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ARTICLE

The Change From Brand-Name to Generic Aromatase Inhibitors and Hormone Therapy Adherence for Early-Stage Breast Cancer

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Background Nonadherence to hormonal therapy is common and is associated with increased copayment amount. We investigated the change in adherence after the introduction of generic aromatase inhibitors (AIs) in 2010.

Methods Using deidentified pharmacy and claims data from OptumInsight, we identified women older than 50 years on brand-name AIs (BAIs) and/or generic AIs (GAIs) for early breast cancer between January 1, 2007 and December 31, 2012. Clinical, demographic, and financial variables were evaluated. Adherence was defined as a medication possession ratio (MPR) 80% or greater.

Results We identified 5511 women, 2815 (51.1%) on BAI, 1411 (25.6%) on GAI, and 1285 (23.3%) who switched from BAI to GAI. The median 30-day copayment was higher for BAI ($33.3) than for GAI ($9.04). In a multivariable Cox-proportional hazard analysis, women who took GAI were less likely to discontinue therapy (hazard ratio [HR] = 0.69, 95% confidence interval [CI] = 0.57 to 0.84) compared with BAI. Discontinuation was positively associated with a higher monthly copayment of $15 to $30 (HR = 1.21, 95% CI = 1.01 to 1.44) and more than $30 (HR = 1.49, 95% CI = 1.23 to 1.80) compared with less than $15. In a multivariable logistic regression analysis, adherence (medication possession ratio ≥ 80%) was positively associated with GAI use (odds ratio = 1.53, 95% CI = 1.22 to 1.91) compared with BAI and inversely associated with increased monthly copayment. In addition, adherence was associated with a high annual income of more than $100k/year (odds ratio = 1.58, 95% CI = 1.17 to 2.11).

Conclusions Higher prescription copayment amount was associated with nonadherence and discontinuation of AIs. After controlling for copayment, discontinuation was higher and adherence was lower with Brand AIs. Because nonadherence is associated with worse survival, efforts should be directed towards reducing out-of-pocket costs for these life-saving medications.

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Prescription drug prices have increased from an average of $38.43 in 1998 to $71.69 in 2008, with brand-name prescriptions on average costing $137.90 vs $35.22 for generic prescriptions (1,2). To counteract increasing medication costs, pharmacy benefit plans have added additional tiers of drugs, increased copayment rates, increased deductibles, excluded some drugs from coverage, and increased preauthorization requirements (1). When a pharmaceutical company first markets a drug, it is usually under a patent (12 years on average), which allows only the pharmaceutical company that developed the drug to sell it. During this time, the company is able to set the drug price. A generic drug is a product that is comparable to a brand drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use (3). Generic drugs are usually sold for lower prices than their branded equivalents, because competition increases among producers when drugs no longer are protected by patents (3,4).

One of the unintended consequences of a rise in prescription drug prices and the number of prescriptions per capita is an increasing rate of therapy discontinuation (ie, stopping the medication before completion) and nonadherence (ie, taking less than 80% of the intended dose). In one study of noncancer patients, over 25% admitted to not filling a prescription (1,5). It is well known that the uninsured face barriers for prescription medications, but in 2008 over 5% of those with private insurance and 13% of those with public insurance could not afford a prescription (6). One study recently estimated the national costs of medication nonadherence at $289 billion, 13% of total US health care expenditures (1,7).

Lack of compliance (discontinuation and/or nonadherence) with medications is a well-known problem in the medical literature (8–10). Oral hormonal therapy for the adjuvant treatment of breast cancer results in a greater than 30% reduction in breast cancer recurrence (11). Despite this, approximately 7% to 10% of patients discontinue therapy annually (12–18), with only 40% to 60% finishing their recommended five-year course. This nonadherence reduces the survival benefits associated with hormonal therapy (19–22). Our work and work by

others suggests that treatment toxicity, patient race, prescribing physician specialty, the number and type of other prescriptions, and the degree to which the patient and physician believe in the drug's efficacy are all associated with early discontinuation of hormonal therapy (12,16,18,23,24). One modifiable factor that may affect adherence is out-of-pocket costs. For example, doubling the copayment for various noncancer-related chronic medications reduced adherence rates between 8% and 45% (25). In a prior study by our group, we found that higher copayments were inversely associated with adherence to adjuvant aromatase inhibitor (AI) therapy (26). Less is known about the influence of brand-name vs generic drugs on adherence patterns, though generic drugs generally are cheaper with lower copayment amounts.

