of adherence for low-income women. However, little evidence exists about which AET medications at initiation are associated with 12-month adherence in a diverse cohort of postmenopausal women and whether out-of-pocket costs for AET explain the adherence disparities. Therefore, the objective of this study was to identify whether there are racial/ethnic and sociodemographic differences in 1-year adherence to AET overall and adherence to tamoxifen and the AIs separately and to determine to what extent out-of-pocket costs explain the racial/ethnic disparities in AI and tamoxifen adherence.

METHODS

Data Source

This study used the National Cancer Institute's SEER-Medicare linked database for patients from 2007 to 2009 with Medicare Part D claims up to December 2010.[27,30,31] Briefly, information collected includes patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up vital statistics.

Study Design and Population

This was a retrospective cohort study restricted to women who were indicated for AET treatment.[14] We included women ≥ 65 years of age with stage I to III hormone receptor–positive breast cancer enrolled in Medicare for at least 12 months before and after the date they filled their first AET prescription (either tamoxifen or AI; Fig 1). Women were excluded if they had unknown or estrogen receptor– and progesterone receptor–negative hormone receptor status, were not enrolled in Medicare Part D or both Parts A and B, or were enrolled in a health maintenance organization from the year of diagnosis to the last follow-up.
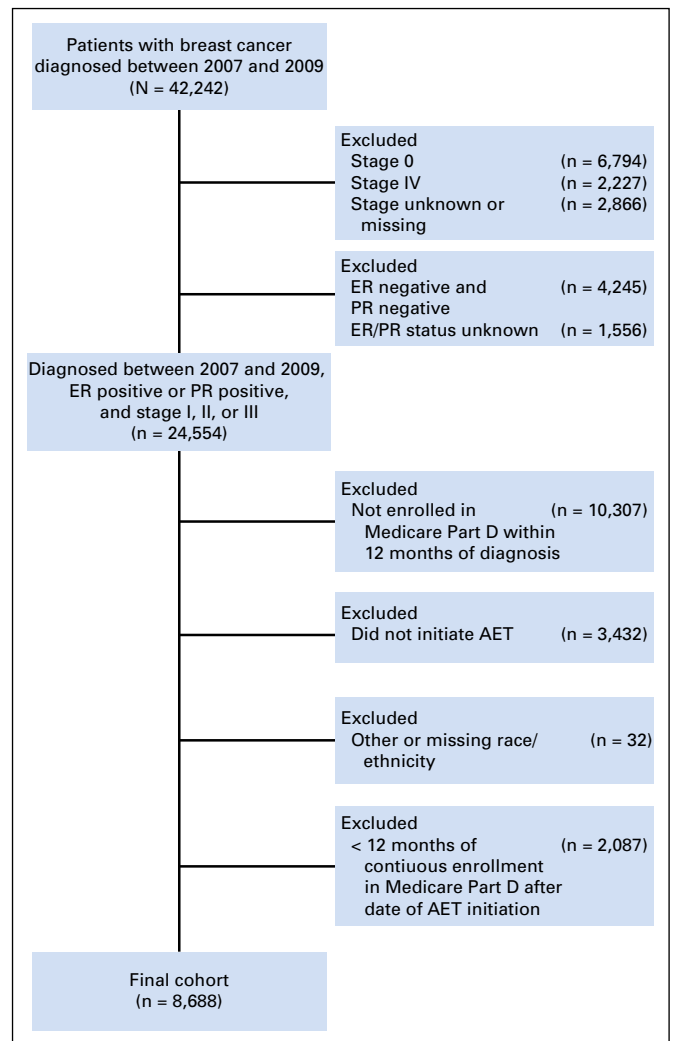
Fig 1. Study diagram for identifying the cohort of women with hormone receptor–positive breast cancer who initiated adjuvant endocrine therapy (AET) from 2007 to 2009. ER, estrogen receptor; PR, progesterone receptor.

Dependent Variable

Medicare Part D drug claims contain information on person-specific drug use, such as date of service, product generic name identifier, quantity dispensed, and days of supply. Initiation of AET was defined as a single prescription for tamoxifen or an AI on the basis of the generic drug name up to 1 year after the date of breast cancer diagnosis. AIs were defined as anastrozole, exemestane, or letrozole. Adherence was defined by the medication possession ratio (≥ 80%) on the basis of the number of pills supplied over the 12 months following the initial AET prescription.

Independent Variables

We identified women who belonged to four racial/ethnic groups: non-Hispanic white, black/African American, Hispanic, and Asian. Race was identified using the SEER variable combined with the Hispanic origin variable.[32] If race/ethnicity data were missing or unknown in the SEER registry, we used Medicare data to identify the patient's race/ethnicity (Fig 1).

