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EPIDEMIOLOGY

Adjuvant endocrine therapy initiation and persistence in a diverse sample of patients with breast cancer

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Abstract Adjuvant endocrine therapy for breast cancer reduces recurrence and improves survival rates. Many patients never start treatment or discontinue prematurely. A better understanding of factors associated with endocrine therapy initiation and persistence could inform practitioners how to support patients. We analyzed data from a longitudinal study of 2,268 women diagnosed with breast cancer and reported to the Metropolitan Detroit and Los Angeles SEER cancer registries in 2005–2007. Patients were surveyed approximately both 9 months and 4 years after diagnosis. At the 4-year mark, patients were asked if they had initiated endocrine therapy, terminated therapy, or were currently taking therapy (defined as persistence). Multivariable logistic regression models examined factors associated with initiation and persistence. Of the 743 patients eligible for endocrine therapy, 80 (10.8 %) never initiated therapy, 112 (15.1 %) started therapy but discontinued prematurely, and 551 (74.2 %) continued use at the second time point. Compared with whites, Latinas (OR 2.80, 95 % CI 1.08–7.23) and black women (OR 3.63, 95 % CI 1.22–10.78) were more likely to initiate therapy. Other factors associated with initiation included worry about recurrence (OR 3.54, 95 % CI 1.31–9.56) and inadequate information about side effects (OR 0.24, 95 % CI 0.10–0.55). Factors associated with persistence included two or more medications taken weekly (OR 4.19, 95 % CI 2.28–7.68) and increased age (OR 0.98, 95 % CI 0.95–0.99). Enhanced patient education about potential side effects and the effectiveness of adjuvant endocrine therapy in improving outcomes may improve initiation and persistence rates and optimize breast cancer survival.

Keywords Breast neoplasms · Aromatase inhibitors · Selective estrogen receptor modulators · Medication taking · Health services research

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Introduction

Adjuvant endocrine therapy for invasive breast cancer has well-established benefits in reducing recurrence and improving survival. Tamoxifen [1] and aromatase inhibitors [2] reduce mortality and longer duration of therapy provides greater benefit versus shorter duration [1, 3–5]. Despite this, not all eligible patients initiate (ever take) or persist with (defined as completing a prescribed course of clinically indicated) endocrine therapy [6–9].

The favorable efficacy data have culminated in clinical practice guidelines that recommend 5 years of adjuvant endocrine therapy—tamoxifen and, in postmenopausal women, aromatase inhibitors or sequential therapy with both tamoxifen and aromatase inhibitors for all women who have a hormone receptor-positive tumor over 1 cm [10–12]. Two clinical trials recently documented efficacy when endocrine therapy was extended to 10 years [13, 14].

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These data may encourage clinicians to prescribe therapy beyond the current 5-year recommendation. Common side effects of all agents include hot flashes and vaginal discharge or dryness. Serious side effects, such as thromboembolism and uterine cancer, have been reported with tamoxifen. Although the aromatase inhibitors are generally well tolerated [15], their use can cause loss of bone mineral density and arthralgias [16].

Initiation of treatment and persistence remains a continuing challenge to clinicians. While rates of guideline-concordant prescribing of adjuvant hormonal therapy are high [17–19], a number of studies have documented that long-term persistence with prescribed endocrine therapy for breast cancer is alarmingly low [6–9, 20–26]. Between 33 and 40 % of patients terminate therapy before the recommended 5-year period, a discontinuation rate that is substantively higher than that reported in clinical trials [27]. The high termination rate is consistent, however, with studies of medication use for other chronic conditions [28, 29]. Chronic care researchers have proposed several factors that may influence suboptimal use of endocrine therapy. Patient attributes such as older age, greater uncertainty about the marginal benefit of treatment, clinical indication for treatment, and more comorbid conditions have been associated with lower persistence, as have side effects from therapy [21, 22, 30] and higher out-of-pocket costs [31–33].