In 2010, generic versions of all the AIs were made available. This provided the opportunity for a natural experiment in which we investigated the change in adherence patterns before and after the introduction of generic aromatase inhibitors.

Methods

Data Source

OptumInsight maintains a proprietary research database containing claims, membership, provider, and ancillary data for over 36 million members. These include 25 million commercial members from UnitedHealthcare and six million Medicare managed care members. The deidentified database is updated frequently. Membership and provider records are linked to pharmacy claims (OptumRx) and medical claims, including diagnosis and procedure codes (CPT, HCPCS, as well as ICD9 procedures) with their dates of service and providers.

The OptumInsight database provided information on each prescription filled, including the drug, the prescriber and his/her specialty, the out-of-pocket payment and copayment. In addition to the data above, OptumInsight uses a major data syndicator, knowledge based marketing solutions (KBM) (27). The marketing database collects data from primary sources including public records, purchase transactions, census data and consumer surveys to determine income, net worth, and lifestyle information.

Sample Selection

We identified all women in the database who had filled a prescription for a brand-name AI (BAI) (Arimidex, Femara, Aromasin) and/or a generic AI (GAI) (anastrozole,exemestane,and letrozole) between January 1, 2007 and December 31, 2012. Subjects were classified based on their first prescription for hormonal therapy as BAI or GAI. We restricted our sample to patients with a diagnosis of early-stage breast cancer in the six months prior to first prescription who were at least 50 years of age at the time of the initial prescription. We defined early stage as having had a surgical resection (lumpectomy or mastectomy) within 12 months prior to the initiation of hormonal therapy. Age at diagnosis was categorized in five-year intervals. Race was classified as white, black, Asian, or Hispanic. In addition, subjects were categorized by geographic location. The pregeneric and postgeneric periods were defined as before or after July 1, 2010.

Comorbid Disease. To assess the prevalence of comorbid disease in our cohort, we used the Episode Treatment Groups (ETGs) (28,29). This methodology uses an algorithm to compile clinical information, including prescriptions and claims for medical encounters, into episodes of care that can then be used to create a metric for chronic disease comorbidity. Subjects were categorized as having one to five or six or more comorbid conditions.

Clinical Characteristics. For each patient, we determined the specialty of the provider who prescribed hormone therapy most frequently, categorizing the physician as medical oncologist or primary care physician/other specialty.

Financial Factors. The copayment for the hormonal therapy was the amount paid by a subscriber for a 30-day prescription. Copayment amount for 60- or 90-day prescriptions were adjusted to 30-day copayment amounts. Copayment was categorized in roughly equal groups as less than $15, $15 to $30, or more than $30 based on common copayment amounts (multiples of $5), and so there was a roughly even distribution across the patient population. Insurance was categorized as commercial or Medicare. The number of patients on Medicaid was low, and therefore these patients were excluded from the analysis. The deductible was categorized as none, pharmacy only, or pharmacy/medical shared.

Outcomes. We categorized patients as having discontinued therapy if the calculated drug supply, based on the last prescription date plus any surplus from a prior prescription, indicated a minimum 45-day supply gap with no hormone therapy on hand. Adherence was determined by the medication possession ratio (MPR) (ie, the number of pills supplied over a fixed period of time). We categorized subjects as being adherent if the MPR was 80% or greater during the initial two years on therapy (30).

Follow-up and Censoring. All patients were followed for up to two years from the time of first prescription**.** Follow-up was available through December 31, 2012. We censored patients at the date at which they disenrolled from Optum if the patient switched AI category or if subsequent discontinuation data was missing.

Statistical Analysis. We used multivariable Cox proportional hazards regression models to estimate the association between the effect of therapy type and discontinuation rates for hormone therapy use, controlling for clinical, financial, and demographic factors. We used multivariable logistic regression models to analyze the association between therapy type and two-year hormone therapy adherence, classified as a dichotomous variable (MPR $\geq$ 80% vs MPR < 80%). All variables were included that were thought to be clinically significant. Interactions were assessed using likelihood ratio tests in the models, and, when significant, a stratified analysis was performed. In an exploratory analysis, the two-year discontinuation data on the group that switched hormonal therapy was included in the model. We estimated adjusted Kaplan-Meier survival curves (STS GRAPH ADJUSTFOR) to show time to discontinuation stratified by each of the hormone therapy categories (GAI and BAI) and copayment categories, adjusting for the variables in the final model. The assumption

of proportionality was confirmed visually. For all models, we rejected the null hypothesis at the *P* less than .05 level of statistical significance. All analyses were conducted using STATA version 12 (StataCorp, College Station, TX). All statistical tests were two-sided.

