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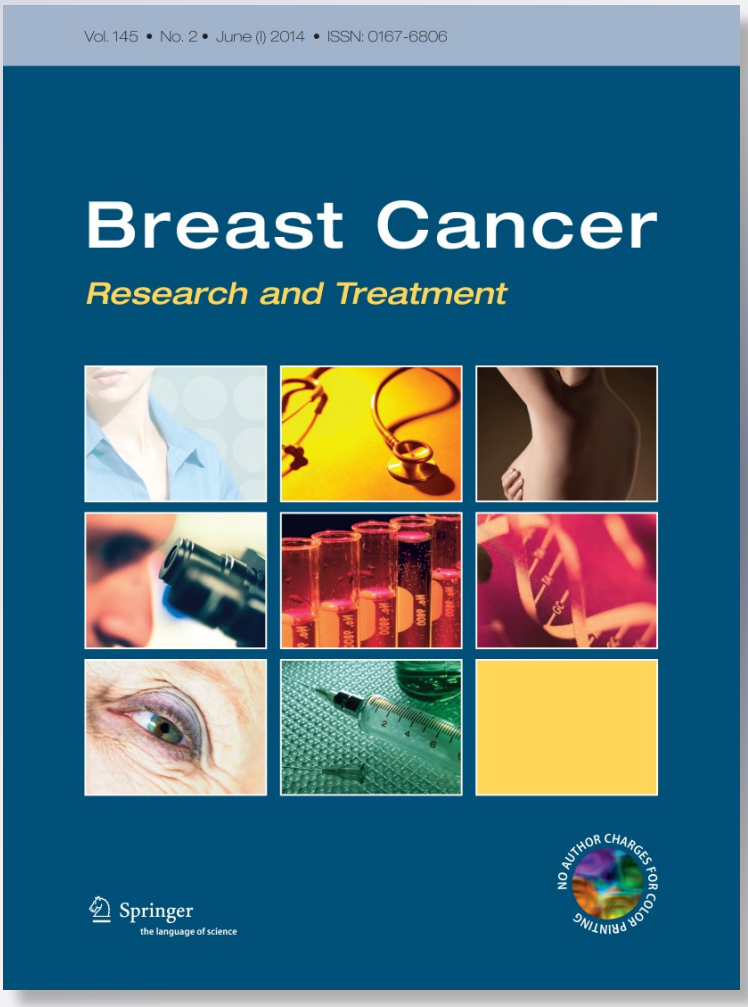

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Contributors to nonadherence and nonpersistence with endocrine therapy in breast cancer survivors recruited from an online research registry

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Abstract Rates of adherence and persistence with endocrine therapy regimens (i.e., tamoxifen, aromatase inhibitors) by breast cancer survivors are suboptimal, with negative implications for prognosis. This study identified potential contributors to nonadherence and nonpersistence. From an online breast cancer research registry (Army of Women) including approximately 51,000 breast cancer survivors, we recruited 1,371 women who currently were taking endocrine therapy and 94 nonpersisters (i.e., diagnosed during the prior 5 years and on endocrine therapy within the prior 12 months, but no longer taking it). Participants completed an online questionnaire assessing demographic/medical characteristics, general and cancer-related psychosocial variables (i.e., depressive symptoms, anxiety, patient–oncologist relationship quality, cancer recurrence worry, general symptoms), and endocrine therapy-specific variables (i.e., endocrine therapy-related symptoms, perceived endocrine therapy necessity, long-term therapy use concern, endocrine therapy-related emotions). Two weeks later, current users were re-contacted to complete an endocrine therapy adherence measure. In a final regression model, patient-reported nonadherence among current users was significantly associated with lower financial status, a prior switch in endocrine therapies, a poorer relationship with the oncologist, and lower perceived need for and more negative emotions regarding endocrine therapy (adjusted $R^2 = 0.15$, $P < 0.001$). In a final logistic regression model, endocrine therapy nonpersisters were significantly more likely than current users to report depressive symptoms, as well as more negative emotions and lower positive emotions related to endocrine therapy (adjusted $R^2 = 0.10$, $P < 0.001$). In addition to demographic/medical variables, several potentially modifiable psychosocial characteristics are likely to contribute to endocrine therapy nonadherence and nonpersistence.