Demographic information included age (65 to 115 years) and marital status. Socioeconomic information obtained from the 2000 US Census included the percentage of residents living below federal poverty level (FPL) at the census tract level and whether they lived in a metropolitan region.[4,31] Tumor characteristics included American Joint Committee on

Cancer tumor stage, size, grade, and lymph node status. Chemotherapy use, radiation therapy, and surgery were identified through procedure codes on Medicare claims made within 6 months of diagnosis.[4] The 18 comorbid conditions were ascertained from diagnoses or procedure codes in Medicare claims data that were made between 1 year before and 1 month after breast cancer diagnosis. Comorbidity scores were then generated using the Charlson comorbidity index, which assigns different weights according to the severity of different conditions,[33] described in detail elsewhere.[31,33-35]

Out-of-pocket costs for AET medications were measured as the total out-of-pocket payments made by the patient for the 12-month study period at the time AET medications were filled. The dollar sum of the total payments made by the patient was divided by the number of days of medication supplied to obtain the cost per pill; this was multiplied by 30 to standardize the 30-day amounts because prescriptions could have been for a 30-, 60-, or 90-day supply at each fill. These costs included copayments, deductibles, and coinsurance associated with the prescription. The mean 30-day out-of-pocket cost for AET medication was categorized into quintiles: $0 to $2.65, $2.66 to $10.00, $10.01 to $41.25, $41.26 to $105.55, or > $105.55.

Statistical Analysis

Differences in the distribution of sociodemographic and tumor characteristics were first examined across racial/ethnic groups and then by adherence to AET (combined, tamoxifen at initiation, and AI at initiation). We used the χ^2 tests to assess significant differences between groups with respect to categorical variables, and analysis of variance tests were used to assess differences for continuous variable age. Three multivariable logistic regression models were performed to assess the association of race/ethnicity and AET adherence, tamoxifen only, and AIs only. Collinearity of all independent variables was tested using multiple collinearity tests, and no variable was removed because none had a value > 0.7, and the variance inflation factor was > 10. We considered a priori significance level at $P < .05$. To assess whether racial/ethnic differences in adherence were explained by covariates, each variable was screened individually in the model along with race/ethnicity. The association between race and adherence was assessed after demographic, prognostic, and clinic factors and out-of-pocket AET costs were added. As a sensitivity analysis, we ran these regression models excluding patients with continuous Medicare-Medicaid dual coverage during the 12-month study period to see whether the main effects changed. Analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC).

RESULTS

We identified 8,688 patients diagnosed with hormone receptor–positive breast cancer who initiated AET therapy (Fig 1). The mean age at diagnosis was 75.1 years (standard deviation, 7.0; range, 65 to 103 years) for all patients and was 75.2, 75.3, 73.8, and 75.1 years for non-Hispanic whites, blacks, Hispanics, and Asians, respectively. The mean ages and other demographic, treatment, and prognostic factors differed significantly among racial/ethnic groups except for year at diagnosis ($P < .05$; Table 1). The majority of women were non-Hispanic white (82.9%), followed by black (6.3%) and Hispanic (6.0%). The majority of black (73.3%) and Hispanic (60.6%) patients lived in areas where > 11.8% of the population were below the FPL compared with non-Hispanic white patients (29.6%). A greater proportion of black patients (31.4%) had comorbidity scores of ≥ 2 compared with non-Hispanic white patients (15.2%). A larger proportion of black, Hispanic, and Asian patients had out-of-pocket costs of $0 to $2.65 for a 30-day supply of AET medication compared with non-Hispanic white patients (41.4%, 45.9%, and 44.2% v 15.3%, respectively).

Of the 8,688 patients, 5,491 (63.2%) were adherent during the 12-month study period. Non-Hispanic whites were 3% to 13% less adherent than blacks, Hispanics, or Asians (62.1% v 64.8%, 68.0%, and 75.4%, respectively). Adherence to tamoxifen (72.2%) was higher than AIs (61.4%). Adherence to tamoxifen was lowest for patients who paid > $105.55 for mean out-of-pocket costs for a 30-day supply of AET (38.5%) and higher for those who paid ≤ $2.65 (74.7%; Table 2).