Results

We identified 5511 women who initiated hormone therapy, 2815 (51.1%) on BAI, 1411 (25.6%) on GAI, and 1285 (23.3%) who switched from BAI to GAI. Following the introduction of GAIs, 35.6% started BAI while 64.4% started GAI. Of patients who started with AI brand prior to generic availability, 73.2% switched to a GAI after they became available.

Table 1 gives the characteristics of the total cohort. The mean age of subjects at the time of breast cancer (BC) diagnosis in our study was 61 years. The majority of the study cohort was non-Hispanic white (59.9%) and had commercial insurance (88.5%). The median copayment was higher for the BAI ($33.3) than for the GAI group ($9.04). Of the patients in this cohort, 39% had copayments under $15, and 29% had copayments over $30 per month. The majority of hormone therapy prescriptions were written by hematologists/oncologists (74.5%). Most patients (85.1%) did not pay a deductible for their prescriptions.

Hormone therapy early discontinuation was identified in 1146 (27.1%) subjects, and nonadherence was identified in 1050 (24.8%) of subjects. Among the women on BAI, 32.6% discontinued therapy compared with 16.2% on GAI. In a multivariable Cox-proportional hazard analysis, discontinuation was decreased among women who took GAI (hazard ratio [HR] = 0.69, 95% confidence interval [CI] = 0.57 to 0.84) compared with BAI. Discontinuation was linearly associated with higher monthly copayments of $15 to $30 (HR = 1.21, 95% CI = 1.01 to 1.44) and more than $30 (HR = 1.49, 95% CI = 1.23 to 1.80) compared with less than $15. Women with more comorbid conditions (HR = 1.15, 95% CI = 1.01 to 1.34) and those over 75 years old (HR = 1.46, 95% CI = 1.16 to 1.75) were more likely to discontinue therapy early (Table 2).

In a multivariable logistic regression analysis, GAI users were more likely to be adherent (MPR ≥ 80%) with hormone therapy (OR = 1.53, 95% CI = 1.22 to 1.91) compared with BAI (Table 3). Women with a high annual household income of more than $100k/year (OR = 1.58, 95% CI = 1.17 to 2.11) were also more likely to be adherent with hormone therapy compared with those with a low annual income (<$40k/year). Adherence was inversely associated with copayment amount with patients with copayments of $15 to $30 per month (OR = 0.74, 95% CI = 0.59 to 0.92) and over $30 per month (OR = 0.51, 95% CI = 0.41 to 0.65) compared with patients with copayments of less than $15 per month. Medicare patients were also less likely to be adherent (OR = 0.52, 95% CI = 0.38 to 0.72) compared with those with commercial insurance. Patients with increased comorbid conditions (OR = 0.78, 95% CI = 0.65 to 0.93) and increased age (OR = 0.67, 95% CI = 0.51 to 0.88) had statistically significantly lower odds of adherence. Asian patients were more likely to be adherent compared with non-Hispanic white patients (OR = 1.98, 95% CI = 0.99 to 1.57). A sensitivity analysis was performed classifying both copayment and income as continuous variables, and the results were unchanged.

There was a statistically significant interaction between annual income and GAI/BAI and a statistically significant interaction between copayment amount and GAI/BAI ($P_{interaction}$ < .01). In the stratified analysis, women on BAI in the lower annual income group were more likely to discontinue therapy compared with patients on GAI. No association was found in the high annual income group. In subject with a low copayment (<$15), the BAI group was twice as likely to discontinue hormone therapy compared with GAI. No association was found in the high copayment group (Supplementary Table 1, available online). Kaplan-Meier curves were generated to show differences in hormone therapy discontinuation (Figure 1) and discontinuation by copayment amount (Figure 2) over time.

In an exploratory multivariable Cox-proportional hazard analysis including patients that switched from BAI to GAI, discontinuation was decreased among women who took GAI (HR = 0.44, 95% CI = 0.35 to 0.55) and those who switched (HR = 0.63, 95% CI = 0.52 to 0.76) compared with BAI. The association between age, comorbidity, and copayment amount and discontinuation did not change (Supplementary Table 2, available online).