There are noteworthy gaps in our understanding of adjuvant endocrine therapy initiation and persistence. These include a lack of studies investigating endocrine therapy use in populations not identified through clinical trials, convenience samples, or enrolled in specific health plans, the absence of data obtained directly from patients, and a reliance on cross-sectional designs. To address these gaps, we examined data on factors associated with endocrine therapy initiation and persistence in women diagnosed with invasive breast cancer, selected from two Surveillance, Epidemiology and End Results (SEER) population-based cancer registries in the US, who participated in a longitudinal study.

Methods

Study sample and data collection

Our sampling strategy has been reported previously [34]. Women who lived in Los Angeles county or the Detroit metropolitan area who were between 20 and 79 years of age, diagnosed with AJCC stages I–III breast cancer or ductal carcinoma in situ (DCIS) between June 2005 and February 2007, and reported to the Los Angeles County and Metropolitan Detroit SEER tumor registries were eligible to participate. The recruitment strategy included a 20 % random sample of non-Hispanic whites, all eligible black patients in Detroit and Los Angeles, and all eligible Latinas in Los Angeles. We did not survey Asian women in Los Angeles due to a concurrent study in that population. We excluded women with diagnoses of inflammatory breast cancer or metastatic disease at presentation, women for whom we did not have race/ethnicity information, and women who could not complete a questionnaire in English or Spanish. The final analyses included only women with invasive disease that was estrogen or progesterone receptive positive. We excluded women who were too ill or incompetent or whose doctor refused permission to contact the participant. We obtained a 73.1 % response rate [34].

We used a modified version of the Dillman survey method to maximize response rates, which involved intensive telephone follow-up, second mailings of materials, and phone interviews when required [35]. Women were surveyed at two points in time: a baseline survey $\sim$9 months after diagnosis (range of 5–14 months after diagnosis) and a follow-up survey $\sim$4 years later (range of 36–65 months after initial diagnosis). After physician notification of our intention to contact their patients, we mailed eligible patients a recruitment letter, questionnaire, and a $10 cash gift. Non-responders received a postcard reminder at 3 weeks, followed by a telephone call and an option to complete the questionnaire by telephone. To increase Latina participation, we used surnames to identify women who were likely to report Latina ethnicity and provided study materials in both English and Spanish [36]. Clinical data from the SEER registries were merged with survey data obtained by patients at both time points. Study procedures received approval from the Institutional Review Boards of the University of Michigan, the University of Southern California, and Wayne State University.

Measures

Dependent variables

The dependent variables of endocrine therapy initiation and persistence were obtained from the follow-up questionnaire completed approximately 4 years after diagnosis. First, we asked women if they had taken any of the following hormonal breast cancer medicines in the past week: exemestane (Aromasin), letrozole (Femara), anastrozole (Arimedex), tamoxifen (Nolvadex), or raloxifene (Evista). Respondents who answered "yes" were classified as being persistent with endocrine therapy. Respondents who answered "no" were asked if they had ever taken any of the medications listed above. Those who answered "yes" were classified as having initiated therapy. The third group was composed of those women who reported "no" to having taken endocrine

therapy in the past week and also reported "no" to ever taking endocrine therapy.

Independent variables

The SEER registries provided the following information: age at diagnosis, race/ethnicity (white, Latina, black), stage (I, II, III), grade (1, 2, 3, or unknown), tumor size (in cm), and estrogen/progesterone receptor status. The baseline questionnaire completed by patients ~9 months after diagnosis assessed the presence of comorbid conditions (none, 1, 2 or more), education (high school or less, some college, college graduate), and married or partnered (yes/no). In addition to the outcome measures defined above, the follow-up questionnaire completed ~4 years after diagnosis queried patients on their primary provider for cancer follow-up (surgeon, medical oncologist, or other) and whether patients had received enough information from their doctor about endocrine therapy (yes/no). The number of medications taken weekly (none, 1, 2 or more) was asked at the follow-up survey and was included in analyses of the persistence outcome only. Two scales were included in the follow-up questionnaire to measure medication beliefs and worry about recurrence. To assess medication beliefs, items modified from the previously validated beliefs about medicine questionnaire [37] assessed patients' agreement about statements with regard to medicine, including "medicines do more harm than good." Five items on a five-point Likert scale were used and a mean score (range of 1–5), with higher scores reflecting more positive beliefs toward medication use. As in our previous report [38], worry about recurrence was measured on a five-point Likert scale from three items: concern the cancer would recur in the same breast, the other breast, or in another part of the body. An overall worry score was calculated as a mean across the three items. Higher scores reflect greater worry about recurrence (range 1–5; Cronbach alpha = 0.86). For modeling purposes, we categorized the worry about recurrence score into three levels: low ($\leq$2.0 on a 5-point scale), medium (2.1–4.0), and high (>4.0). Finally, women who never initiated endocrine therapy or discontinued therapy prematurely were asked their reasons for doing so. These included physician instructions to discontinue, concerns for side effects, and cost/insurance issues. Participants could select multiple responses to this question.

