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ORIGINAL REPORT

Association Between Prescription Co-Payment Amount and Compliance With Adjuvant Hormonal Therapy in Women With Early-Stage Breast Cancer

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ABSTRACT

Purpose
Noncompliance with adjuvant hormonal therapy among women with breast cancer is common. Little is known about the impact of financial factors, such as co-payments, on noncompliance.

Patients and Methods
We conducted a retrospective cohort study by using the pharmacy and medical claims database at Medco Health Solutions. Women older than age 50 years who were taking aromatase inhibitors (AIs) for resected breast cancer with two or more mail-order prescriptions, from January 1, 2007, to December 31, 2008, were identified. Patients who were eligible for Medicare were analyzed separately. Nonpersistence was defined as a prescription supply gap of more than 45 days without subsequent refill. Nonadherence was defined as a medication possession ratio less than 80% of eligible days.

Results
Of 8,110 women younger than age 65 years, 1,721 (21.1%) were nonpersistent and 863 (10.6%) were nonadherent. Among 14,050 women age 65 years or older, 3,476 (24.7%) were nonpersistent and 1,248 (8.9%) were nonadherent. In a multivariate analysis, nonpersistence (ever/never) in both age groups was associated with older age, having a non-oncologist write the prescription, and having a higher number of other prescriptions. Compared with a co-payment of less than $30, a co-payment of $30 to $89.99 for a 90-day prescription was associated with less persistence in women age 65 years or older (odds ratio [OR], 0.69; 95% CI, 0.62 to 0.75) but not among women younger than age 65, although a co-payment of more than $90 was associated with less persistence both in women younger than age 65 (OR, 0.82; 95% CI, 0.72 to 0.94) and those age 65 years or older (OR, 0.72; 95% CI, 0.65 to 0.80). Similar results were seen with nonadherence.

Conclusion
We found that higher prescription co-payments were associated with both nonpersistence and nonadherence to AIs. This relationship was stronger in older women. Because noncompliance is associated with worse outcomes, future policy efforts should be directed toward interventions that would help patients with financial difficulties obtain life-saving medications.

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INTRODUCTION

Lack of compliance with prescribed medications is a well-known problem in the medical literature.[1-3] For long-term medications taken for chronic conditions, patients may fail to fill the initial prescription (noninitiation), fail to take the drug on a daily basis as prescribed (nonadherence/medication possession ratio $< 80\%$), or stop taking the drug entirely before the end of the full course of treatment (nonpersistence). Overall, such deviations from appropriate treatment occur in up to 50% of patients and may compromise survival outcomes.[1]

Adjuvant hormonal therapy for women with nonmetastatic hormone receptor–positive breast cancer (BC) has been shown to have a significant impact on mortality, and 5 years of such therapy is usually prescribed.[4] The recent guidelines of the American Society of Clinical Oncology recommend that postmenopausal women with hormone receptor–positive BC consider incorporating an aromatase inhibitor (AI) at some point during adjuvant treatment, either as initial therapy or as sequential treatment after tamoxifen.[5] We conducted a study among women with early-stage BC who had a prescription benefit plan and found that 32%

discontinued their oral hormonal therapy early. Of those who continued their therapy for 4.5 years, 28% were nonadherent at some point.[6] Women who discontinued early had a higher mortality rate compared with those who finished the full course of therapy. Similar results were observed for patients who were nonadherent.[7]

Although some prior studies on predictors of adherence to hormonal therapy have focused on factors related to age, race, the specialty of the prescribing physician, and adverse effects, little attention has been paid to the cost of the medication itself.[8-13] Currently, a 3-month supply of an AI can cost as much as $590.[14] Even for women with prescription drug benefits, prescription co-payments can range from nothing to more than $30 per month.[15] In addition, for women who are in the Medicare part D coverage gap (ie, the so-called "donut hole"), there are often months at the end of the year when they have no prescription coverage at all.

One modifiable factor that may affect adherence to oral therapy is the size of the co-payment required by the prescription drug plan. Substantial literature[15-21] addresses the relationship between the size of co-payments and adherence to hypertension and asthma medications. For example, one study of 3,240 patients within the Geisinger Clinic found that 87% of patients with a co-pay of $10 or less initiated a first prescription for antihypertensive medication, but only 72% of patients with a higher co-pay amount initiated treatment.[22] Similarly, Goldman et al[23] found that doubling the co-payment for various chronic medications reduced adherence rates between 8% and 45%.

In this study, we investigate the relationship between co-payment amount and persistence/adherence to AIs among women with early-stage BC whose prescription benefits are administered by a large national prescription benefits manager.