Discussion

In this study of women with BC whose pharmacy benefits were administered through a large US health plan manager, we found that as monthly out-of-pocket copayment amount increased, rates of adherence to AI hormone therapy decreased and discontinuation increased. We also found that, even after controlling for monthly copayment amount, discontinuation was higher and adherence was lower in patients on brand-name AIs compared with generic AIs. Not surprisingly, the majority of women on AIs were on generic AIs after they became available in 2010.

Medication adherence is an increasingly recognized issue in oncology, particularly as the number of oral agents used for therapy increases (31). It is estimated that more than one quarter of the 400 antineoplastic agents now in the pipeline are oral drugs. As with other new cancer therapies, they are accompanied by increased costs and financial burdens for patients (32,33). While we have focused on adherence to AI hormonal therapy in this paper, there are also concerns about nonadherence with imatinib (34,35), thiopurine (36), and capecitabine (37). This issue will become increasingly important as more oral antinoeplastic drugs come into use (38). The monthly total cost of brand-name and generic AIs are, on average, $380 and $150, respectively, while the average monthly total cost of oral biologic therapies ranges from $5000 to $8000 per month. These total costs for the payer industry have translated into substantially higher out-of-pocket costs for patients.

It is increasingly recognized that the financial burden from health care costs results in patient distress. The Centers for Disease Control and Prevention estimates that one in three persons is in a family that experiences the financial burden of cancer care, and one in ten is in a family that has health care–related bills that they are not able to pay (39). As a result, increased attention has been paid to the financial toxicity of oncologic treatments. In a population-based study of treatment-related financial changes in patients with stage III colorectal cancer, a statistically significant percentage of patients (38%) reported at least one treatment-related financial hardship, defined as debt accumulation,

Table 1. Baseline characteristics of patients diagnosed with localized breast cancer at age 50 years or older who received adjuvant hormonal therapy

Categories	All patients (n = 4226) No. (%)	AI-brand (n = 2815) No. (%)	AI-generic (n = 1411) No. (%)
Type of therapy			
AI-brand	2815 (66.6)	2815 (100.0)	
AI-generic	1411 (33.4)		1411 (100.0)
HT start year*			
2007	698 (16.5)	698 (24.8)	0 (0)
2008	1002 (23.7)	1002 (35.6)	0 (0)
2009	787 (18.6)	787 (28.0)	0 (0)
2010	1007 (23.8)	309 (11.0)	698 (49.5)
2011	732 (17.3)	19 (0.7)	713 (50.5)
Start year			
Pregeneric	2110 (50.0)	2110 (75.0)	0 (0)
Postgeneric	2116 (50.0)	705 (25.0)	1411 (100.0)
Prescription coverage Characteristics			
Adjusted 30-day copay*			
<$15	1666 (39.4)	458 (16.3)	1208 (85.6)
$15-$30	1350 (32.0)	1167 (41.5)	183 (13.0)
>$30	1210 (28.6)	1190 (42.3)	20 (1.4)
Pharmacy deductible type			
No deductible	2390 (85.1)	1641 (85.3)	749 (84.6)
Pharmacy deductible only	234 (8.3)	161 (8.4)	73 (8.3)
Shared pharmacy/medical	185 (6.6)	122 (6.3)	63 (7.1)
Coverage type*			
Commercial	3739 (88.5)	2541 (90.3)	1198 (84.9)
Medicare	487 (11.5)	274 (9.7)	213 (15.1)
Clinical characteristics			
Provider specialty*			
Primary care/other	1076 (25.5)	742 (26.4)	334 (23.7)
Hematology/oncology	3150 (74.5)	2073 (73.6)	1077 (76.3)
Surgery*			
Lumpectomy/other	1946 (46.1)	1245 (44.2)	701 (49.7)
Mastectomy	2280 (53.9)	1570 (55.8	710 (50.3)
Comorbidities			
1–5	3390 (80.2)	2243 (79.7)	1147 (81.3)
6 +	836 (19.8)	572 (20.3)	264 (18.7)
Age at diagnosis, y*			
50–55	719 (17.0)	487 (17.3)	232 (16.4)
56–65	2379 (56.3)	1612 (57.3)	767 (54.4)
66–75	728 (17.2)	445 (15.8)	283 (20.1)
75+	400 (9.5)	271 (9.6)	129 (9.1)
Sociodemographic characteristics			
Race/ethnicity			
White	2530 (59.9)	1699 (60.4)	831 (58.9)
Black	312 (7.4)	207 (7.4)	105 (7.4)
Hispanic	217 (5.1)	145 (5.2)	72 (5.1)
Asian	75 (1.8)	49 (1.7)	26 (1.8)
Other/unknown race	1092 (25.8)	715 (25.4)	377 (26.7)
Education*			
High school or less	922 (21.8)	639 (22.7)	283 (20.1)
More than high school	3034 (78.2)	2176 (77.3)	1128 (79.9)
Household income*			
Low (<$40 000)	701 (15.6)	508 (18.1)	193 (13.7)
Middle ($40K-$100K)	1835 (43.4)	1189 (42.2)	646 (45.8)
High (>$100K)	674 (17.4)	447 (15.9)	227 (16.1)
Unknown	1016 (23.7)	671 (23.8)	345 (24.5)
Region			
Northeast	744 (17.6)	476 (16.9)	268 (19.0)
West	891 (21.1)	582 (20.7)	296 (21.0)
Midwest	1699 (40.2)	595 (21.2)	541 (38.3)
South	888 (21.0)	1158 (41.2)	306 (21.7)