Statistical analyses

We first calculated descriptive statistics for the entire analytical sample and the subgroups of women who initiated or persisted with therapy. To compare the patients who initiated (or persisted) with those who did not initiate (or persist), we used Chi square tests for categorical variables and ANOVA for continuous variables. Several clinical variables that may influence use of endocrine therapy were included in all analyses. These include tumor stage, tumor grade, and age. Additional measures described above were candidates for model inclusion. To achieve model parsimony, backward variable selection procedures were used to eliminate non-clinical variables that did not reach the statistical significance level of 0.10. All analyses were adjusted for geographic location (Los Angeles versus Detroit). Odds ratios (OR) and 95 % confidence intervals (95 % CI) were calculated and presented. The *F* tests were used to examine the overall association of independent variables with the outcome of interest. Finally, we used descriptive statistics to examine reported reasons for non-initiation of and non-persistence with adjuvant endocrine therapy.

Survey weighting

In the initial descriptive statistics and multivariable models, we incorporated survey weights to make our statistical inference representative of the population. We created design weights to account for oversampling of blacks and Latinas, as well as disproportionate selection across locations. We also weighted the sample for non-response to recognize that certain patient characteristics are likely to influence response to both the baseline and follow-up questionnaire. Multivariable logistic regression models were used to create the non-response weights, with the final weight calculated as the product of the design and non-response weights. All statistical tests were two-sided, and a p value $<.05$ was considered statistically significant. All analyses were performed using STATA (College Station, TX).

Results

These analyses are based on 743 respondents with invasive disease (see Fig. 1 for details on how the analytic sample was derived). 1,536 women completed both the baseline and follow-up surveys. To restrict our sample to women who met clinical indications for endocrine therapy, we excluded 793 respondents: those who did not have invasive disease ($n = 381$), had negative or unknown ER and/or PR receptor status ($n = 315$), had experienced a recurrence at the time of our follow-up survey ($n = 42$), or had incomplete data on study measures ($n = 55$).

Of the 743 women in our analytic sample, 663 (89.2 %) initiated endocrine therapy. Of those who initiated therapy, 551 (83.1 %) were persistent with therapy at ~4 years after diagnosis (74.2 % of the entire analytic sample).