PATIENTS AND METHODS

Data Source

Medco Health Solutions, a large pharmacy benefits manager in the United States, administers drug benefits to more than 65 million people for its clients, which generally include employers, government agencies, health plans, unions, and managed care organizations. Approximately 60% of Medco's members fill prescriptions by using 90-day mail-order services with the remainder filled in retail pharmacies.

Medco maintains a de-identified Information Warehouse database on all prescriptions filled. This database captures patient age, sex, region of country, the total number of other prescriptions, and out-of-pocket payments as well as the specialty of the physician who wrote the prescription. For a subset of members (approximately 12 million), this prescription database is linked to administrative claims data, including diagnosis and procedure codes (Current Procedural Terminology, Healthcare Common Procedure Coding System, and International Classification of Diseases, Ninth Revision, procedures) with their dates of service and providers. These data are obtained from more than 80 data suppliers, mostly health plans. By using algorithms licensed from Symmetry Health Data Systems, medical and pharmacy claims are linked to episodes of care, which can determine whether an episode of care is extended or whether a recurrence has occurred on the basis of additional claims.[24,25] Medical claims data for patients age 65 years or older are more limited. Medco does not receive medical claims from Medicare and, for some clients, these data reflect only balance billing to commercial payers that is supplemental to Medicare; therefore, we separated patients who were ever eligible for Medicare from those who did not reach the age of Medicare eligibility at any time during our analyses. Our analysis covered the period from January 1, 2007, to December 31, 2008. In addition to the types of data already mentioned, Medco uses a major data syndicator, Acxiom, to provide geographic, demographic, and lifestyle data at the individual and household levels.

Patients

Sample selection. We identified all women in the Medco Information Warehouse who had filled at least two 90-day mail-order prescriptions for an AI (anastrozole, letrozole, and/or aromasin) between January 1, 2007, and December 31, 2008, and who used only the mail-order service during this time. We restricted our sample to patients who were at least 50 years of age at the time of the initial AI prescription who had a diagnosis of early-stage BC, defined as having had a surgical resection for BC (lumpectomy or mastectomy) within 12 months of the initiation of AI. Age at diagnosis was categorized as 50 to 54, 55 to 59, and 60 to 62 years. For the Medicare cohort, we categorized patients as age 63 to 69, 70 to 74, 75 to 79, 80 to 84, and older than 85 years old. Race was classified as white, black, Asian, or Hispanic. In addition, patients were categorized by marital status and geographic location. We used the annual household income from Acxiom as a surrogate for socioeconomic status to classify patients into five socioeconomic categories.

Comorbid disease. To assess the prevalence of comorbid disease in our cohort, we used an episode treatment groups method.[24,25] This method uses an algorithm to compile clinical information, including prescriptions and claims (pre-Medicare only) for medical encounters, into episodes of care that can then be used to create a metric for chronic disease comorbidity. Patients were categorized as having no comorbid conditions, or 1 to 5, 6 to 10, 11 to 15, or more than 15 comorbid conditions.

Clinical variables. We determined the total number of prescriptions filled or refilled for each patient within the prior 12 months. We also determined the specialty of the first physician who prescribed the AI, categorizing the physician as medical oncologist, primary care physician, or other.

Co-payments. The co-payment for the AI was the amount paid by a subscriber for a 90-day mail-order prescription. Co-payment was categorized in roughly equal groups as less than $30, $30.00 to $89.99, or ≥ $90 on the basis of common co-payment amounts.

Outcomes. We categorized patients as having discontinued therapy (nonpersistence) 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 AI on hand, with no subsequent refills before the end of the study period. We categorized patients who were persistent as being adherent if the medication possession ratio was ≥ 80%.[26]

Follow-up and censoring. Follow-up was available through December 31, 2008. We censored patients at the date at which they dis-enrolled from Medco, had a claim that indicated recurrence, or changed therapy to tamoxifen (n = 435).

Statistical Analysis

We used multivariate logistic regression models to analyze the association between co-payment amount and either nonpersistence or nonadherence, classified as a dichotomous variable. These analyses were performed separately for women age 65 years or older at any point during the 2-year follow-up and for those age 50 to 64 years because of differences in the available covariates. All variables were included that were thought to be clinically significant. Data were pooled within each group before performing the analyses. For each of our models, we could reject the null hypothesis at the 0.001 level of significance.

We generated Kaplan-Meier curves to show time to nonpersistence stratified by each of the co-payment categories. The assumption of proportionality was confirmed visually. Cox proportional hazards modeling was used to estimate the hazard ratio for the effect of the co-payment categories, controlling for other covariates, over time. All analyses were conducted by using SAS, Version 9.13 (SAS Institute, Cary, NC).