* Two-sided X^2 for all comparisons, $P < .01$. AI-brand = brand name aromatase inhibitor; AI-generic = generic aromatase inhibitor.

Table 2. Early discontinuation of patients diagnosed with localized breast cancer at age 50 or older who received adjuvant hormonal therapy*

	Unadjusted frequencies		Multivariable analysis	
	Continued therapy	Early discontinued		
Categories	**No. (%)**	**No. (%)**	**HR (95% CI)**	***P***
Total	3080 (72.9)	1146 (27.1)		
Type of therapy				
AI-brand	1898 (67.4)	917 (32.6)	1.0 (reference)	
AI-generic	1182 (83.8)	229 (16.2)	0.69 (0.57 to 0.84)	<.001
Prescription coverage characteristics				
Adjusted 30-day copay				
<$15	1356 (81.4)	310 (18.6)	1.0 (reference)	
$15-$30	970 (71.9)	380 (28.5)	1.21 (1.01 to 1.44)	.04
>$30	754 (62.3)	456 (37.7)	1.49 (1.23 to 1.80)	<.001
Pharmacy deductible type				
No deductible	1813 (75.9)	577 (24.1)	1.0 (reference)	
Pharmacy deductible only	168 (71.8)	66 (28.2)	1.12 (0.87 to 1.43)	.40
Shared pharmacy/medical deductible	140 (75.7)	45 (24.3)	1.18 (0.87 to 1.61)	.28
Coverage type				
Commercial	2806 (75.0)	933 (24.9)	1.0 (reference)	
Medicare	274 (56.3)	213 (43.7)	1.27 (0.99 to 1.62)	.06
Clinical characteristics				
Provider specialty (most common prov)				
Primary care/other	787 (73.1)	289 (26.9)	1.0 (reference)	
Hematology/oncology	2293 (72.8)	857 (27.2)	0.93 (0.82 to 1.08)	.37
Surgery				
Lumpectomy/other	1440 (74.0)	506 (26.0)	1.0 (reference)	
Mastectomy	1640 (71.9)	640 (28.1)	0.99 (0.88 to 1.11)	.83
Comorbidities (used ETG Score)				
1–5	2482 (73.2)	908 (26.8)	1.0 (reference)	
6+	598 (71.5)	238 (28.5)	1.15 (1.01 to 1.34)	.04
Age at diagnosis, y				
50–55	535 (74.4)	184 (25.6)	1.11 (0.94 to 1.31)	.21
56–65	1804 (75.8)	575 (24.2)	1.0 (reference)	
66–75	523 (71.8)	205 (28.2)	0.96 (0.94 to 1.31)	.69
75+	218 (54.5)	182 (45.5)	1.46 (1.16 to 1.75)	<.001
Sociodemographic characteristics				
Race/ethnicity				
White	1912 (75.6)	618 (24.4)	1.0 (reference)	
Black	221 (70.8)	91 (29.2)	1.09 (0.86 to 1.37)	.47
Hispanic	156 (71.9)	61 (28.1)	0.77 (0.52 to 1.13)	.18
Asian	59 (78.7)	16 (21.3)	0.57 (0.32 to 1.01)	.86
Other/unknown race	947 (68.4)	437 (31.6)	1.40 (1.04 to 1.89)	.02
Education				
High school or less	673 (73.0)	249 (27.0)	1.0 (reference)	
More than high school	2407 (72.8)	897 (27.2)	0.96 (0.83 to 1.18)	.86
Household income				
Low (<$40 000)	502 (71.6)	199 (28.4)	1.0 (reference)	
Middle ($40K-$100K)	1377 (75.0)	458 (25.0)	0.95 (0.79 to 1.14)	.61
High (>$100K)	518 (76.8)	156 (23.1)	0.93 (0.73 to 1.18)	.54
Unknown	683 (67.2)	333 (32.8)	0.89 (0.63 to 1.25)	.52
Region				
Northeast	582 (78.2)	162 (21.8)	1.0 (reference)	
West	599 (67.5)	289 (32.5)	1.24 (0.99 to 1.56)	.06
Midwest	689 (77.3)	202 (22.7)	1.07 (0.85 to 1.36)	.55
South	1209 (71.2)	490 (28.8)	1.27 (1.03 to 1.57)	.02