Keywords Breast cancer · Adherence · Tamoxifen · Aromatase inhibitor · Compliance

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Introduction

Current guidelines recommend at least 5 years of tamoxifen or aromatase inhibitors after primary treatment for hormone receptor-positive breast cancer [1]. Nonadherence (i.e., failing to take the medication as prescribed) and nonpersistence (i.e., discontinuing the medication prior to the prescribed duration) with endocrine therapy are common. A recent systematic review of 29 studies of breast cancer patients in clinical practice (excluding randomized controlled trials) [2] documented 12–59 % nonadherence prevalence (i.e., medication possession ratio of less than 80 %) for tamoxifen and 9–50 % for the aromatase inhibitors. After 5 years, nonpersistence ranged from 31 to 73 %. The evidence that nonadherence and nonpersistence with endocrine therapy predict lower survival [3–5, cf. 6]

renders it critical to identify factors that influence adherence, with translation into adherence-promoting interventions. Accordingly, we sought to identify contributors to nonadherence and nonpersistence in breast cancer survivors prescribed endocrine therapy.

The literature on determinants of adherence to endocrine therapies suggests that at least three domains warrant study: demographic and medical parameters, psychosocial variables, and factors specific to endocrine therapy. Regarding demographic and medical parameters [2], such significant correlates of nonadherence as younger or older age (e.g., <50 or >65 years), complexity of the general medication regimen, and lower financial status are related to nonadherence and were examined in this research.

Psychosocial factors, which often are more robust predictors of adherence to long-term medical regimens than are demographic/medical factors [7], constitute a second set of contributors. We focused on five such factors, all of which have some evidence for their links with adherence to endocrine therapy or other medical regimens: a problematic patient-oncologist relationship [8]; the presence of depressive symptoms or anxiety [9–11]; low worry regarding cancer recurrence, which could result in low motivation to adhere [12]; and bothersome symptoms [7]. We examined whether the report of general symptoms or symptoms women attributed specifically to endocrine therapy was more strongly related to nonadherence.

Psychosocial variables specifically related to endocrine therapy might be the factors most amenable to adherence-promoting interventions. These include the experience of more severe endocrine therapy-related symptoms [8, 13–16; cf. 17, 18]; low perceived need for endocrine therapy and high concern regarding long-term use of endocrine therapies, as included in the necessity-concerns framework of adherence [14, 19]; as well as more negative emotions and fewer positive emotions related to endocrine therapy. We hypothesized that these factors would be associated with poorer adherence and greater likelihood of nonpersistence, over and above the contribution of demographic, medical, and general psychosocial factors.

Method

Participants

Recruited from Dr. Susan Love Research Foundation's Love/Avon Army of Women research registry (AOW), participants met the following eligibility criteria: (1) woman at least 18 years old diagnosed with breast cancer; (2) currently taking, or has taken within the past 12 months, one of the following medications: tamoxifen (Nolvadex), anastrazole (Arimidex), exemestane (Aromasin), or letrozole (Femara); (3) able to complete an online survey; (4) lives in the United States. Self-report of taking endocrine therapy was assumed to reflect the presence of a hormone receptor-positive carcinoma where endocrine therapy was indicated.

Procedure

Upon IRB approval, participants were recruited via email from the AOW, a registry of 362,314 individuals (at study recruitment) who volunteer for breast cancer research. AOW members are recruited from several sources (i.e., scientific conferences, organizations, public events, media). Approximately 14 % has a breast cancer diagnosis.

In January 2012, a "call-to-action" email was sent to all registry participants. The email described endocrine therapies [i.e., "Endocrine therapies such as (four medications) are medications for breast cancer that block or remove hormones"], stated the study's purpose as gathering information "to understand women's thoughts, feelings, and behaviors relevant to taking endocrine therapies," and requested interested women to affirm that they met eligibility criteria. Upon confirmation of eligibility, women were routed to the online survey, which required no more than 30 min to complete. All data were collected via online survey. Fourteen days after the first invitation, women who reported current endocrine therapy use received a second invitation via email to complete adherence items online, with a reminder sent 1 week later.

