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Symptoms and Symptom Attribution Among Women on Endocrine Therapy for Breast Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Tamoxifen • Aromatase inhibitors • Breast cancer • Symptoms

ABSTRACT

Background. Adherence to adjuvant endocrine therapy (ET) influences breast cancer survival. Because ET side effects are frequently cited as reasons for nonadherence, understanding how perceptions and motivations in relation to ET are associated with symptom attribution can help promote timely symptom management.

Materials and Methods. Participants were 2,086 breast cancer survivors recruited through the Army of Women registry who were current tamoxifen or aromatase inhibitor (AI) users. Participants reported whether they were bothered by each of 47 symptoms during the past month and whether they thought each symptom was related to taking ET. Frequencies of overall symptoms and symptoms attributed and misattributed to ET were calculated, and linear regression was used to assess sociodemographics, emotions, and illness perceptions as predictors of symptoms attributed to ET.

Results. Women attributed a mean of 8.9 symptoms and misattributed a mean of 1.5 symptoms to ET. In the multivariable analysis, younger age, a more recent diagnosis, AI use (vs. tamoxifen), anxiety, depressive symptoms, more ET-related negative emotions, more concern about long-term ET use, and greater perceived ET necessity were independently associated with attribution of more symptoms to ET. More perceived ET necessity was associated with correctly attributing symptoms to ET, whereas higher depressive symptoms and more concern about ET use were associated with misattribution of symptoms to ET.

Conclusion. Given that many women perceive a range of symptoms as a consequence of ET, attention to these symptoms may reduce symptom burden and improve quality of life, potentially improving ET adherence and optimizing survival.

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Implications for Practice: Many breast cancer survivors on endocrine therapy (ET) experience a range of side effects while taking ET. Targeting potentially modifiable factors associated with attributing a greater number of symptoms to ET, including perceived need for ET, concerns about long-term ET use, negative emotions toward ET, and symptoms of anxiety and depression, may reduce symptom burden and improve quality of life.

INTRODUCTION

In light of substantial evidence that tamoxifen and aromatase inhibitors (AIs) decrease breast cancer recurrence and mortality [1, 2], recently updated guidelines recommend 10 years of adjuvant endocrine therapy (ET) in women with hormone receptor-positive breast cancer [3]. Despite significant implications for survival, ensuring that breast cancer survivors adhere to the prescribed duration of therapy remains challenging, with the prevalence of nonadherence (i.e., failure to take medication as prescribed) as high as 59% for tamoxifen and 50% for aromatase inhibitors reported in some studies [4]. Nonpersistence, or discontinuation, is also of concern, with studies demonstrating that 31%–73% of women stop therapy early [4].

Side effects from tamoxifen and AIs can negatively affect both health-related and psychosocial quality of life (QOL) and are one of the most commonly cited reasons for nonadherence and discontinuation of ET [5–9]. Side effects generally increase patient concerns about taking therapy and thereby reduce adherence [10]. In one study, among women who stopped taking AIs, more than 70% did so because of musculoskeletal side effects [8]. In another study, two thirds of women who stopped their adjuvant ET early cited side effects as the reason for doing so [11]. Although most prior research has evaluated the association between symptoms reported during treatment and ET compliance, a recent analysis found that women who

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reported a high symptom burden *before* starting treatment with AIs were more likely to have stopped their ET within the first year of treatment [12].

Because bothersome side effects can contribute to both nonadherence and nonpersistence to therapy, identifying who is mostly likely to attribute their symptoms to ET, together with a better understanding of how perceptions and motivations about ET are associated with symptom burden, can help promote effective and timely symptom management, targeting those most burdened by their ET. Furthermore, women who stop treatment early are more apt to attribute side effects to their ET than women who are compliant with treatment [11]. In this study, we aim to describe symptom burden and symptom attribution patterns in a large sample of breast cancer survivors, as well as assess the relationship of socio-demographic characteristics, emotions, and perceptions surrounding ET with symptoms attributed to this therapy.

MATERIALS AND METHODS

Participants

Upon approval by the relevant institutional review boards, participants were recruited via e-mail from the Dr. Susan Love Research Foundation's Love/Avon Army of Women (AOW) research registry. The AOW is a registry of 362,314 individuals (at the point of study recruitment) who have joined as potential participants for research pertaining to breast cancer; approximately 14% of the women in the registry have a history of breast cancer. AOW participants are recruited from scientific conferences, social media, private and public events, partnerships with other organizations, and other media outlets. All studies conducted as part of the AOW must be funded and institutional review board-approved.