* AI-Brand =brand name aromatase inhibitor; AI-Generic = generic aromatase inhibitor; CI = confidence interval; ETG = episode treatment group.

borrowing money from family/friends, ≥20% income decline, or selling/refinancing primary home, and a minority of respondents reported discussing treatment-related expenses with their physicians (40).

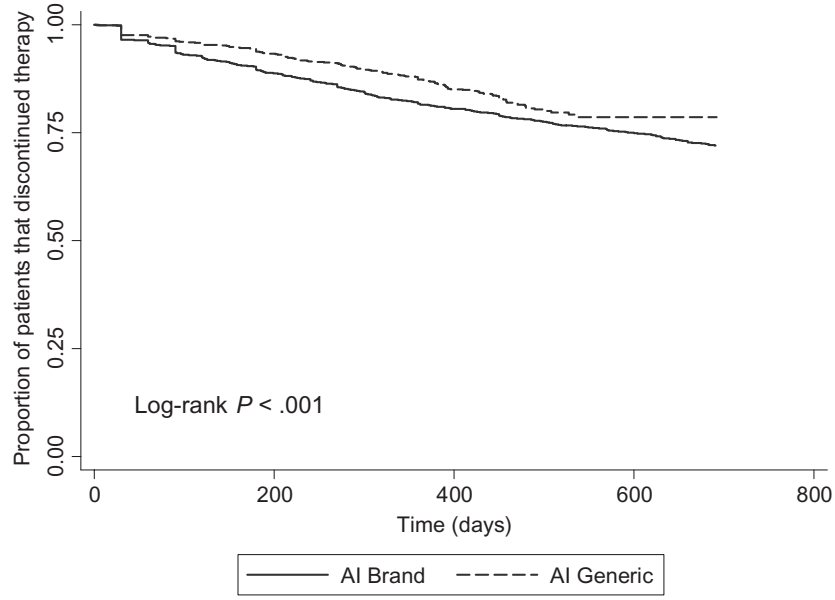
Other investigators have evaluated the association between financial factors and medication adherence. In a study using the 5% Medicare random sample, Medicare beneficiaries had reduced adherence during the drug coverage gap. Patients without drug

Table 3. Adherence (Medication Possession Ration >80%) of patients diagnosed with localized breast cancer at age 50 years or older who received adjuvant hormonal therapy*