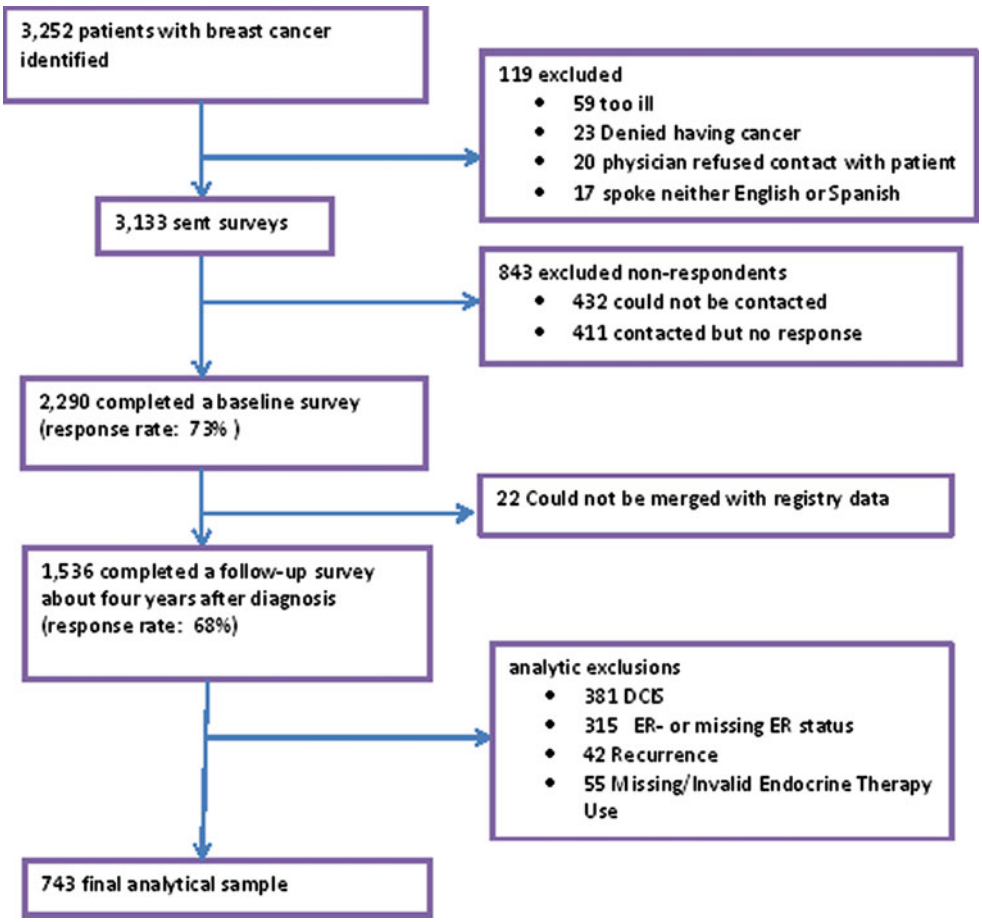

Fig. 1 The derivation of the analytic sample is shown, with reasons for exclusion

Table 1 shows the characteristics of the study sample and the distribution of the outcome variables, initiation, and persistence. In the bivariate analyses, significant differences were observed on rates of endocrine therapy initiation by age, SEER tumor grade, the presence of comorbid conditions, worry about recurrence score, receipt of information about endocrine therapy, and primary provider for cancer care follow-up. Initiation rates varied by the presence of comorbid conditions ($p < .01$) with 82, 94, and 90 % for women with two or more conditions, one condition, and none, respectively. The degree of worry about recurrence was significantly associated with the rate of initiation ($p = 0.02$); patients with higher worry about recurrence had higher rates of initiation (93, 89, and 83 % for high, medium, and low worry scores, respectively).

In bivariate analyses (Table 1), fewer variables differed significantly on the persistence outcome. Weekly medication use was associated with different rates of persistence ($p < .001$) with 87 % of patients who took two or more medications weekly persisting on therapy, compared with a persistence rate of 68 % for women who took fewer than two medications weekly. Higher scores on the worry about recurrence scale were associated with significantly higher rates of persistence ($p = .05$). Those who reported that they did not receive adequate information about endocrine therapy had lower rates of persistence (77 vs. 84 %, $p < .001$).

Factors associated with endocrine therapy initiation

After backward variable selection procedures, several variables were removed from the initiation model, including tumor size, comorbid conditions, education, marital status, and the medication belief scale. The final weighted multivariable model is presented in Table 2. Initiation of therapy was associated with the Latina ethnicity (OR 2.80, 95 % CI 1.08–7.23), black race versus non-Hispanic white (OR 3.63, 95 % CI 1.22–10.78), and grade 2 tumors (vs. Grade 1, OR 2.59, 95 % CI 1.13–5.94). Women with higher scores on the worry about recurrence scale were more likely to report initiation (medium vs. low OR 2.25, 95 % CI 1.06–4.82; high vs. low OR 3.54, 95 % CI 1.31–9.56), as were women who reported that their primary provider for cancer follow-up was a medical oncologist rather than a surgeon (OR 3.21, 95 % CI 1.02–9.60). Women who reported that they had received inadequate information about endocrine therapy were significantly less likely to initiate treatment than women who did not report