RESULTS

During the 2-year study period, 22,160 women who were older than age 50 years had a diagnosis of early-stage BC and filled at least two prescriptions for an AI. Of the 8,110 women who were younger than age 65 years, 1,721 (21.2%) were nonpersistent and of those who

persisted, 863 (10.3%) were nonadherent over the 2-year period. Among 14,050 women 65 years old or older, 3,476 (24.7%) were nonpersistent and during the time they persisted, 1,248 (8.9%) were nonadherent.

Table 1 provides the characteristics of the total cohort, and the characteristics within each of the two age ranges. The mean age of patients in our study was 67.4 years. The majority of the study cohort was white (89.5%) and married (74.3%). The median co-payment for

Table 1. Baseline Characteristics of Patients Older Than Age 50 Years With Localized Breast Cancer Who Received 90-Day Mail-Order Prescriptions for Aromatase Inhibitor Therapy, Medco, 2007-2008

	Total (N = 22,160)		Pre-Medicare (n = 8,110)		Medicare (n = 14,050)	
Characteristic	No.	%	No.	%	No.	%
90-day out-of-pocket cost, $						
0-29.99	9,524	43.0	3,027	37.3	6,497	46.2
30.00-89.99	6,676	30.1	2,639	32.5	4,037	28.7
≥ 90	5,960	26.9	2,444	30.2	3,516	25.1
No. of other prescriptions						
0-4	3,751	16.9	1,833	22.6	1,918	13.7
5-9	6,721	30.3	2,606	32.1	4,115	29.3
10-14	5,413	24.4	1,833	22.6	3,580	25.5
≥ 15	6,275	28.3	1,838	22.7	4,437	31.6
Specialist						
Oncologist	14,139	63.8	5,502	67.8	8,637	61.5
Primary care physician	2,762	12.5	756	9.3	2,006	14.3
Other	2,752	12.4	899	11.1	1,853	13.2
Missing	2,507	11.3	953	11.8	1,554	11.1
Age, years						
50-54	1,857	8.4	1,857	22.9		
55-59	3,383	15.3	3,383	41.7		
60-62	2,870	13.0	2,870	35.4		
63-69	4,934	22.3			4,934	35.1
70-74	3,313	15.0			3,313	23.6
75-79	3,021	13.6			3,021	21.5
80-84	1,881	8.5			1,881	13.4
≥ 85	901	4.1			901	6.4
Race						
Asian	400	1.8	173	2.1	227	1.6
Black	1,048	4.7	389	4.8	659	4.7
Hispanic	673	3.0	302	3.7	371	2.6
White and other	19,836	89.5	7,071	87.2	12,765	90.9
Missing	203	0.9	175	2.2	28	0.2
Marital status						
Married	16,471	74.3	6,371	78.6	10,100	71.9
Single	4,347	19.6	1,358	16.7	2,989	21.3
Missing	1,342	6.1	381	4.7	961	6.8
Income, $						
0-29,999	4,191	18.9	690	8.5	3,501	24.9
30,000-59,999	7,075	31.9	2,261	27.9	4,814	34.3
60,000-89,999	4,667	21.1	2,094	25.8	2,573	18.3
90,000-149,999	4,007	18.1	2,098	25.9	1,909	13.6
≥ 150,000	874	3.9	580	7.2	294	2.1
Missing	1,346	6.1	387	4.8	959	6.8
Region						
1, Northeast	4,010	18.1	1,463	18.0	2,547	18.1
2, North Central	6,761	30.5	2,163	26.7	4,598	32.7
3, South	6,683	30.2	2,512	30.9	4,171	29.7
4, West	4,706	21.2	1,972	24.3	2,734	19.5
Comorbidities (ETG)						
None	1,263	5.7	256	3.2	1,007	7.2
1-5	925	4.2	494	6.1	431	3.1
6-10	2,856	12.9	1,201	14.8	1,655	11.8
11-15	2,833	12.8	967	11.9	1,866	13.3
≥ 15	2,578	11.6	738	9.1	1,840	13.1
Missing	11,705	52.8	4,454	54.9	7,251	51.6

Abbreviation: ETG, episode treatment groups.