	Unadjusted frequencies		Multivariable analysis	
	Adhered	Nonadhered		
Categories	**No. (%)**	**No. (%)**	**OR (95% CI)**	***P***
Total	3176 (75.1)	1050 (24.8)		
Type of therapy				
AI-brand	1996 (70.9)	819 (29.1)	1.0 (reference)	
AI-generic	1180 (83.6)	231 (16.4)	1.53 (122 to 1.91)	<.001
Prescription coverage characteristics				
Adjusted 30-day copay				
<$15	1380 (82.8)	286 (17.2)	1.0 (reference)	
$15-$30	1012 (75.0)	338 (25.0)	0.74 (0.59 to 0.92)	.008
>$30	784 (64.8)	426 (35.2)	0.51 (0.41 to 0.65)	<.001
Pharmacy deductible type				
No deductible	1858 (77.7)	1038 (22.3)	1.0 (reference)	
Pharmacy deductible only	169 (72.2)	123 (27.8)	0.81 (0.59 to 1.10)	.17
Shared pharmacy/medical deductible	144 (77.8)	94 (22.2)	0.87 (0.60 to 1.27)	.48
Coverage type				
Commercial	2885 (77.2)	854 (22.8)	1.0 (reference)	
Medicare	291 (59.7)	196 (40.2)	0.52 (0.38 to 0.72)	<.001
Clinical characteristics				
Provider specialty (most common prov)				
Primary care/other	819 (76.1)	257 (23.9)	1.0 (reference)	
Hematology/oncology	2357 (74.8)	793 (25.2)	0.95 (0.80 to 1.12)	.55
Surgery				
Lumpectomy/other	1463 (75.2)	483 (24.8)	1.0 (reference)	
Mastectomy	1713 (75.1)	567 (24.9)	1.10 (0.95 to 1.27)	.19
Comorbidities (used ETG score)				
1–5	2573 (75.9)	817 (24.1)	1.0 (reference)	
6+	603 (72.1)	233 (27.9)	0.78 (0.65 to 0.93)	.007
Age at diagnosis, y				
50–55	539 (75.0)	180 (25.0)	0.86 (0.71 to 1.06)	.17
56–65	1842 (77.4)	537 (22.6)	1.0 (reference)	
66–75	555 (76.2)	173 (23.8)	1.24 (0.99 to 1.57)	.06
75+	240 (60.0)	160 (40.0)	0.67 (0.51 to 0.88)	.004
Sociodemographic characteristics				
Race/ethnicity				
White	1965 (77.7)	565 (22.3)	1.0 (reference)	
Black	230 (73.7)	82 (26.3)	0.93 (0.69 to 1.24)	.55
Hispanic	154 (71.0)	63 (29.0)	1.15 (0.72 to 1.85)	.55
Asian	61 (81.3)	14 (18.7)	1.98 (0.99 to 3.96)	.05
Other/unknown race	766 (70.0)	326 (29.9)	0.64 (0.44 to 0.93)	.02
Education				
High school or less	691 (75.0)	431 (25.0)	1.0 (reference)	
More than high school	2485 (75.2)	1542 (24.8)	0.92 (0.75 to 1.13)	.44
Household income				
Low (<$40 000)	504 (71.9)	197 (28.1)	1.0 (reference)	
Middle ($40K-$100K)	1409 (76.8)	426 (23.2)	1.19 (0.95 to 1.49)	.12
High (>$100K)	546 (81.0)	128 (19.0)	1.58 (1.17 to 2.11)	.002
Unknown	717 (70.6)	299 (29.4)	1.52 (0.99 to 2.32)	.06
Region				
Northeast	600 (80.6)	144 (19.3)	1.0 (reference)	
West	617 (69.5)	271 (30.5)	0.70 (0.53 to 0.93)	.01
Midwest	709 (79.6)	182 (20.4)	0.88 (0.67 to 1.17)	.38
South	1249 (73.5)	450 (26.5)	0.71 (0.55 to 0.91)	.006

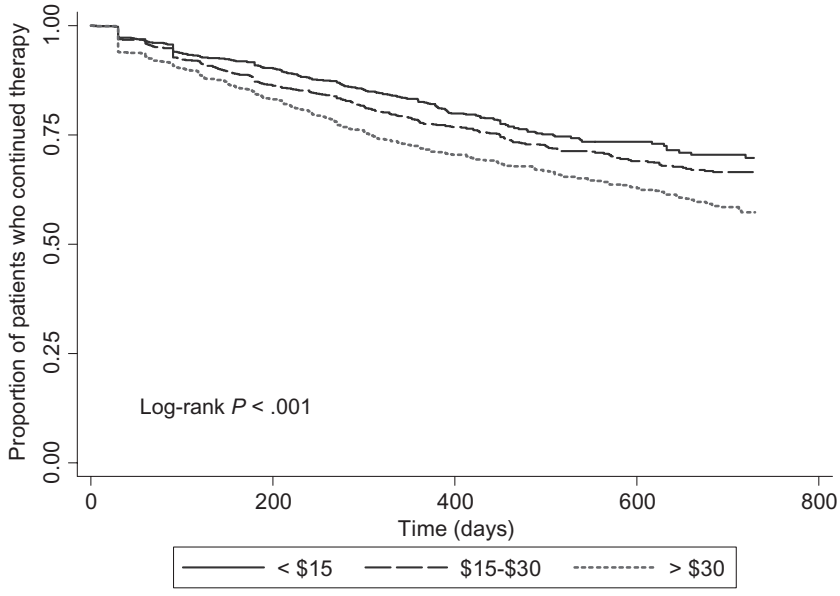
* AI-brand = brand name aromatase inhibitor; AI-generic = generic aromatase inhibitor; CI = confidence interval; ETG = episode treatment group.

coverage had the number of prescriptions refilled reduced by 16% per month, while those with generic drug coverage reduced the number of prescriptions refilled by 10%. Patients on generic drugs had greater adherence during this timeframe than those on brand-name drugs (41). In another study that evaluated cardiac medication use following an acute myocardial infarction, Stuart and colleagues found that during the Part D coverage gap, there were statistically significant reductions in the MPR for beta blockers,



	0	200	400	600
Brand name AI	2815	1794	1394	648
Generic AI	1411	1086	465	48

Figure 1. Adjusted Kaplan-Meier curve for continuation of hormonal therapy by aromatase inhibitor (AI) class among women diagnosed with localized breast cancer. The log-rank *P* value is two-sided.