In the adjusted analyses, adherence to any AET was not significantly associated with being Hispanic or black compared with being non-Hispanic white (Table 3). However, being Asian, compared with being non-Hispanic white, was significantly associated with higher adherence (odds ratio [OR], 1.48; 95% CI, 1.15 to 1.89). Blacks compared with non-Hispanic whites were associated with lower odds of adherence to tamoxifen at initiation (OR, 0.54; 95% CI, 0.31 to 0.93), even after controlling for all other study variables. Patients who initiated AI therapy had significantly lower odds of adherence than those who initiated tamoxifen therapy (OR, 0.81; 95% CI, 0.71 to 0.94). Mean out-of-pocket costs for a 30-day supply of AET medication for all cost categories (> $10.01) compared with the lowest quintile (≤ $2.65; $P < 0.01$) was associated with lower odds of adherence to any AET, tamoxifen, or AI at initiation. For instance, women with mean 30-day, out-of-pocket costs of $10.01 to $41.25 had significantly lower odds of adherence than did those with out-of-pocket costs of ≤ $2.65 (OR, 0.65; 95% CI, 0.56 to 0.76). Unmarried women had significantly lower odds of adherence compared with married women (OR, 0.89; 95% CI, 0.79 to 0.97). Those who lived in areas where > 11.8% of the population was below the FPL had lower odds of adherence compared with those living in areas where < 5.4% was below the FPL (OR, 0.89; 95% CI, 0.76 to 0.99). Patients with comorbidity scores > 3 had lower odds of adherence compared with patients without comorbidities (OR, 0.68; 95% CI, 0.57 to 0.82). In this cohort, 15.4% of patients had Medicare-Medicaid dual coverage. After excluding these patients from the analysis, the main results remained significant, although the effect size moved away from the null. For example, patients who paid between $10.01 and $41.25 compared with those who paid 0$ to $2.65 had an adjusted odds of adherence of 0.65 (95% CI, 0.56 to 0.76), whereas in the sensitivity analysis, excluding dual coverage patients, the adjusted odds of adherence was 0.29 (95% CI, 0.23 to 0.35) for the same groups.

The relationships between race, out-of-pocket AET costs, and adherence are illustrated in multiple models (Table 4). In the unadjusted models, the odds of AET adherence for Hispanics were 30% greater than for non-Hispanic whites. After adjustment for comorbidities and FPL, the association persisted. Including FPL in the model, however, did affect the OR for the association between race/ethnicity and adherence for patients who initiated with tamoxifen or an AI, but the association persisted. However, after considering copay, the association was no longer significant (OR, 0.95; 95% CI, 0.78 to 1.17). The addition of further clinical and sociodemographic variables only had a slight additional effect on the relationship between Hispanics and adherence in the full model (OR, 0.94; 95% CI, 0.76 to 1.15). The same relationship between race, copayment, and adherence was observed among Hispanics and blacks who initiated treatment with AIs compared with non-Hispanic whites. Asians had significantly greater odds of adherence

Table 1. Characteristics of Women, by Race/Ethnicity, Diagnosed With Stage I to III Hormone Receptor–Positive Breast Cancer From 2007 to 2009 Who Initiated AET