Table 2. Multivariate Analysis of Predictors of Persistence Among Women With Early-Stage Breast Cancer Who Received 90-Day Prescriptions for Aromatase Inhibitors (2007-2008)

	Pre-Medicare (n = 8,110)						Medicare (n = 14,050)					
	Persistent		Nonpersistent				Persistent		Nonpersistent			
Characteristic	No.	%	No.	%	OR	95% CI	No.	%	No.	%	OR	95% CI
Total patients	6,389	78.8	1,721	21.1			10,574	75.3	3,476	24.7		
90-day out-of-pocket cost, $												
0-29.99	2,410	79.6	617	20.4	1.00	—	4,930	78.0	1,398	22.0	1.00	—
30.00-89.99	2,089	79.2	550	20.8	0.93	0.81 to 1.06	2,997	72.5	1,107	27.5	0.69	0.62 to 0.75
≥ 90	1,890	77.3	554	22.7	0.82	0.72 to 0.94	2,647	73.2	971	26.8	0.72	0.65 to 0.80
No. of other prescriptions												
0-4	1,493	81.4	340	18.6	1.00	—	1,530	79.8	388	20.2	1.00	—
5-9	2,102	80.7	504	19.3	0.92	0.79 to 1.07	3,180	77.3	935	22.7	0.84	0.73 to 0.96
10-14	1,429	77.9	404	22.1	0.75	0.64 to 0.89	2,696	75.3	884	24.7	0.74	0.64 to 0.85
≥ 15	1,365	74.2	473	25.8	0.57	0.48 to 0.67	3,168	71.4	1,269	28.6	0.60	0.52 to 0.68
Specialist												
Oncologist	4,352	79.1	1,150	20.9	1.00	—	6,585	76.2	2,052	23.8	1.00	—
Primary care physician	572	75.7	184	24.3	0.82	0.69 to 0.99	1,432	71.4	574	28.6	0.79	0.71 to 0.89
Other	700	77.8	199	22.2	0.93	0.78 to 1.10	1,373	74.1	480	25.9	0.88	0.78 to 0.99
Missing	765	80.3	188	19.7	1.09	0.91 to 1.29	1,184	76.2	370	23.8	0.99	0.87 to 1.13
Age, years												
50-54	1,443	77.7	414	22.3	1.00	—						
55-59	2,674	79.0	709	21.0	1.10	0.95 to 1.26						
60-62	2,272	79.2	598	20.8	1.12	0.97 to 1.30						
63-69							3,713	75.2	1,221	24.8	1.00	—
70-74							2,541	76.7	772	23.3	1.07	0.97 to 1.19
75-79							2,276	75.3	745	24.7	1.02	0.91 to 1.13
80-84							1,418	75.4	463	24.6	1.01	0.89 to 1.15
85+							626	69.5	275	30.5	0.75	0.64 to 0.88
Race												
White and other	5,575	78.3	1,496	21.7	1.00	—	9,627	75.4	3,138	24.6	1.00	—
Asian	132	76.3	41	23.7	0.87	0.61 to 1.25	168	74.0	59	26.0	0.93	0.69 to 1.26
Black	300	77.1	89	22.9	0.91	0.71 to 1.17	479	72.7	180	27.3	0.85	0.71 to 1.01
Hispanic	246	81.4	56	18.6	1.29	0.96 to 1.74	278	74.9	93	25.1	0.97	0.77 to 1.24
Missing	136	77.7	39	22.3	0.92	0.55 to 1.52	22	78.5	6	21.5	0.94	0.37 to 2.38
Marital status												
Married	5,038	79.1	1,333	20.9	1.00	—	7,610	75.3	2,490	24.7	1.00	—
Single	1,054	77.6	304	22.4	0.94	0.81 to 1.08	2,244	75.1	745	24.9	1.01	0.92 to 1.12
Missing	297	77.9	84	22.1	0.92	0.52 to 1.63	720	74.9	241	25.1	0.77	0.54 to 1.11
Income, $												
0-29,999	531	76.9	159	23.1	1.00	—	2,663	76.1	838	23.9	1.00	—
30,000-59,999	1,808	80.0	453	20.0	1.19	0.97 to 1.46	3,609	75.0	1,205	26.2	0.94	0.85 to 1.05
60,000-89,999	1,632	77.9	462	22.1	1.05	0.85 to 1.29	1,900	73.8	673	25.0	0.90	0.79 to 1.01
90,000-149,999	1,656	78.9	442	21.1	1.12	0.90 to 1.38	1,455	76.2	454	23.8	1.04	0.90 to 1.19
≥ 150,000	460	79.3	120	20.7	1.15	0.88 to 1.51	221	75.2	73	24.8	0.99	0.75 to 1.31
Missing	302	78.0	85	22.0	1.16	0.65 to 2.09	726	75.7	233	24.3	1.21	0.83 to 1.76
Region												
3, South	1,962	78.1	550	21.9	1.00	—	3,112	74.6	1,059	23.4	1.00	—
1, Northeast	1,170	80.0	293	20.0	1.04	0.89 to 1.23	1,970	77.3	577	22.7	1.06	0.94 to 1.19
2, North Central	1,742	80.5	421	19.5	1.13	0.98 to 1.31	3,489	75.9	1,109	24.1	1.00	0.91 to 1.11
4, West	1,515	76.8	457	23.2	0.85	0.73 to 0.99	2,003	73.3	731	26.3	0.86	0.76 to 0.96
Comorbidities (ETG)												
None	194	75.8	62	24.2	1.00	—	770	76.5	237	23.5	1.00	—
1-5	375	75.8	119	24.2	0.93	0.65 to 1.33	336	78.0	95	22.0	0.86	0.65 to 1.14
6-10	943	78.5	258	21.5	1.12	0.81 to 1.54	1,272	76.8	383	23.2	0.87	0.72 to 1.05
11-15	756	78.2	211	21.8	1.21	0.87 to 1.68	1,407	75.4	459	24.6	0.86	0.71 to 1.03
≥ 15	611	82.8	127	17.2	1.84	1.29 to 2.61	1,388	75.4	452	24.6	0.97	0.80 to 1.17
Missing	3,510	78.8	944	21.2	1.27	0.94 to 1.71	5,401	74.5	1,850	23.5	0.89	0.76 to 1.05