Table 1 Participant characteristics by initiation and persistence of endocrine therapy

	Entire sample ($n = 743$)	% Initiated therapy ($n = 663$)	p	% Persist on therapy ($n = 551$)	p
Age, mean (SD)	58.9 (11.7)	57.5 (11.2)	.05	57.1 (11.1)	.11
Education			.59		.26
High school or less	264 (39.9)	90		82	
Some college	253 (33.2)	87		82	
College graduate +	217 (26.8)	91		88	
Race			.46		.10
White	409 (48.3)	87		81	
Latina	183 (37.6)	91		88	
Black	140 (14.2)	91		78	
SEER stage			.31		.21
Stage I	395 (48.5)	88		81	
Stage II	263 (38.6)	89		84	
Stage III	83 (12.9)	93		91	
SEER grade			<.01		.07
Grade 1	177 (21.8)	85		81	
Grade 2	326 (45.7)	94		84	
Grade 3	193 (25.6)	86		91	
Unknown grade	47 (6.9)	100		50	
Comorbid conditions			<.01		.57
None reported	297 (40.0)	90		83	
One reported	223 (31.1)	94		85	
2 or more reported	223 (28.8)	82		81	
Number of medications taken in the week prior to the follow-up survey					<.001
0–1	157 (21.6)			68	
2 or more	578 (78.5)			87	
Medication beliefs scale, mean (SD)	2.91(0.57)	2.83 (0.59)	0.28	2.82 (0.59)	.13
Worry about recurrence score			.020		.05
Low (≤2.0)	154 (18.7)	83		81	
Medium (2.1–4.0)	413 (54.5)	89		81	
High (>4.0)	174 (26.8)	93		90	
Received enough information about endocrine therapy			<.001		<.001
Yes	622 (83.8)	92		84	
No	110 (16.2)	74		77	
Primary oncology provider			<.01		.14
Surgeon	46 (6.3)	84		77	
Medical oncologist	561 (77.2)	94		87	
Other provider	136 (16.5)	70		65	

Values weighted to account for differential probabilities of sample selection and non-response

Table 2 Multivariable model to assess factors associated with endocrine therapy initiation ($n = 598$)

Factor	Adjusted odds ratio	95 % CI	p
Race			
White	1.0	Ref.	.02
Latina	2.80	1.08–7.23	
Black	3.63	1.22–10.78	
SEER stage			
Stage I	1.0	Ref.	.35
Stage II	1.62	0.76–3.51	
Stage III	1.84	0.55–6.19	
SEER grade			
Grade 1	1.0	Ref.	<.001
Grade 2	2.59	1.13–5.94	
Grade 3	1.84	0.55–6.19	
Age	1.00	0.97–1.04	.80
Worry about recurrence score			
Low	1.0	Ref.	.03
Medium	2.25	1.06–4.82	
High	3.54	1.31–9.56	
Received enough information about endocrine therapy			
Yes	1.0	Ref.	<.001
No	0.24	0.10–0.55	
Primary oncology provider			
Surgeon	1.0	Ref.	<.001
Medical oncologist	3.12	1.02–9.60	
Other provider	0.44	0.14–1.40	

Parameter estimates weighted to account for differential probabilities of sample selection and non-response. Model includes adjustment for SEER site (Detroit vs. Los Angeles)

inadequate information (OR 0.25, 95 % CI 0.10–0.55). Age and tumor stage were not significantly associated with initiation.

Factors associated with endocrine therapy persistence at 4 years

Table 3 shows the weighted multivariable model for persistence with measures retained after backward variable selection procedures. Lower likelihood of persistence was associated significantly with increasing age (OR 0.98, OR 0.95–1.00, $p < .04$). Compared with those who reported taking none or one medication weekly, women who took two or more medications weekly as reported in the follow-up survey were more likely to persist on therapy (OR 4.19, 95 % CI 2.28–7.68). No significant differences in persistence were observed by race/ethnicity, tumor stage, tumor grade, worry about recurrence, or type of provider for follow-up oncology care.