Characteristic	Non-Hispanic White No. (%)	Black No. (%)	Hispanic No. (%)	Asian No. (%)	P*
Median age, years (range)	75.2 (65-103)	75.3 (65-101)	73.8 (65-93)	75.1 (65-97)	< .001
Age, years					< .001
65-69	1,906 (26.5)	134 (24.7)	164 (31.2)	107 (25.9)	
70-74	1,808 (25.1)	154 (28.4)	144 (27.4)	87 (21.0)	
75-79	1,476 (20.5)	111 (20.4)	116 (22.1)	126 (30.4)	
≥ 80	2,016 (28.0)	144 (26.5)	101 (19.2)	94 (22.7)	
Marital status					< .001
Married	3,115 (43.2)	106 (19.5)	191 (36.4)	208 (50.2)	
Unmarried	3,809 (52.9)	412 (75.9)	316 (60.2)	< 48%†	
Unknown	282 (3.9)	25 (4.6)	18 (3.4)	< 3%†	
SES (% living below poverty)					< .001
First tertile (< 5.4%)	2,649 (36.8)	48 (8.8)	80 (15.2)	126 (30.4)	
Second tertile (5.4%-11.8%)	2,493 (34.6)	97 (17.9)	127 (24.2)	152 (36.7)	
Third tertile (> 11.8%)	2,064 (28.6)	398 (73.3)	318 (60.6)	136 (32.9)	
SEER registry region					< .001
Northeast	1,608 (22.3)	110 (20.3)	82 (15.6)	37 (8.9)	
South	1,874 (26.0)	265 (48.8)	< 5%†	< 3%†	
Midwest	913 (12.7)	62 (11.4)	< 3%†	< 3%†	
West	2,811 (39.0)	106 (19.5)	418 (79.6)	362 (87.4)	
Metropolitan area (yes)‡	5,766 (80.0)	462 (85.1)	472 (89.9)	395 (95.4)	< .001
Comorbidity scores					< .001
0	4,335 (60.2)	219 (40.3)	282 (53.7)	217 (52.4)	
1	1,775 (24.6)	154 (28.4)	152 (29.0)	136 (32.9)	
2	630 (8.7)	85 (15.7)	48 (9.1)	38 (9.2)	
≥ 3	466 (6.5)	85 (15.7)	43 (8.2)	23 (5.6)	
Year of diagnosis					.60
2007	2,828 (39.3)	218 (40.2)	205 (39.1)	149 (36.0)	
2008	2,701 (37.5)	212 (39.0)	207 (39.4)	164 (39.6)	
2009	1,677 (23.3)	113 (20.8)	113 (21.5)	101 (24.4)	
Tumor stage					< .001
I	4,109 (57.0)	240 (44.2)	269 (51.2)	229 (55.3)	
II	2,433 (33.8)	232 (42.7)	179 (34.1)	142 (34.3)	
III	664 (9.2)	71 (13.1)	77 (14.7)	43 (10.4)	
Tumor size (cm)					< .001
< 1.0	4,190 (58.2)	243 (44.8)	266 (50.7)	228 (55.1)	
≥ 1.0	2,705 (37.5)	276 (50.8)	235 (44.8)	168 (40.6)	
Unknown	311 (4.3)	24 (4.4)	24 (4.6)	18 (4.4)	
Lymph node positivity					< .001
0 (negative)	4,712 (65.4)	297 (54.7)	330 (62.9)	278 (67.2)	
≥ 1	1,780 (24.7)	153 (28.2)	151 (28.8)	103 (24.9)	
Unknown	714 (9.9)	93 (17.1)	44 (8.4)	33 (8.0)	
Tumor grade					< .001
Well differentiated	2,030 (28.2)	110 (20.3)	128 (24.4)	110 (26.6)	
Moderately differentiated	3,569 (49.5)	255 (47.0)	269 (51.2)	200 (48.3)	
Poorly differentiated	1,281 (17.8)	143 (26.3)	106 (20.2)	88 (21.3)	
Unknown	326 (4.5)	35 (6.5)	22 (4.2)	16 (3.9)	
Surgery					< .001
None	148 (2.1)	36 (6.6)	13 (2.5)	< 3%†	
BCS	4,403 (61.1)	264 (48.6)	308 (58.7)	229 (55.3)	
Mastectomy	2,655 (36.8)	243 (44.8)	204 (38.9)	< 44%†	
Receiving chemotherapy	1,459 (20.3)	135 (24.9)	149 (28.4)	92 (22.2)	< .001
Receiving radiation therapy	4,349 (60.4)	271 (49.9)	335 (63.8)	232 (56.0)	< .001
Mean out-of-pocket costs for 30-day supply of AET, $					< .001
≤ 2.65	1,105 (15.3)	225 (41.4)	241 (45.9)	183 (44.2)	
2.66-10.00	1,337 (18.6)	188 (34.6)	133 (25.3)	80 (19.3)	
10.01-41.25	1,538 (21.3)	51 (9.4)	51 (9.7)	82 (19.8)	
41.26-105.55	1,600 (22.2)	40 (7.4)	64 (12.2)	32 (7.7)	
> 105.55	1,626 (22.6)	39 (7.2)	36 (6.9)	37 (8.9)	
Total	7,206 (82.9)	543 (6.3)	525 (6.0)	414 (4.8)	

Abbreviations: AET, adjuvant endocrine therapy; BCS, breast-conserving surgery; SES, socioeconomic status.
*P value for χ^2 test of significance for categorical variables and an analysis of variance for the continuous variable age.
†Actual percentages were not reported to avoid n < 11 reporting, as required by the data-user agreement.
‡Percentage living in a metropolitan area.

Table 2. Percentage of Patients With Adherence to AET Treatment Among Those With Stage I to III Hormone Receptor–Positive Breast Cancer Who Initiated AET, by AET Type