Abbreviations: OR, odds ratio; ETG, episode treatment groups.

a 90-day prescription was higher for the younger ($50) than for the older age group ($40). Although the bulk of AI prescriptions were written by oncologists (63.8%), primary care physicians wrote 9%, and other specialists wrote 11% of the prescriptions for patients in the younger age group. For patients in the older age group, 15% and 13% were written by primary care physicians and by other specialists, respectively. Women in the older age group had a higher number of prescriptions in addition to those for AIs filled during the study period.

In a multivariate analysis within the younger cohort, we found that having a 90-day co-payment of $90 or more was significantly associated with decreased persistence (yes/no) compared with a co-payment of less than $30 (odds ratio [OR], 0.82; 95% CI, 0.72 to 0.94; Table 2). We also found that those for whom a primary care physician wrote the prescription (OR, 0.82; 95% CI, 0.69 to 0.99) and who had more than 15 other prescriptions (OR, 0.57; 95% CI, 0.48 to 0.67) had lower odds of persistence, although persistence was increased in those with more comorbid conditions. Similar results were seen for adherence; however, being black (OR, 0.51; 95% CI, 0.39 to 0.68), being single (OR, 0.77; 95% CI, 0.64 to 0.92), and being of younger age were also predictors of decreased odds of adherence (Table 3).

For women age 65 years or older, compared with co-payment amounts of less than $30, co-payment amounts of both $30.00 to $89.99 (OR, 0.69; 95% CI, 0.62 to 0.75) and $90 or more (OR, 0.72; 95% CI, 0.65 to 0.80) were associated with decreased persistence (Table 2). Age older than 84 years (OR, 0.75; 95% CI, 0.64 to 0.88), having the prescription written by a primary care physician (OR, 0.79; 95% CI, 0.71 to 0.89) or by a different specialist (OR, 0.88; 95% CI, 0.78 to 0.99), and an increased number of co-prescriptions were associated with decreased persistence. Findings for adherence were similar (Table 3). Co-payments of $30.00 to $89.99 (OR, 0.83; 95% CI, 0.72 to 0.96) and co-payments of $90 or more (OR, 0.70; 95% CI, 0.60 to 0.82), compared with co-payments less than $30, were associated with less adherence in the older age group.

We performed Cox proportional hazards models to evaluate time to nonpersistence. For both age categories, a co-payment amount of $90 or more was associated with increased nonpersistence over time compared with those who had co-payments of less than $30 (22.7% *v* 20.4% for those younger than age 65 years; 26.8% *v* 22.0% for those age 65 years or older). However, only for women age 65 years or older, a copayment between $30.00 and $89.99 was also associated with increased nonpersistence over time (27.5% *v* 22.0). Figures 1A and 1B show Kaplan-Meier curves for persistence to AIs over time for the pre-Medicare and Medicare age groups, stratified by co-payment category.

DISCUSSION

In this study, which evaluated compliance to adjuvant AI therapy among women with BC whose pharmacy benefits were administered by one of the largest pharmacy benefit managers in the United States, we found that higher co-payments required by the patients' pharmacy benefit plan were negatively associated with the probability of being both persistent and adherent to adjuvant AI therapy. In addition, we found that the threshold appears to be different for women who are age 65 years or older compared with that for women younger than age 65 years; older women appeared to be affected by co-payments of more than $30 for a 90-day prescription, although younger women were not affected until the co-payment reached $90 or more.