Measures

Demographic and medical characteristics

Demographic characteristics were age, race/ethnicity, education, marital status, employment, and perceived financial status (i.e., enough money for special things; little spare money for special things; money to pay bills only because cut back; difficulty paying bills; [20]). Self-reported medical characteristics were menopausal status, medication payment method, number of prescription medications taken regularly, breast cancer diagnosis date, cancer stage, surgery, chemotherapy, trastuzumab, radiotherapy, and reconstruction. Breast cancer treatment items had multiple choice responses, which were collapsed into yes/no categories. Items regarding endocrine therapy included current endocrine therapy type (tamoxifen, anastrazole, exemestane, letrozole) or no current endocrine therapy (endocrine therapy in the past 12 months was an eligibility criterion), duration of current endocrine therapy (open-ended question to specify years and/or months), and prior different endocrine therapy and reason for switching (i.e., decrease risk of cancer coming back, decrease side effects, other). After reviewing "other reason" responses, two independent raters coded them into additional categories. Inter-rater agreement was 99 %.

General and cancer-related psychological factors

Anxiety and depressive symptoms were assessed with the 14-item Hospital Anxiety and Depression Scale (HADS) [21], which has evidence of validity in cancer patients [22]. Internal consistency reliability in this sample was Cronbach $\alpha = 0.86$ depression, $\alpha = 0.83$ anxiety.

Quality of the oncologist-patient relationship was measured with the 10-item Working Alliance Inventory Short-Client Form specific to participants' current oncologist [23] (e.g., my doctor understands all that I am going through with my health problem; 1 = strongly disagree; 5 = strongly agree). Studies support the scale's reliability and validity [24, 25]. Internal consistency was $\alpha = 0.93$.

One item assessed recurrence worry (i.e., how worried are you about your breast cancer recurring?; 0 = not at all; 10 = a great deal).

Symptoms potentially related to endocrine therapy were assessed with the Breast Cancer Prevention Trial (BCPT) Symptom Scales, which has sound psychometric properties in breast cancer patients [26]. Items for AI side effects [27] were added. Participants reported whether they were bothered by each of 47 symptoms during the past 4 weeks (no; yes, related to my endocrine therapy; yes, not related to my endocrine therapy). The two resulting scales consisted of the endorsed symptom total each woman did or did not attribute to endocrine therapy.

Other endocrine therapy-related measures

In line with the necessity-concerns framework [19], two items measured perceived therapy necessity: how much do you feel your endocrine therapy can help reduce your risk of breast cancer recurring? (0 = not at all; 10 = a great deal); how much do you feel you need the endocrine therapy prescribed for your breast cancer? (0 = I don't need it at all; 10 = it is absolutely essential for me). Items ($r = 0.58$, $P < 0.001$) were averaged. One item assessed long-term use concern (i.e., how concerned are you about the long-term use of your current endocrine medication?; 0 = not at all; 10 = extremely concerned).

Negative and positive emotions regarding endocrine therapy were adapted from items for affective properties of attitudes [28]. Respondents rated the extent to which items described their feelings toward endocrine therapy (i.e., does not describe, slightly describes, definitely describes). Internal consistencies were high for the five-item negative emotion scale ($\alpha = 0.83$; sad, annoyed, tense, reluctant, angry) and positive emotion scale ($\alpha = 0.81$; happy, calm, enthusiastic, comforted, accepting).

Adherence

An adapted Morisky Medication Adherence Scale [29], commonly used across several diseases [30], assessed adherence to endocrine therapy. The response scale was adapted from a dichotomous (yes/no) to a Likert-type scale (1 = never; 5 = always). One non-relevant item was deleted ("When you feel better do you sometimes stop taking your medicine?") and replaced with two items regarding intentional nonadherence (i.e., I alter the dose of my current endocrine therapy from what has been prescribed by my doctor; I decide to miss a dose of my current endocrine therapy) [31]. Higher total scores indicate greater nonadherence. Internal consistency was $\alpha = 0.76$. Correlations with self-reported number of doses missed in the past week, 2 weeks, and month were $r = 0.60$–0.67, $P < 0.001$.

Persistence

At the beginning of the online survey, participants indicated on a checklist their current endocrine therapy or no endocrine treatment. Women were classified as being nonpersistent if they reported breast cancer diagnosis within the past 5 years and not currently taking endocrine therapy but that they had taken endocrine therapy within the past 12 months (an eligibility criterion).