Reasons for non-initiation and non-persistence

Therapy-eligible participants who never initiated therapy ($n = 80$) were asked why they did not, and these unweighted descriptive responses are shown in Table 4. Participants could choose multiple responses. Clinician factors were primarily cited, including statements such as doctor said they did not need therapy ($n = 27$, 33.8 %) or the doctor left it up to the patient ($n = 17$, 21.3). Reported patient factors included concerns about side effects ($n = 23$, 28.8 %) and cost ($n = 4$, 5.0 %). Patient factors were cited by many of the 112 women who discontinued treatment; 45 (40.2 %) cited side effects, 28 (25 %) cited concerns about the risks from the medication, and 26 (23.2 %) reported a general dislike of medication (see Table 5).

Table 3 Multivariable model to assess factors associated with endocrine therapy persistence ($n = 539$)

Factor	Adjusted odds ratio	95 % CI	p
Race			
White	1.0	Ref	.43
Latina	1.29	0.59–2.80	
Black	0.72	0.38–1.38	
SEER stage			
Stage I	1.0	Ref	
Stage II	1.37	0.76–2.46	.37
Stage III	1.90	0.65–5.59	
SEER grade			
Grade 1	1.0	Ref	.06
Grade 2	1.18	0.58–2.39	
Grade 3	0.55	0.25–1.20	
Age	0.98	0.95–1.00	.04
Number of medications taken in the week prior to the follow-up survey			
0–1	1.0	Ref	<.001
2 or more	4.19	2.28–7.68	
Worry about recurrence score			
Low	1.0	Ref	.14
Medium	0.66	0.33–1.32	
High	1.29	0.49–3.41	
Primary oncology provider			
Surgeon	1.0	Ref	.11
Medical oncologist	1.44	0.51–4.04	
Other provider	0.40	0.13–1.22	

Parameter estimates weighted to account for differential probabilities of sample selection and non-response. Model includes adjustment for SEER site (Detroit vs. Los Angeles)

Discussion

The majority of women in our population-based sample eligible for endocrine therapy both initiated and persisted

Table 4 Reasons for never initiating endocrine therapy ($n = 80$)

	Never initiated *n* (%)
Clinician factors	
Doctor said I did not need	27 (33.8)
Doctor left it up to me	17 (21.3)
Doctor never discussed	6 (7.5)
Patient factors	
Worried about side effects	23 (28.8)
Doctor recommended, but I chose not to	15 (18.8)
Too expensive	4 (5.0)

Table 5 Reasons for premature discontinuation of endocrine therapy ($n = 112$)

	Discontinued *n* (%)
Patient factors	
Side effects	45 (40.2)
Worried about risks	28 (25.0)
Dislike medication	26 (23.2)
I was not sure if it was helping	25 (22.3)
Too expensive	21 (18.8)
I had taken it long enough	20 (17.9)
I wanted to move on from cancer	14 (16.1)
I stopped for insurance reasons	8 (7.1)
Clinician factors	
Doctor told me to stop	28 (25.0)
Completed course of treatment	14 (12.5)

Percentages do not add up to 100 % as participants could choose multiple responses

on therapy: Of the 743 patients eligible for endocrine therapy, 80 (10.8 %) never initiated therapy, 112 (15.1 %) started therapy but discontinued prematurely, and 551 (74.2 %) continued use at the second time point. Our findings are consistent with previously published reports. A study that used commercial claims data to assess adherence with adjuvant anastrozole therapy [8] showed that women enrolled in three different insurance plans had adherence rates of 62–79 % by the third year of treatment. Women in our study were treated more recently (2005–2010) compared with a timeframe of 2002–2004 in above-cited study [8]. A single-site study performed in 2006 reported similar rates of initiation and persistence [39].

Blacks and Latinas had the highest rates of initiation and persistence in our sample. Ours is not the first study to document null findings or higher rates of treatment completion in groups historically considered disadvantaged. Recent reports have documented the absence of racial disparities in adjuvant endocrine therapy in the Medicare [40] and Medicaid [41] populations, as well in the receipt of systemic chemotherapy [34, 42]. Poverty, insurance coverage, family support, and overall treatment experiences are contextual factors that may explain endocrine therapy persistence [43–46]. Our study did not examine the effects of peer support or breast cancer navigator programs, both of which may have supported blacks and Latinas through treatment during the study period.