	0	200	400	600
<$15	1666	1236	575	131
$15-$30	1350	886	494	277
>$30	1210	758	439	264

Figure 2. Adjusted Kaplan-Meier curve for continuation of hormonal therapy by average 30-day aromatase inhibitor prescription copayment amount among women diagnosed with localized breast cancer at age 50 years or older. The log-rank *P* value is two-sided.

statins and ACE inhibitors, despite the mortality benefit associated with these drugs (42).

The findings are consistent with prior work by our group reporting that copayment amount was associated with adherence in patients who received 90-day mail-order prescriptions (26). Ito and colleagues estimated the incremental cost effectiveness of providing Medicare beneficiaries with full coverage for AIs. They reported that full prescription coverage would result in greater

quality-adjusted survival and less resource use per beneficiary, with an incremental cost-effectiveness ratio of $15 128 per quality-adjusted life-year gained (43). We were surprised to see that, despite controlling for copayment, there was increased adherence and decreased discontinuation with AI-generic users compared with brand-name AIs.

Women in the highest income bracket were statistically significantly more likely to be adherent than women in the lowest income group despite controlling for copayment amount and type of hormonal therapy. Low-income groups have traditionally been found to be vulnerable with regard to quality health care, and this may be exacerbated by the overlap in the timeframe of this study with the economic downturn in the United States. However, nonfinancial interventions may be successful in improving compliance. In the California statewide survey of low-income women with breast cancer, one study found that adherence was higher in those who reported better provider-patient communication on standardized patient-reported outcome measures (44).

This study had several strengths. We utilized a large database with a nationwide sample, including patients with a wide variety of prescription benefit plans, allowing for a diversity of copayment amounts, income, and age. This study also compared changes in adherence and discontinuation rates after the introduction of generic AIs, providing support that lower out-of-pocket costs for drugs with similar effectiveness can improve compliance. Prior studies were done prior to the introduction of generic AIs. In addition, we evaluated a timeframe in which generic aromatase inhibitors were introduced to the market so we could see how this change in availability affected adherence rates. Furthermore, in addition to copayment amount and type of therapy, the dataset has information on patient income, insurance type, and deductible amount.

Some study limitations should be mentioned. All of our patients received some form of prescription coverage, and therefore our results are not generalizable to patients without prescription coverage. In addition, mail-order pharmacies such as Optum have autorefill programs, and therefore these results may underestimate the true adherence rate. Furthermore, we did not have a full five years of follow-up following the change from brand-name to generic AI availability. In addition, we did not have detailed information on tumor stage or pathologic characteristics that may have influenced adherence. While we would not expect that stage would have a large influence on uptake of generic AIs, it is possible that patients with worse prognosis prefer brand name and may be more likely to be adherent. However, this effect would reduce the association we observed. Finally, we did not have individual information on why patients discontinued therapy, some of which may have been because of toxicity or patient preference. However, all of the AIs have similar side effects, the most common being joint discomfort and stiffness, and there are no differences in side effects between brand-name and generic AIs. We also don't know what patient characteristics may be associated with staying on brand-name AIs or discontinuing as opposed to switching. Prior studies by our group and others have shown that attitudes and belief in efficacy contribute to initiation and adherence to hormone therapy (45,46).

In summary, copayment amount had a large impact on discontinuation and nonadherence to AI therapy. In addition, shifts in use from brand-name to generic aromatase inhibitors were associated with decreased discontinuation and increased adherence to hormone therapy that persisted after controlling for copayment amount. Since previous studies have shown that poor adherence and early discontinuation of hormonal therapy are associated with worse survival (19,21,47), public health efforts, such as the Cancer Treatment Fairness Act, should be directed towards increased drug price transparency, improving access, and reducing out-of-pocket costs for life-saving cancer treatments. This is especially important given the rapid increase of expensive oral cancer therapies.

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