As the number of BC survivors continues to grow, there has been increasing interest in transferring their long-term care from medical oncologists to primary care providers. In fact, prior studies[27-30] have shown that clinical outcomes for women whose care is managed by a primary care physician are similar to those for women whose care is managed by a medical oncologist. Our study, however, raises some concerns about that approach. We found that women who were given prescriptions by their primary care physician were 18% to 21% less likely to continue on AI therapy over only 2 years. This is consistent with at least one prior study,[31] which suggested that being seen by a medical oncologist increases adherence. Presumably, this reflects increased knowledge and beliefs on the part of the oncologist about the positive effects of the medication on the BC outcomes; this information and belief may be communicated to the patient, which may in turn affect her behavior. Other studies[8-10,32] have also shown that a predictor of adherence is a stronger belief that the medication has benefit. However, it is also possible that patients who are seeing a primary care physician only after a diagnosis of cancer are less likely to be compliant for other reasons.

Another factor that has been linked to reduced compliance is the number of other medications prescribed to the patient.[10,11] We found that having 10 or more other prescriptions significantly reduced the ORs for persistence. This may reflect a greater economic burden placed on the patient by the higher cumulative co-payment amount,[23] or it may reflect the complexity of the overall medical regimen[33] and the ability to acquire medications through a mail-order system when multiple providers are involved. This relationship did not change when comorbidity was removed from the model. Interestingly, some studies do suggest that patients will differentially decrease discretionary medications in preference to medications that are perceived as essential.[23,34,35] We were surprised that there was no association between income and compliance. The relationship between co-payment and compliance was not altered when income was removed from the model. This suggests financial barriers are complex and not solely based on ability to pay.

Medication adherence is an increasingly recognized issue in oncology, particularly as the number of oral agents used for therapy increases.[36] Although we have focused in this article on adherence to hormonal therapy, which represents the largest population of patients with cancer who are taking oral antineoplastic agents, there are also concerns about nonadherence with imatinib for chronic myelogenous leukemia,[37,38] with thiopurine in pediatric leukemia,[39] and with capecitabine.[40] This issue may become increasingly important as more oral antinoeplastic drugs come into use.[41]

There is a large body of literature regarding interventions for increasing medication adherence. The vast majority of these studies[42-44] have been limited to a single institution, pharmacy, or clinic. These studies have generally been focused on medications used for chronic conditions, such as diabetes, hypertension, or asthma. Little research has been conducted in the field of oncology. Most of these interventions were either behavior-based interventions or cognitive/educational interventions. Newer approaches to improving adherence are under study. One approach has been to use text messaging to provide reminders, which has been done with some success to increase adherence to medications for HIV.[45,46] There has also been

Table 3. Multivariate Analysis of Predictors of Adherence Among Women With Early-Stage Breast Cancer Who Received 90-Day Prescriptions for Aromatase Inhibitors and Who Were Persistent (2007-2008)