Data analysis

Descriptive statistics and analyses to examine differences on all variables between current endocrine therapy users who completed versus did not complete the 2-week adherence assessment were conducted.

In major analyses, a more stringent $P \leq 0.01$ rather than $P \leq 0.05$ was required to provide some control for family-wise error. In hierarchical multiple regressions, adapted Morisky Adherence Scale scores were regressed on the three variable sets. First, hypothesized demographic/medical characteristics were entered as a set. The remaining demographic/medical characteristics were entered and included if they were significantly associated with adherence. Next, the set of general psychosocial variables was entered, followed by endocrine therapy-specific variables.

Next, *t*-tests and X^2 compared current endocrine therapy users with nonpersisters on the three hypothesized sets of variables: demographic/medical characteristics, general psychosocial variables, and endocrine therapy-specific factors. Group differences also were explored on all other demographic/medical characteristics. A final logistic regression including variables demonstrated to have

significant zero-order relations with nonpersistence was performed to assess its most potent correlates.

Results

Sample characteristics

Of the estimated 51,000 women with breast cancer who were emailed an invitation, 2,341 met eligibility criteria and completed the first survey. Of those, 2,086 reported current use of endocrine therapy, and 1,371 (66 %) of that group completed a second survey regarding medication adherence and were categorized as current users ($n = 715$ did not complete the second survey). An additional 94 women completed the first survey and were categorized as nonpersisters. Analyses included 1,371 current users and 94 nonpersisters. (Note that an additional 161 women were not current users and had been diagnosed for at least 6 years, but whether they were regimen completers or nonpersisters was unclear; therefore, their data were not analyzed.)

On average, participants were 56 years old and taking nearly three medications in addition to endocrine therapy (see Table 1). The majority was non-Hispanic white (94 %), employed (58 %), married (78 %), and had completed college (74 %). On average, women had been diagnosed for nearly 5 years, and most had early-stage disease. In current users, anastrazole was the most frequently prescribed therapy. On average, women had been taking endocrine therapy for more than 2 years, and 49 % had taken a different therapy prior to their current prescription. Nearly half who had switched therapies reported side effects as the primary reason. On average, current endocrine therapy users reported being nonadherent "never" to "rarely" (see Table 2).

T-tests and X^2 conducted to compare current therapy users who completed versus did not complete the 2-week adherence assessment revealed only four significant differences at $P < 0.01$. Women who completed the 2-week adherence assessment had been diagnosed for a longer time (mean, 5.07 vs. 4.26 years; $P < 0.001$), were more likely to have had chemotherapy (65 vs. 58 %; $P < 0.001$), reported more physical symptoms from endocrine therapy (mean, 9.04 vs. 8.04; $P = 0.003$), and had a different prescription pattern ($P < 0.001$); specifically, they were less likely to be prescribed tamoxifen (30 vs. 43 %) and more likely take exemestane (12 vs. 4 %) and letrozole (22 vs. 16 %) (36 % anastrozole in both groups) than were women who did not take part in the 2-week assessment of adherence.

Regression of adherence indicator on hypothesized contributors

Within current users, the adapted Morisky Adherence Scale score was regressed on each set of hypothesized contributors.

Table 1 Participant characteristics ($N = 1,465$)

Characteristic	*n* (%) or mean ± SD (range)
Age, years	56.03
	SD = 8.72 (range = 25–86)
Race/ethnicity	
Non-Hispanic white	1,380 (94 %)
African American	25 (2 %)
Asian American	17 (1 %)
Latina	22 (2 %)
American Indian	4 (0 %)
Other	8 (0 %)
Education	
<College graduate	381 (26 %)
College graduate	541 (38 %)
>College graduate	517 (36 %)
Employed at least part-time outside home	838 (58 %)
Married/living as married	1,117 (78 %)
Post-menopausal	1,228 (85 %)
Number of prescription medications (excluding endocrine therapy)	2.97
	SD = 2.00 (range = 0–11)
Perceived financial status	
Money for extras	949 (66 %)
Little money for extras	330 (23 %)
Pay bills through cutting back	77 (5 %)
Difficulty paying bills	74 (5 %)
Time since breast cancer diagnosis, years	4.96
	SD = 3.82 (range = 0–31)
Breast cancer stage	
0	66 (4 %)
1	513 (37 %)
2	522 (37 %)
3	166 (12 %)
4	128 (9 %)
Don't know	70 (5 %)
Surgical treatment	
Breast conservation	722 (51 %)
Mastectomy	324 (23 %)
Bilateral mastectomy	377 (26 %)
Breast reconstruction	547 (37 %)
Radiation receipt	1,081 (74 %)
Chemotherapy receipt	936 (64 %)
Trastuzumab (Herceptin) receipt	188 (13 %)
Endocrine therapy receipt	
Tamoxifen (Nolvadex)	406 (28 %)
Anastrazole (Arimidex)	498 (34 %)
Exemestane (Aromasin)	171 (12 %)
Letrozole (Femara)	296 (20 %)