Characteristic	Patients Adherent to AET (%)	P	Patients Adherent Who Initiated With Tamoxifen (%)	P	Patients Adherent Who Initiated With AIs (%)	P
Race/ethnicity		< .001		.25		< .001
Non-Hispanic white	62.1		75.5		59.8	
Non-Hispanic black	64.8		62.0		65.3	
Hispanic	68.0		72.3		67.4	
Asian	75.4		75.9		75.3	
Age, years		.40		.56		.33
65-69	64.3		74.1		62.7	
70-74	62.8		72.6		60.8	
75-79	63.9		73.2		61.9	
≥ 80	62.2		69.9		60.0	
Marital status		.95		.47		.91
Married	63.3		73.5		61.3	
Unmarried	63.3		71.0		61.5	
Unknown	62.5		76.1		60.3	
SES, % living below poverty		.62		.09		.22
First tertile (< 5.4)	63.4		68.1		62.6	
Second tertile (5.4-11.8)	62.6		73.4		60.1	
Third tertile (> 11.8%)	63.8		74.1		61.4	
SEER registry region		< .001		.04		< .001
Northeast	65.5		72.1		64.6	
South	59.6		67.7		57.8	
Midwest	62.0		78.0		56.2	
West	64.6		72.6		62.9	
Metropolitan area (yes)	63.3	.82	70.7	.05	61.9	.33
Comorbidity scores		.10		.64		.09
0	64.0		71.7		62.4	
1	61.2		71.3		59.1	
2	64.8		76.6		62.6	
≥ 3	62.4		74.0		60.0	
Year of diagnosis		< .01		.89		.01
2007	62.9		71.5		61.0	
2008	61.9		72.7		59.8	
2009	66.1		72.4		64.6	
AJCC tumor stage		.07		.46		.04
I	62.8		71.2		60.7	
II	64.7		73.4		63.2	
III	60.8		76.0		58.8	
Tumor size (cm)		.45		.52		.48
< 1.0	62.7		71.1		60.8	
≥ 1.0	64.0		73.9		62.2	
Unknown	64.2		73.0		61.5	
Number of positive nodes		.40		.07		.35
0 (node negative)	63.6		73.3		61.4	
≥ 1	62.1		72.3		60.5	
Unknown	63.9		65.0		63.6	
Tumor grade		.43		.23		.45
Well differentiated	62.2		70.2		60.3	
Moderately differentiated	63.6		74.3		61.4	
Poorly differentiated	63.1		68.5		62.2	
Unknown	65.2		74.3		64.4	
Surgery treatment		.96		.48		.78
No surgery	64.2		72.0		63.1	
BCS	63.3		71.1		61.6	
Mastectomy	63.2		74.0		61.0	
Chemotherapy		< .001		.48		< .01
Yes	64.2		72.5		62.3	
No	59.7		70.1		58.4	
Radiation therapy		.37		.95		.64
Yes	63.8		72.2		61.7	
No	62.9		72.1		61.2	

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Table 2. Percentage of Patients With Adherence to AET Treatment Among Those With Stage I to III Hormone Receptor–Positive Breast Cancer Who Initiated AET, by AET Type (continued)

Characteristic	Patients Adherent to AET (%)	P	Patients Adherent Who Initiated With Tamoxifen (%)	P	Patients Adherent Who Initiated With AIs (%)	P
Mean out-of-pocket costs for 30-day supply of AET, $		< .001		< .001		< .001
0-2.65	78.1		74.7		79.4	
2.66-10.00	71.2		75.9		68.0	
10.01-41.25	45.6		62.4		43.0	
41.26-105.55	55.2		58.0		55.1	
> 105.55	65.9		38.5		66.3	
Total	63.2		72.2		61.4	

Abbreviations: AET, adjuvant endocrine therapy; AI, aromatase inhibitor; AJCC, American Joint Committee on Cancer; BCS, breast-conserving surgery; SES, socioeconomic status.

compared with non-Hispanic whites, even after controlling for comorbidities, FPL status, copayment, and all other study variables for AET (OR, 1.48; 95% CI, 1.15 to 1.89) and for the AIs (OR, 1.59; 95% CI, 1.22 to 2.08).

DISCUSSION

This study found that out-of-pocket cost for a 30-day supply of AET medication was a main driver of the observed association of AET adherence for Hispanics compared with non-Hispanic whites. Prior studies did not find significant differences in AET adherence by race/ethnicity in younger, privately insured populations.[25,36] However, to our knowledge, this is the first study to examine racial/ethnic differences by type of AET in Medicare beneficiaries ≥ 65 years of age. Despite controlling for out-of-pocket AET costs, black women who initiated tamoxifen still had significantly lower odds of adherence than non-Hispanic white women. This finding is different from a recent study by Hershman et al,[25] which found that after controlling for net worth and copayment, there was no significant association between race and adherence. That study, however, examined overall AET use and not specifically AIs or tamoxifen.[25]

We observed that a suboptimal proportion of women (63.2%) were adherent to AET medication. This is lower than previous reports using similar claims-based methodology among insured women, which reported 72% to 81% 12-month adherence to AET.[28,37-39] Such studies, however, included a larger proportion of younger women taking tamoxifen.[28,37-39] This is important because our study had more women taking AIs (82.6%), which was associated with lower odds of adherence. Furthermore, the mean age of our study cohort was between 74 and 75 years, and extreme ages have been found to be associated with lower adherence as well as a higher number of comorbidities.[40,41]

Adherence to tamoxifen was better than to the AIs, which may be driven largely by cost because tamoxifen is available to patients in generic form.[29] However, even after adjustment, women who initiated treatment with an AI had significantly lower odds of adherence than did those who began with tamoxifen (OR, 0.81; 95% CI, 0.71 to 0.94), which may be affected by other factors, such as the AI adverse effects.[10,11,42,43] It should be noted that Arimidex (anastrozole; AstraZeneca, Wilmington, DE), although available now in generic form, was only available in brand name until the tail

end of our study (August 2010). This is significant, given that we previously found that Hispanic and black women were significantly more likely to have initiated therapy with AI than were non-Hispanic white women,[27] which, together with the findings from this study, may partly explain the racial/ethnic disparities in adherence.