	Pre-Medicare (n = 8,118)						Medicare (n = 14,050)					
	Adherence		Nonadherence				Adherence		Nonadherence			
Characteristic	No.	%	No.	%	OR	95% CI	No.	%	No.	%	OR	95% CI
Total patients	7,274	89.4	863	10.6			12,802	91.1	1,248	8.9		
90-day out-of-pocket cost,$												
0-29.99	2,733	90.3	294	9.7	1.00	—	5,837	92.1	491	7.9	1.00	—
30.00-89.99	2,382	90.3	257	9.7	0.94	0.78 to 1.13	3,741	91.1	363	8.9	0.83	0.72 to 0.96
≥ 90	2,132	87.2	312	12.8	0.69	0.58 to 0.83	3,224	89.3	394	10.7	0.70	0.60 to 0.82
No. of other prescriptions												
0-4	1,650	90.0	183	10.0	1.00	—	1,754	91.4	164	8.6	1.00	—
5-9	2,333	89.5	273	10.5	0.93	0.76 to 1.14	3,788	92.1	327	7.9	1.10	0.90 to 1.34
10-14	1,627	88.8	206	11.2	0.86	0.70 to 1.07	3,279	91.6	301	8.4	1.04	0.85 to 1.28
≥ 15	1,637	89.1	201	10.9	0.85	0.68 to 1.07	3,981	89.7	456	10.3	0.85	0.70 to 1.04
Specialist												
Oncologist	4,932	89.6	570	10.4	1.00	—	7,891	91.4	746	8.6	1.00	—
Primary care physician	670	88.6	86	11.4	0.91	0.71 to 1.16	1,793	89.4	213	10.6	0.81	0.69 to 0.96
Other	800	90.0	99	10.0	0.92	0.73 to 1.16	1,693	91.4	160	8.6	1.00	0.83 to 1.19
Missing	845	88.7	108	11.3	0.90	0.72 to 1.12	1,425	91.7	129	8.3	1.03	0.85 to 1.25
Age, years												
50-54	1,632	87.9	225	12.1	1.00	—						
55-59	3,018	89.2	365	10.7	1.15	0.96 to 1.37						
60-62	2,597	90.5	273	9.5	1.33	1.10 to 1.61						
63-69							4,551	92.2	383	7.8	1.00	—
70-74							3,013	90.9	300	9.1	0.84	0.72 to 0.99
75-79							2,737	90.6	284	9.4	0.84	0.71 to 0.99
80-84							1,701	90.4	180	9.6	0.84	0.69 to 1.01
85+							800	88.7	101	11.3	0.69	0.55 to 0.88
Race												
White and other	6,368	90.1	703	9.9	1.00	—	11,674	91.6	1,091	8.4	1.00	—
Asian	150	86.7	23	13.3	0.72	0.46 to 1.14	212	93.4	15	6.6	1.34	0.79 to 2.29
Black	317	81.5	72	18.5	0.51	0.39 to 0.68	558	84.6	101	13.41	0.51	0.40 to 0.63
Hispanic	263	87.1	39	12.9	0.76	0.54 to 1.08	335	90.3	36	9.7	0.86	0.60 to 1.22
Missing	149	85.1	26	14.9	0.67	0.36 to 1.24	23	82.1	5	17.9	0.42	0.15 to 1.16
Marital status												
Married	5,735	90.0	636	10.0	1.00	—	9,220	91.3	880	8.7	1.00	—
Single	1,182	87.0	176	13.0	0.77	0.64 to 0.92	2,709	90.6	280	9.4	0.97	0.84 to 1.13
Missing	330	86.6	51	13.4	0.58	0.28 to 1.19	873	90.8	88	9.2	0.78	0.46 to 1.33
Income, $												
0-29,999	614	89.0	76	11.0	1.00	—	3,176	90.7	325	9.3	1.00	—
30,000-59,999	2,003	88.6	258	11.4	0.91	0.69 to 1.20	4,392	91.2	422	8.8	1.02	0.87 to 1.19
60,000-89,999	1,869	89.2	225	10.81	0.97	0.73 to 1.28	2,334	90.7	239	9.3	0.95	0.79 to 1.14
90,000-149,999	1,899	90.5	199	9.5	1.09	0.82 to 1.45	1,758	92.1	151	7.9	1.12	0.91 to 1.38
≥ 150,000	524	90.3	56	9.7	1.11	0.76 to 1.60	268	91.2	26	8.8	1.02	0.67 to 1.56
Missing	338	87.3	49	12.7	1.48	0.69 to 3.19	874	90.6	85	8.9	1.26	0.73 to 2.18
Region												
3, South	2,225	88.6	287	11.4	1.00	—	3,797	91.0	374	9.0	1.00	—
1, Northeast	1,317	90.0	146	10.0	1.05	0.85 to 1.30	2,336	91.7	211	8.3	0.96	0.80 to 1.15
2, North Central	1,935	89.4	228	10.6	1.00	0.83 to 1.21	4,193	91.2	405	8.8	0.93	0.79 to 1.08
4, West	1,770	89.8	202	10.2	0.96	0.78 to 1.18	2,476	90.6	258	9.4	0.83	0.69 to 0.99
Comorbidities (ETG)												
None	226	88.3	30	11.7	1.00	—	910	90.4	97	9.6	1.00	—
1-5	438	88.7	56	11.3	0.96	0.59 to 1.55	402	93.3	29	6.7	1.24	0.80 to 1.92
6-10	1,070	89.1	131	10.9	1.03	0.67 to 1.57	1,537	92.9	118	7.1	1.21	0.90 to 1.61
11-15	853	88.2	114	11.8	0.94	0.61 to 1.44	1,720	92.2	146	7.8	1.12	0.85 to 1.47
≥ 15	664	90.0	74	10.0	1.14	0.72 to 1.80	1,661	90.3	179	9.7	0.96	0.74 to 1.26
Missing	3,996	89.7	458	10.3	1.09	0.73 to 1.63	6,572	90.6	679	9.4	1.03	0.82 to 1.29

Abbreviations: OR, odds ratio; ETG, episode treatment groups.