In January of 2012, a "call-to-action" e-mail was sent to registry participants. The e-mail described endocrine therapies and stated the study's purpose as gathering information "to understand women's thoughts, feelings, and behaviors relevant to taking endocrine therapies." Women who were interested in participating in the study were asked to affirm that they met the following eligibility criteria: (a) at least 18 years of age with a history of breast cancer; (b) currently taking, or has taken within the past 12 months, one of the following medications: Nolvadex (tamoxifen), Arimidex (anastrozole), Aromasin (exemestane), or Femara (letrozole); (c) has Internet access and is willing to complete an online survey; and (d) lives in the United States. Upon confirmation of eligibility, women were automatically routed to the online survey. Of the estimated 51,000 women with breast cancer who were emailed an invitation, 2,341 met the eligibility criteria and completed the online survey. Of those, 2,086 reported that they were currently on ET.

Measures

Sociodemographic and Medical Characteristics

Age, ethnic background, education, marital status, and perceived financial status (enough money for special things; little spare money for special things; money to pay bills only because you have to cut back; difficulty paying bills) were self-reported.

Clinical factors including current ET type (tamoxifen, anastrozole, exemestane, and letrozole), duration of current ET use, patterns of ET use (e.g., switching between therapies and reasons for switching), breast cancer stage, surgery, chemotherapy, radiotherapy, and time from diagnosis were also self-reported.

Psychological and Emotional Factors

Symptoms of anxiety and depression were measured with the 14-item Hospital Anxiety and Depression Scale (HADS) [13], with higher scores on the HADS representing more symptoms. Women were asked to rate their worry about recurrence on a 0–10 scale (0 = not at all; 10 = a great deal). Additional items measured on a 0–10 scale were adapted from the Brief Illness Perception Questionnaire [14, 15] and included concern about their breast cancer diagnosis and treatment (0 = not at all concerned; 10 = extremely concerned) and emotional impact of their breast cancer diagnosis and treatment (0 = not at all affected emotionally; 10 = extremely affected emotionally).

Symptoms

Symptoms were assessed with the Breast Cancer Prevention Trial Symptom Scales, which has sound psychometric properties in breast cancer patients [16]. Items accounting for side effects specifically related to AIs (e.g., bone pain) and other general symptoms (e.g., constipation) were added. Participants reported whether they were bothered by each of 47 symptoms during the past 4 weeks and, if they were bothered by a particular symptom, whether they thought it was related to their ET or not related to their ET. The two resulting scales consisted of the sum of the endorsed symptom total each woman did or did not attribute to endocrine therapy. If a respondent did not endorse a response for a particular item, this was scored as not endorsing the symptom as bothersome. Respondents who did not answer any of the 47 symptom attribution questions ($n = 51$) were excluded from all analyses.

Other Endocrine Therapy-Related Measures

Two items based on the necessity-concerns framework [10] measured perceived therapy necessity: (a) 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) and (b) How much do you feel that you need your current endocrine medication for your breast cancer? (0 = I don't need it at all; 10 = it is absolutely essential for me). An additional question assessed long-term use concern: 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 about ET were adapted from items for affective properties of attitudes [17]. Respondents endorsed the degree to which five positive emotions (happy, calm, enthusiastic, comforted, accepting) and five negative emotions (sad, annoyed, tense, reluctant, angry) described their feelings toward endocrine therapy (i.e., does not describe, slightly describes, definitely describes). Positive and negative emotion scales were generated by summing the endorsed items (each item scored as follows: does not describe = 1, slightly describes = 2, definitely describes = 3) corresponding to each of these dimensions.

Statistical Analysis

Descriptive statistics, including means, medians, and frequency distributions, were used to characterize the study population, including sociodemographics and treatment history, as well as to describe the prevalence and types of symptoms attributed to ET. Linear regression models were fit to evaluate the relationship between symptom attribution (dependent variable was number of symptoms attributed to ET) and the following factors: age, time since diagnosis, ET type (aromatase inhibitor vs. tamoxifen), anxiety, depression, emotions and perceptions toward ET, emotional impact of breast cancer, and worries and perceptions about breast cancer recurrence. Because time on drug and time since diagnosis were correlated ($r = .49$), we did not include time on drug in the regression analyses because of collinearity.

As a secondary analysis, we grouped symptoms that have been documented as side effects [18–23] (i.e., hot flashes, night sweats, vaginal dryness, muscle stiffness, joint pain, low sexual enjoyment, pain with intercourse, bone pain, genital irritation, vaginal discharge, vaginal bleeding) separately from symptoms likely unrelated or not specific to ET (i.e., unhappiness with appearance, headache, feeling irritable, constipation, decreased range of motion in arm, dizziness, palpitations/irregular heartbeat, arm swelling, nightmares, diarrhea, breathing problems, increased appetite, abdominal pain, chest pain, tremor, vomiting, anxiety/nervousness, depressed mood). To examine whether certain perceptions and characteristics might differ between women who misattribute side effects and those who do not, we fit separate logistic regression models to evaluate which factors were associated with (a) misattribution of at least one symptom among all women and (b) attribution of at least one documented symptom among women who did not misattribute any symptoms. A third category of symptoms categorized as “possibly” related to ET (i.e., lack of interest in sex, general aches and pains, sleep problems, tiredness, difficulty concentrating, forgetfulness, easily distracted, difficulty with bladder control when laughing and crying, difficulty with bladder control at other times, breast tenderness, breast pain, breast sensitivity, lack of energy, weight gain, hair loss/thinning, nausea, skin rash, reduced appetite) were not considered in this secondary analysis.