Tamoxifen adherence was higher in patients who lived in areas with > 11.8% of the population below the FPL compared with those in areas with fewer people below the FPL, even after controlling for all other characteristics. This can be explained, in part, by the fact that minority patients (black and Hispanic) also had lower out-of-pocket costs ($0 to $2.65) and may be more likely to have Medicare-Medicaid dual coverage, which would cover the cost of medications.[44] The finding on the association between higher out-of-pocket AET costs and lower risk of adherence is similar to other retrospective cohort studies, which report that, on average, copayments decrease the odds of adherence to AIs or tamoxifen.[28,29,37,39] Similarly, we found that older women and women with fewer comorbidities had higher odds of adherence.[28,37-39]

This study has several strengths and could add new information to the literature on AET adherence for elderly women with breast cancer. Because Medicare data were linked with SEER registry data, we were able to assess the date of cancer diagnosis, which allowed us to study AET adherence during the first year of initiating therapy, which may be the most critical to address suboptimal adherence because women who discontinue AET do so within the first few months.[18,37] Next, we were able to include detailed baseline demographic and clinical characteristics, which may have confounded the observed associations with adherence and which were not available in other studies.[25,28,39,45] Prior reports on AET adherence that use insurance claims data alone may have misclassified patients initiating adjuvant treatment because those data did not have information on cancer diagnosis date, stage at diagnosis, and estrogen-receptor status.[25,28]

Our study was limited first, by the population, which included only women ≥ 65 years of age enrolled in Medicare Part D. Therefore, results may not be generalizable to younger patients or those not enrolled in Part D. Second, there could be unmeasured confounding factors, such as psychosocial factors related to the quality of care that women receive, including physician-patient communication, for example, that may influence women's AET adherence but could not be captured in this study.[46] Third, there may have been misclassification of race/ethnicity in the database.

Table 3. Multivariable Logistic Regression for Adherence to AET Among Women Diagnosed With Stage I to III Hormone Receptor–Positive Breast Cancer