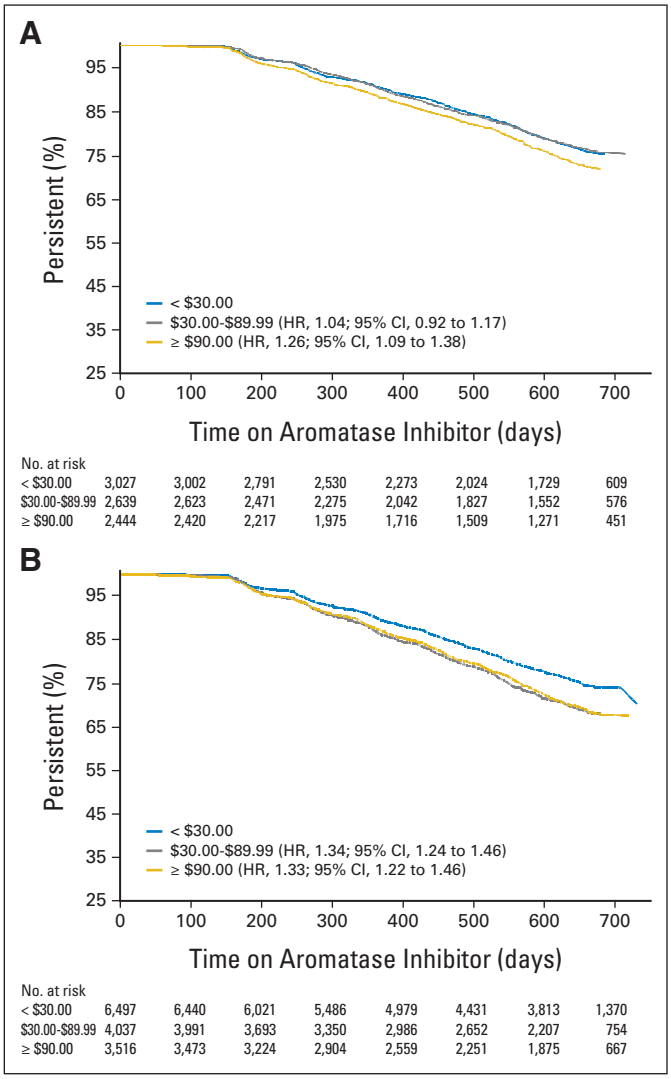

Fig 1. Kaplan-Meier curves for persistence of aromatase inhibitor use among patients with breast cancer who filled at least two 90-day mail-order prescriptions by co-payment amount, Medco, January 1, 2007, to December 31, 2008, for women younger than age 65 years (A) and women age 65 years or older (B). HR, hazard ratio.

increasing interest in the potential role of financial incentives in patient behavior, as well as for medication adherence.[47,48] One pilot study[48] explored the use of financial incentives to increase adherence to warfarin. Although changes in co-payment amounts have been found to affect adherence, these studies[15,49] have been primarily studies of trends over time, not studies of individual patients.

We found that other factors previously associated with nonadherence and/or nonpersistence also predicted nonpersistence or nonadherence in our sample, thus, supporting our findings. Our rates of nonpersistence after 2 years also mirror the previous literature.[6,11,50] For example, similar to other studies, African American race was associated with a 50% reduction in adherence in both age groups.[31,51] In addition, older age, being unmarried, and higher numbers of comorbid conditions were associated with either nonpersistence, nonadherence, or both in our study as well as in others.[6,11,33]

This study had several strengths. We used a large database with a nationwide sample that included patients with a wide variety of prescription benefit plans, thus allowing for a diversity of co-payment amounts, income, and age.

Our study also had several limitations. All of our patients received some form of prescription coverage, and therefore our results are not generalizable to patients without prescription coverage. Furthermore, we restricted our analysis to those who used a 90-day mail-order pharmacy. Medco encourages those using medications over the long term to use this option. Studies by our group and by others[6,52,53] indicate that compliance is higher for those who have 90-day prescription refill plans and that patients who fill by retail only are generally younger or older and have a higher number of co-prescriptions. Higher co-payment amounts may also be experienced when retail pharmacies are used compared with mail-order pharmacies. In addition, pharmacists in Medco's Oncology Therapeutic Resource Center attempt to contact women to whom they have previously dispensed an AI but who are delinquent in refilling to encourage compliance. As a result, the estimates of nonpersistence are probably lower than in the absence of such a system. Furthermore, some of the covariates, such as comorbidity, had a considerable amount of missing data, particularly in the older group of women, because Medco does not receive claims data from Medicare. In addition, we did not have detailed information on tumor stage or pathologic characteristics which may have influenced adherence but were unlikely to have affected the relationship between co-payment amount and adherence. Finally, we did not have information on why patients discontinued therapy; some discontinuation may have been due to toxicity, but we do not believe that this would have differed by co-payment amount.

In summary, this is the first study, to the best of our knowledge, to demonstrate that increasing the amount of a prescription co-payment is associated with the degree of noncompliance to adjuvant AI therapy in women with early-stage BC, and the threshold may be lower for patients older than age 65 years who are more likely to have a fixed income. Since previous studies[6,54,55] have shown that poor adherence and early discontinuation of hormonal therapy are associated with worse survival, future public health efforts should be directed toward assistance programs or other interventions that would aid BC patients who encounter financial difficulties with continuing appropriate use of these life-saving medications.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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