Table 1 continued

Characteristic	*n* (%) or mean ± SD (range)
No current endocrine therapy	94 (6 %)
Length of current endocrine therapy, months	28.8 SD = 22.06 (range = 1–144)
Payment for current endocrine therapy	
Self	53 (4 %)
Co-pay	1,261 (88 %)
Full coverage	64 (5 %)
Other	55 (4 %)
Switched from another endocrine therapy	675 (49 %)
Reason for switching endocrine therapy	(n = 675)
Better decrease risk of cancer recurring	119 (18 %)
Decrease side effects	326 (48 %)
Diagnosed with another breast cancer/recurrence/progression	54 (8 %)
New agent after 5 years on another endocrine therapy	28 (4 %)
Completed menopause	80 (12 %)
Cost/medical insurance refused	33 (5 %)
Poor metabolism of originally prescribed therapy	4 (1 %)
Adverse event (e.g., pulmonary embolism, uterine polyps)	14 (2 %)
Other/unclear reason	17 (2 %)

Lower perceived financial status was associated significantly with poorer adherence. Other demographic/medical variables were not related to nonadherence, except in two cases: poorer adherence was associated significantly with having switched from another endocrine therapy ($P < 0.001$) and therapy type ($P < 0.002$) (see Ref. [32] and Table 3 note).

Of the general and cancer-related factors, only having a poorer-quality relationship with the oncologist was related significantly to nonadherence. Among the endocrine therapy-specific variables, reporting lower endocrine therapy necessity and more therapy-related negative emotions were associated significantly with nonadherence.

The final regression model accounted for 15 % of the variance in nonadherence (Table 3). As predicted, endocrine therapy-specific variables accounted for the largest proportion (7 %) of variance, followed by general psychosocial factors (6 %), and demographic/medical factors (3 %).

Comparison of endocrine therapy current users to nonpersisters

Age, financial status, and number of other medications were not associated with nonpersistence, contrary to hypothesis (Table 4). Nonpersisters had been diagnosed

Table 2 Self-reported adherence data for current endocrine therapy users

Measure	*n* (%)
How many doses of your current endocrine therapy have you missed in the last month (31 days)? (0–31 from dropdown menu); (n = 1,367)	
0 (100 % adherent)	833 (61 %)
1–6 (80–99 % adherent)	490 (36 %)
7–31 (<80 % adherent)	44 (3 %)
Do you ever forget to take your current endocrine therapy? (adapted Morisky Adherence Scale item); n = 1,371	
Never	671 (49 %)
Rarely	562 (41 %)
Sometimes	111 (8 %)
Often	13 (1 %)
Always	12 (1 %)
Are you careless at times about taking your current endocrine therapy? (adapted Morisky Adherence Scale item); n = 1,371	
Never	965 (70 %)
Rarely	335 (24 %)
Sometimes	62 (4 %)
Often	8 (1 %)
Always	1 (0 %)
Sometimes if you feel worse when you take your current endocrine therapy, do you stop taking it? (adapted Morisky Adherence Scale item); n = 1,371	
Never	1,249 (91 %)
Rarely	59 (4 %)
Sometimes	47 (3 %)
Often	8 (1 %)
Always	8 (1 %)
I alter the dose of my current endocrine therapy from what has been prescribed by my doctor (adapted Morisky Adherence Scale item); n = 1,371	
Never	1,331 (97 %)
Rarely	15 (1 %)
Sometimes	10 (1 %)
Often	6 (0 %)
Always	9 (1 %)
I decide to miss a dose of my current endocrine therapy (adapted Morisky Adherence Scale item); n = 1,371	
Never	1,182 (86 %)
Rarely	126 (9 %)
Sometimes	49 (4 %)
Often	9 (1 %)
Always	5 (0 %)