Characteristic	Adherence to Any AET (n = 8,688)		Adherence to Tamoxifen at Initiation (n = 1,515)		Adherence to AI at Initiation (n = 7,173)	
	AOR	95% CI*	AOR	95% CI*	AOR	95% CI*
Race/ethnicity						
Non-Hispanic white	1		1		1	
Non-Hispanic black	0.92	0.75 to 1.12	0.54	0.31 to 0.93	1.01	0.81 to 1.26
Hispanic	0.94	0.76 to 1.15	0.75	0.41 to 1.36	0.98	0.78 to 1.22
Asian	1.48	1.15 to 1.89	1.10	0.57 to 2.12	1.59	1.22 to 2.08
Age, years						
65-69	1		1		1	
70-74	0.93	0.82 to 1.05	0.83	0.59 to 2.12	0.93	0.81 to 1.07
75-79	0.94	0.82 to 1.08	0.87	0.60 to 1.27	0.96	0.83 to 1.11
≥ 80	0.84	0.73 to 0.96	0.79	0.55 to 1.14	0.85	0.73 to 0.99
Marital status						
Married	1		1		1	
Unmarried	0.89	0.79 to 0.97	0.86	0.67 to 1.12	0.87	0.78 to 0.98
Unknown	0.91	0.71 to 1.16	0.97	0.47 to 2.00	0.90	0.69 to 1.17
SES, % living below poverty						
First tertile (< 5.4)	1		1		1	
Second tertile (5.4-11.8)	0.92	0.82 to 1.04	1.32	0.97 to 1.80	0.86	0.76 to 0.98
Third tertile (> 11.8)	0.87	0.76 to 0.99	1.56	1.11 to 2.20	0.79	0.68 to 0.91
SEER registry region						
Northeast	1		1		1	
South	0.74	0.64 to 0.86	0.62	0.41 to 0.93	0.78	0.67 to 0.92
Midwest	0.77	0.64 to 0.92	1.14	0.72 to 1.80	0.69	0.57 to 0.84
West	0.91	0.80 to 1.04	0.87	0.60 to 1.27	0.91	0.79 to 1.05
Metropolitan area (yes *v* no)	0.91	0.80 to 1.04	0.95	0.69 to 1.30	0.92	0.79 to 1.06
Comorbidity scores						
0	1		1		1	
1	0.78	0.70 to 0.87	1.00	0.76 to 1.32	0.74	0.66 to 0.83
2	0.85	0.72 to 1.00	1.40	0.89 to 2.21	0.77	0.64 to 0.93
≥ 3	0.68	0.57 to 0.82	1.21	0.74 to 1.99	0.61	0.50 to 0.75
Year of diagnosis						
2007	1		1		1	
2008	0.93	0.84 to 1.03	0.99	0.76 to 1.30	0.92	0.82 to 1.03
2009	1.11	0.98 to 1.25	0.96	0.71 to 1.30	1.16	0.75 to 1.33
AJCC tumor stage						
I	1		1		1	
II	1.21	1.01 to 1.45	1.39	0.85 to 2.26	1.20	0.99 to 1.45
III	1.06	0.82 to 1.38	1.75	0.84 to 3.67	1.00	0.75 to 1.33
Tumor size (cm)						
< 1.0	1		1		1	
≥ 1.0	0.96	0.83 to 1.11	0.97	0.65 to 1.43	0.94	0.90 to 1.11
Unknown size	1.03	0.82 to 1.29	1.15	0.69 to 1.91	1.02	0.79 to 1.32
Number of positive nodes						
0 (node negative)	1		1		1	
≥ 1	0.90	0.77 to 1.06	0.76	0.48 to 1.21	0.93	0.78 to 1.11
Unknown	0.95	0.79 to 1.13	0.73	0.49 to 1.08	1.00	0.82 to 1.22
Tumor grade						
Well differentiated	1		1		1	
Moderately differentiated	1.06	0.95 to 1.18	1.24	0.95 to 1.62	1.04	0.92 to 1.18
Poorly differentiated	1.08	0.93 to 1.24	0.93	0.65 to 1.34	1.11	0.95 to 1.30
Unknown	1.21	0.95 to 1.24	1.32	0.72 to 2.41	1.22	0.94 to 1.58
Surgery treatment						
No surgery	1		1		1	
BCS	1.01	0.72 to 1.41	0.83	0.32 to 2.17	1.06	0.74 to 1.53
Mastectomy	1.00	0.72 to 1.40	0.90	0.33 to 2.40	1.04	0.72 to 1.49
Chemotherapy (yes *v* no)	0.81	0.71 to 0.92	0.79	0.54 to 1.14	0.81	0.70 to 0.93
Radiation therapy (yes *v* no)	1.01	0.89 to 1.15	1.03	0.75 to 1.42	1.02	0.88 to 1.18
Mean out-of-pocket costs for 30-day supply AET, $						
0-2.65	1		1		1	
2.66-10.00	0.81	0.71 to 0.94	1.05	0.79 to 1.41	0.53	0.44 to 0.65
10.01-41.25	0.65	0.56 to 0.76	0.56	0.39 to 0.80	0.16	0.13 to 0.19
41.26-105.55	0.21	0.18 to 0.24	0.47	0.25 to 0.88	0.26	0.22 to 0.31
> 105.55	0.31	0.26 to 0.37	0.21	0.09 to 0.48	0.44	0.36 to 0.53

(continued on following page)

Table 3. Multivariable Logistic Regression for Adherence to AET Among Women Diagnosed With Stage I to III Hormone Receptor–Positive Breast Cancer (continued)

Characteristic	Adherence to Any AET (n = 8,688)		Adherence to Tamoxifen at Initiation (n = 1,515)		Adherence to AI at Initiation (n = 7,173)	
	AOR	95% CI*	AOR	95% CI*	AOR	95% CI*
AET type						
Tamoxifen	1					
AIs	0.81	0.71 to 0.94				

Abbreviations: AET, adjuvant endocrine therapy; AI, aromatase inhibitor; AJCC, American Joint Committee on Cancer; AOR, adjusted odds ratio; BCS, breast-conserving surgery; SES, socioeconomic status.
*AORs and 95% CIs controlled for all other sociodemographic and tumor characteristics listed in Table 1.

However, misclassification bias may be minimal because the SEER cancer registry uses incidence data for Hispanics on the basis of the validated North American Association of Central Cancer Registries Hispanic/Latino Identification Algorithm.[47] Also, we used race/ethnicity data from the Medicare data set, which was also well validated for accuracy of race/ethnicity to augment the information on missing or unknown race/ethnicity in SEER.[32] Fourth, calculating adherence using prescription claims assumes that patients take the medications as often as they refill prescriptions. However, pharmacy records may be considered the most accurate and valid estimation of actual medication use in large populations over time.[48,49]

Under the Patient Protection and Affordable Care Act, Medicare will cover a larger proportion of generic and brand name drugs. In 2016, patients on Medicare Part D received a 55% discount when buying Part D–covered brand-name drugs and a 58% discount when buying generic-name prescription drugs. Because our results indicated that lower out-of-pocket costs explained most racial/ethnic differences in AET adherence, the influence of the Patient Protection and Affordable Care Act, by decreasing the amount of out-of-pocket costs for AET medication,

will likely improve adherence for all racial/ethnic groups enrolled in Medicare Part D.