Patients who initiated endocrine therapy expressed more worry about recurrence, regardless of tumor stage and grade. While clinicians educate patients to mitigate the anxiety surrounding a breast cancer diagnosis, health behaviorists assert that perceived susceptibility is a strong motivator for desired health behaviors [47]. In our study and in a report by others [25], women who reported receiving less information about endocrine therapy were less likely to initiate therapy. Adequacy of information was associated with initiation, but not persistence. This suggests that clinicians need to address patient information needs regarding therapy prior to initiation of treatment. Treatment initiation was higher for women who saw medical oncologists as opposed to other providers for their follow-up cancer care. It is likely that patients who saw medical oncologists may have clearer indications for endocrine therapy. Other providers of follow-up oncology care may benefit from additional education or resources to support patients receiving endocrine therapy. Women who took two or more medications at the time of the follow-up survey were more likely to persist with endocrine therapy, which suggests that women who were less experienced in medication use prior to a breast cancer diagnosis may be at risk for low persistence.

Patients who did not initiate treatment cited provider factors as the primary reason. These responses likely reflect physician judgment that endocrine therapy is not warranted in these cases. It is interesting to note that few patients endorsed insurance coverage as a reason for not starting therapy, despite the findings from previous investigators [48]. However, a total of 32 patients cited drug expense or insurance issues as one of many reasons for not initiating or persisting with therapy. In our sample, patient attitudes about endocrine therapy and medication in general were associated with premature termination. Side effects, safety concerns, and a general dislike of medication were the most often-cited factors. Severe side effects were the largest predictor of discontinuation of tamoxifen in a prior study [25]. These findings from a population-based sample of patients are timely considering the ATLAS trial results reported at the 2012 San Antonio Breast Cancer Symposium. In this clinical trial, women who completed 10 years of adjuvant tamoxifen therapy compared with 5 years had significantly lower recurrence and breast cancer mortality rates [13]. Outside of a clinical trial, clinicians may be challenged to maintain patients on therapy for 10 years if side effects are a key barrier to persistence. Aggressive supportive care and consultation with oncology pharmacists may be important interventions to consider if the duration of endocrine therapy is extended in forthcoming clinical practice guidelines.

There are several limitations of this study. First, we relied on patient self-report of initiation and persistence to endocrine therapy. We were unable to ascertain if patients who did not initiate were not offered a prescription for endocrine therapy. Measurement of medication use with prescription data or the clinical record would strengthen the validity of our findings [49]. The data was derived from a sample of women who completed surveys at approximately 9 months and 4 years after breast cancer diagnosis. Our sample of women is more likely to persist on therapy than women in the general population. Because routine medication use was measured only at the 4-year follow-up survey, we cannot assess the degree to which routine medical use influences initiation of therapy. Another limitation of this study is that the study participants were recruited from only two sites—Los Angeles county and Metropolitan Detroit—with three racial and ethnic groups: white, black, and Latina women. While our study sample is diverse, findings may not be generalizable to other populations or geographic settings.

In conclusion, adjuvant endocrine therapy initiation and persistence rates are high in a diverse population-based sample of eligible women. Differences by socioeconomic status are small. Initiation is influenced by worry about recurrence, sufficient information receipt about these agents, and primary source of cancer care during treatment

with endocrine therapy. Persistence is associated with younger age and concurrent medication use. Care settings without medical oncologists may benefit from additional resources to support eligible patients. Non-persistence was largely related to patient attitudes toward therapy. These findings highlight the need for additional education and support strategies for women—regardless of race or ethnicity—at risk for not initiating or persisting on adjuvant endocrine therapy to optimize treatment and reduce breast cancer recurrence and improve survival.

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Conflict of interest The authors declare they have no conflict of interest.

Ethical standards Institutional Review Boards of the University of Michigan, the University of Southern California, and Wayne State University approved the study described in this work.

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