Table 3 Self-reported endocrine therapy adherence (adapted Morisky Adherence Scale) regressed on hypothesized contributors to nonadherence (final model)

Predictor	*r*	ΔR^2 (Adj)	*B*	SE	β	*P*
Step 1		0.03				<0.001
Age	−0.07		0.01	0.01	0.05	0.147
Perceived financial status	0.10		0.22	0.08	0.09	0.010
Number of medications	−0.04		−0.11	0.04	−0.08	0.018
Endocrine therapy type	–		−0.04	0.07	−0.02	0.566
Switched from another endocrine therapy	–		−0.42	0.14	−0.10	0.003
Step 2		0.06				<0.001
Depressive symptoms (HADS)	0.15		−0.03	0.03	−0.05	0.243
Anxiety (HADS)	0.13		0.02	0.02	0.05	0.283
Patient–oncologist relationship quality	−0.24		−0.03	0.01	−0.10	0.010
Cancer recurrence worry	−0.01		0.03	0.03	0.04	0.265
Physical symptoms—general	0.03		0.03	0.02	0.06	0.099
Step 3		0.07				<0.001
Physical symptoms—endocrine therapy	0.13		0.01	0.01	0.03	0.491
Perceived endocrine therapy necessity	−0.31		−0.25	0.05	−0.21	<0.001
Endocrine therapy negative emotions	0.30		0.10	0.04	0.12	0.010
Endocrine therapy positive emotions	−0.26		−0.03	0.03	−0.04	0.349
Long-term endocrine therapy use concern	0.17		0.01	0.02	0.02	0.624
Total adjusted R^2		0.15				
Final model *F* (df)		10.60 (15,796)				<0.001

Correlations (*r*) are univariate correlations, with $n = 1029$–1352; any $r \geq |0.07|$ is significant at $P < 0.01$. – = categorical variable, for which analyses demonstrated a significant difference in adherence by endocrine therapy type ($P < 0.002$) and by whether women had switched from a different endocrine therapy ($P < 0.001$). Specifically, women taking tamoxifen were significantly more nonadherent than women taking anastrazole ($M = 6.16$, SD = 1.84), with the other groups (exemestane $M = 6.54$, SD = 2.35; letrozole $M = 6.36$, SD = 1.85) falling between those groups. Women who had switched medications reported higher nonadherence to their current therapy ($M = 6.56$, SD = 2.22) than women who had not switched ($M = 6.25$, SD = 1.86)

more recently and were more likely than current users to be premenopausal (76 vs. 92 %; $P < 0.001$) and not to have received chemotherapy (42 vs. 65 %; $P < 0.001$). No other demographic/medical characteristic was related significantly to persistence (small cell sizes precluded analysis on trastuzumab receipt and endocrine therapy payment).

As hypothesized for general psychological factors, nonpersisters reported significantly more depressive symptoms, a poorer-quality relationship with their oncologist, and more general physical symptoms than did current users (Table 4).

Regarding endocrine therapy-specific variables, the groups did not differ significantly on therapy-related physical symptoms (Table 4). Nonpersisters reported significantly more negative emotions and fewer positive emotions toward endocrine therapy than did users (note that endocrine therapy necessity, concern regarding long-term use, and recurrence worry were not assessed in nonpersisters).

When variables were entered into a logistic regression with nonpersistence as a categorical dependent variable, they accounted for 10 % of the variance, $F(10,1146) = 13.37$, $P < 0.001$. Reporting more depressive symptoms ($\beta = 0.12$, $P = 0.001$), more endocrine therapy-related negative emotions ($\beta = 0.17$, $P < 0.001$), and fewer therapy-related positive emotions ($\beta = -0.13$, $P < 0.001$) each was uniquely associated with nonpersistence.