In conclusion, most women (63.2%) in our study were adherent during the first year of treatment. We did not find a significant difference in AET adherence among Hispanic and black patients compared with non-Hispanic whites after adjusting for out-of-pocket costs of the medication. We did, however, find significantly lower odds of tamoxifen adherence among blacks compared with non-Hispanic whites. Out-of-pocket costs for AET medication is associated with adherence, and racial/ethnic disparities in AET adherence were largely explained by women's differences in socioeconomic status and out-of-pocket AET costs. These results suggest that economic factors may significantly contribute to disparities in the quality of breast cancer care. Future studies should account for economic and treatment factors. Long-term outcomes associated with poor adherence to tamoxifen and AI treatment by race/ethnicity need further investigation. Because out-of-pocket costs for AET medication accounted for the majority of racial/ethnic differences in adherence to AET, health plans, drug companies, and providers should work together to ensure patients pay little-to-no out-of-pocket costs for this treatment, which will

Table 4. Logistic Regression Examining the Effect of Sociodemographic Characteristics on Racial/Ethnic Disparities in Adherence to AET

Multivariable Model	Overall AET OR (95% CI)	Tamoxifen at Initiation OR (95% CI)	Aromatase Inhibitors at Initiation OR (95% CI)
Hispanic versus non-Hispanic white			
Race	**1.30 (1.07 to 1.57)**	0.99 (0.57 to 1.73)	**1.39 (1.14 to 1.70)**
Race and comorbidities	**1.31 (1.08 to 1.58)**	0.99 (0.57 to 1.73)	**1.41 (1.15 to 1.72)**
Race, comorbidities, and poverty status	**1.31 (1.08 to 1.58)**	0.93 (0.53 to 1.64)	**1.44 (1.18 to 1.77)**
Race, comorbidities, poverty status, and copay	0.95 (0.78 to 1.17)	0.82 (0.46 to 1.46)	1.01 (0.81 to 1.26)
Full model*	0.94 (0.76 to 1.15)	0.75 (0.41 to 1.36)	0.98 (0.78 to 1.22)
Black versus non-Hispanic white			
Race	1.13 (0.94 to 1.35)	0.62 (0.38 to 1.01)	**1.27 (1.04 to 1.54)**
Race and comorbidities	1.14 (0.95 to 1.37)	**0.58 (0.35 to 0.96)**	**1.29 (1.06 to 1.57)**
Race, comorbidities, and poverty status	1.14 (0.94 to 1.37)	**0.53 (0.32 to 0.89)**	**1.33 (1.08 to 1.63)**
Race, comorbidities, poverty status, and copay	0.85 (0.69 to 1.03)	**0.50 (0.30 to 0.85)**	0.96 (0.77 to 1.19)
Full model*	0.92 (0.75 to 1.24)	**0.54 (0.31 to 0.93)**	1.01 (0.81 to 1.26)
Asian versus non-Hispanic white			
Race	**1.87 (1.49 to 2.35)**	1.19 (0.65 to 2.20)	**2.05 (1.60 to 2.63)**
Race and comorbidities	**1.89 (1.50 to 2.37)**	1.19 (0.64 to 2.19)	**2.08 (1.62 to 2.66)**
Race, comorbidities, and poverty status	**1.89 (1.50 to 2.38)**	1.22 (0.66 to 2.26)	**2.10 (1.64 to 2.69)**
Race, comorbidities, poverty status, and copay	**1.52 (1.19 to 1.93)**	1.14 (0.61 to 2.15)	**1.68 (1.29 to 2.18)**
Full model*	**1.48 (1.15 to 1.89)**	1.10 (0.57 to 2.12)	**1.59 (1.22 to 2.08)**

NOTE: Boldface type indicates $P < .01$.
Abbreviations: AET, adjuvant endocrine therapy; OR, odds ratio.
*Full model indicates race, copay, poverty status, comorbidities, age, and breast cancer treatment and prognostic factors from Table 1.

likely lead to the reduced racial/ethnic disparities in breast cancer mortality.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
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Data analysis and interpretation: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Association Between Out-Of-Pocket Costs, Race/Ethnicity, and Adjuvant Endocrine Therapy Adherence Among Medicare Patients With Breast Cancer

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