Post-hoc exploratory analyses

Because endorsement of therapy-related negative emotions was associated significantly with both nonadherence and nonpersistence in final regressions, we were interested in its correlates. Negative emotions were related significantly ($P < 0.001$) to lower financial status ($r = 0.15$), younger age ($r = -0.16$), a poorer patient-oncologist relationship ($r = -0.31$), higher depression ($r = 0.40$) and anxiety ($r = 0.38$), more symptoms attributed to therapy ($r = 0.42$), less perceived need for therapy ($r = -0.35$), more concern about long-term therapy use ($r = 0.49$), and lower positive therapy-related emotions ($r = -0.51$).

Because users who reported that they had switched from one therapy to another were significantly less adherent than non-switchers, we assessed whether adherence was related

Table 4 Comparison (*t*-tests) of endocrine therapy current users versus nonpersisters on major variables

Variable	Current users		Nonpersisters		*P*	95 % CI
	n	Mean (SD)	*n*	Mean (SD)		
Age, years	1,259	56.09 (8.68)	85	55.24 (9.39)	0.383	−1.06 to 2.77
Number of medications	1,029	2.96 (1.99)	57	3.10 (2.36)	0.608	−0.68 to 0.40
Perceived financial status	1,337	1.48 (0.81)	93	1.63 (0.94)	0.136	−0.35 to 0.05
Years since diagnosis	1,336	5.07 (3.92)	94	3.38 (1.24)	<0.001	1.36–2.02
Depressive symptoms (HADS)	1,324	10.44 (3.20)	92	12.54 (4.22)	<0.001	−2.99 to −1.21
Anxiety (HADS)	1,319	13.49 (3.99)	94	14.48 (4.18)	0.020	−1.83 to −0.15
Patient–oncologist relationship quality	1,291	43.43 (6.43)	86	37.83 (8.50)	<0.001	3.75–7.46
Cancer recurrence worry	1,338	6.54 (2.89)	–	–	–	–
Physical symptoms—general	1,371	5.31 (4.91)	94	7.89 (7.78)	0.002	−4.20 to −0.97
Physical symptoms—endocrine therapy	1,371	9.05 (7.25)	94	8.97 (9.41)	0.935	−1.88 to 2.05
Perceived need for endocrine therapy	1,349	8.42 (2.09)	–	–	–	–
Endocrine therapy negative emotions	1,314	7.06 (2.41)	83	9.87 (3.23)	<0.001	−3.52 to −2.09
Endocrine therapy positive emotions	1,318	10.09 (2.72)	82	7.29 (2.43)	<0.001	2.24–3.35
Long-term endocrine therapy use concern	1,352	5.68 (3.22)	–	–	–	–
Morisky Adherence Scale (adapted)	1,371	6.41 (2.05)	–	–	–	–

– = not assessed. Analyses on categorical variables demonstrated that chemotherapy receipt and menopausal status also were associated significantly with endocrine therapy persistence (see text). Additional variables that were not significantly related to persistence were: race/ethnicity, education, employment, marital status, breast cancer stage, surgical treatment, radiation, and months on endocrine therapy. Cell sizes were too small to perform reliable analyses on trastuzumab receipt and endocrine therapy payment status

to reason for switching. Reason (see Table 1) was unrelated to adherence, $F(8,675) = 0.78$, $P = 0.62$.

Discussion

Findings from more than 1,400 women who were currently taking endocrine therapy or who had taken it within the prior year indicate that particular demographic and medical characteristics, psychosocial variables, and endocrine therapy-specific variables are related significantly to nonadherence and nonpersistence. In final regression models, lower perceived financial status was the only demographic attribute significantly associated with nonadherence. This finding is consistent with prior research [33], and it is notable that the relation is apparent even in this relatively highly educated, medically insured, and financially comfortable sample. Having switched from a previous endocrine therapy was the only medical factor significantly related to nonadherence. This association was not anticipated, although it is supported by recently published research [34, 35]. Although an attempt to decrease side effects was the most frequent motive for changing prescriptions, nonadherence did not vary as a function of the specific motive for switching.

As hypothesized, psychosocial characteristics were the most robust correlates of both nonadherence (i.e., patient–oncologist relationship quality, perceived need for endocrine therapy, endocrine therapy-related negative emotions) and nonpersistence (i.e., depressive symptoms, endocrine therapy-related emotions) in final regression models. These findings carry implications for identifying women at risk for nonadherence and developing adherence-promoting interventions. Endorsement of negative therapy-related emotions was the sole unique correlate of both nonadherence and nonpersistence; assessment of these emotions could provide a simple indicator of risk for nonadherence/nonpersistence. How soon after prescribing endocrine therapy the related emotions can be usefully assessed is unknown; however, the low correlation ($r = -0.12$) between months since diagnosis and therapy-related negative emotions suggests that emotions could be productively assessed close to prescription initiation.

Post-hoc analyses indicate that therapy-related negative emotions likely reflect potentially modifiable contributors, which also could be targeted for intervention: depressive symptoms, quality of the oncologist-patient relationship, low perceived need for therapy, more concern about long-term use, and more symptoms attributed to therapy. Meta-analyses suggest that depressive symptoms in cancer patients are responsive to psychological intervention [36, 37]. The oncologist–patient relationship also is a promising vehicle for intervention. A meta-analysis of more than 100 studies revealed that physicians' skill in communication (e.g., expressing empathy, providing clear information, checking for understanding) is related to higher adherence

[38]. Moreover, these skills can be taught; physician communication skills training across 21 experimental studies increased adherence likelihood by 1.62 times [38]. Patients also can learn to adopt an active role with their oncologists [39].

Interestingly, the experience of general symptoms and symptoms women attributed specifically to therapy were not uniquely associated with nonadherence; however, the experience of side effects likely contributes to negative therapy-related emotions, and physical symptoms might render women more likely to terminate therapy. Oncologists could work with patients to improve side effects management and emphasize the necessity of therapy for favorable survival.

Study limitations include its cross-sectional design, which precludes causal inference. In addition, the nonsystematic sampling from an online research registry can limit generalizability. The recruitment announcement explicitly requested participation of women who had taken endocrine therapy within the prior 12 months, regardless of whether they had intentionally stopped or switched therapies. However, nonpersisters or the most nonadherent women might have been relatively unlikely to participate in the current study and the research registry more generally. Certainly, this study underestimates nonpersistence in that many patients who stopped therapy could have done so more than 12 months prior to receiving the request to participate. The study's goal to identify potential contributors to nonadherence/nonpersistence rather than to establish their incidence or prevalence in the population prescribed therapy renders the lack of systematic sampling less problematic. However, this sample's high self-reported adherence and the lack of a significant relationship between duration of endocrine therapy and nonadherence, as documented in other studies [40], suggest that generalizability of the findings beyond relatively adherent volunteers requires examination. In addition, findings suggest that women who completed the adherence assessment at 2 weeks might have been motivated to stay in the study by virtue of their higher endocrine therapy-related symptoms and more arduous treatment (i.e., chemotherapy receipt).

Another limitation is self-report of adherence and online collection of all data. Current endocrine therapy users reported low nonadherence, which is typical in this literature [7, 18, 41]. However, patient-reported assessments in adherence research demonstrate at least modest to high concordance with electronic monitoring, with some overestimation [41, 42], and are linked to important disease outcomes [43]. Furthermore, studies support the concordance of distinct modes of data collection, such as self-report versus medical records data on cancer treatments [44] and electronic versus on-paper data collection [45]. Finally, the final regression models accounted for 15 and 10 % of the variance in nonadherence and nonpersistence, respectively. Additional unmeasured factors, such as social support [46], can influence adherence.

Embedded within effective approaches for promoting adherence to long-term medication regimens in general [47, 48], interventions to address important contributors specifically to endocrine therapy adherence and persistence are needed. Women beginning their prescriptions, switching to another endocrine therapy, or having trouble with adherence all stand to benefit. A recent randomized trial suggests that mailed provision of educational materials during the first year of anastrozole therapy may not be sufficient to increase adherence/persistence [49], although another trial suggests somewhat more promising findings with the provision of both relevant information and reminders [50]. Interventions to improve the quality of the oncologist–patient relationship are needed. A stepped care approach might be warranted, whereby some patients would benefit from easily conveyed strategies to promote routine therapy use (e.g., reminders), some would need more active cognitive-behavioral approaches to address endocrine therapy-related beliefs (e.g., necessity) or side effects [51], and others would require intervention to manage depressive symptoms. Now that nonpersistence and nonadherence with endocrine therapies are well documented [52], continued research to specify determinants of nonadherence and to shape them is essential.

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

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