Although both anxiety and depression were among the 47 side effects women were asked to report about, we excluded them from the symptom count (e.g., dependent variable) of all regression analyses because anxiety and depression as measured by the HADS were included as independent variables in all models. Women for whom relevant covariate data were missing ($n = 382$) were also excluded from regression analyses. Sample sizes vary somewhat across analyses because of nonresponse on specific items. All analyses were conducted in SAS version 9.4 (SAS Institute, Inc., Cary, NC, <http://www.sas.com>).

RESULTS

Study Sample Characteristics

Table 1 includes sociodemographic and treatment information for the study sample. Respondents were predominantly white non-Hispanic, were partnered, and had at least a college education. Regarding perceived financial standing, approximately two thirds of women said they had enough money for

special things after paying the bills, 23% said they had enough money to pay the bills but little extra, and 11% said they were able to pay bills but had to cut back (6%) or had difficulty paying the bills (5%). Mean age was 55.8 years, and 79% had stage 0, I, or II disease. Approximately one third of women were current tamoxifen users, with the remainder of women reporting taking an AI. At the time of survey completion, mean duration of current ET use was 29.9 months (range: 0.5–144). Although two thirds of women did not report changing ET regimens, approximately 11% said they had switched from another ET in the prior 12 months, and 23% said they had switched more than 12 months ago. Among the women who switched and provided a reason for doing so ($n = 668$), 17% reported switching to decrease the risk of the cancer coming back, 46% said they switched to decrease the side effects, and 37% said they switched for “some other reason.”

Symptom Prevalence and Attribution Patterns

Women reported a mean total of 14.2 (range: 0–43) symptoms and attributed a mean of 8.9 (range: 0–43) symptoms to ET. When we limited the attribution analysis to the 11 side effects that have been documented in several studies to be commonly associated with ET, women reported a mean of 3.7 of these symptoms (range: 0–10). More than half of women (53%) misattributed at least one symptom to ET, with a mean of 1.5 (range: 0–17) symptoms misattributed.

Figure 1 details the frequency of reporting any type of symptom relative to the frequency of attributing a symptom to ET among documented symptoms. Experiencing hot flashes was the most frequent symptom reported, as well as the most frequently attributed symptom, with 68% of all women reporting that they had bothersome hot flashes and 63% attributing them to their ET. Joint pain (48%), night sweats (47%), vaginal dryness (45%), and muscle stiffness (41%) were also commonly attributed to ET. Irritability (22%), unhappiness with appearance (19%), and depressed mood (17%) were the most common symptoms misattributed to ET (Fig. 2).

Factors Associated With ET Symptom Attribution

Table 2 includes the results of the analysis that examined age, time since diagnosis, ET type, anxiety, depressive symptoms, and ET- and breast cancer-associated emotions and perceptions in relation to the number of symptoms attributed to ET. In the multivariable analysis, younger age, a more recent diagnosis, AI (vs. tamoxifen) use, as well as more symptoms of anxiety and depression, more negative emotions toward ET, more concern about long-term ET use, and greater perceived necessity of ET, all were independently associated with greater symptom attribution to ET.

In the analyses of factors associated with the classification of symptom as documented vs. misattributed (Table 3), higher perceived necessity of ET was associated with higher odds of correctly attributing at least one of the documented symptoms to ET. Reporting more depressive symptoms and more concern about long-term ET use were both associated with higher odds of misattributing at least one symptom; more time since diagnosis and older age were associated with lower odds of misattribution. More ET-related negative emotions were associated with higher odds of correct attribution and misattribution; other results were also similar between the two groups.

Table 1. Participant characteristics (*n* = 2,086)

Characteristics	Missing, <i>n</i>	<i>n</i>	%
Age, yr, mean (range)	199	55.8 (24–86)	
Time since diagnosis, yr, mean (range)	73	4.8 (0–31)	
Time on current ET, mo, mean (range)	39	29.9 (0.5–144)	
Marital status	65		
Married or living as married		1,575	77.9
Divorced or separated		222	11.0
Widowed		70	3.5
Never married		154	7.6
Race/ethnicity	64		
White		1,919	94.9
African American/black		35	1.7
Hispanic		24	1.2
Asian		19	1.0
Native American/ American Indian		6	0.3
Other		19	1.0
Perceived financial status	72		
Money for extras		1,321	65.6
Little money for extras		467	23.2
Pay bills through cutting back		123	6.1
Difficulty paying bills		103	5.1
Education	60		
High school or less/ technical or vocational/ some college		553	27.3
College graduate		728	35.9
Postcollege graduate		745	36.8
Stage	66		
0		124	6.1
1		714	35.4
2		759	37.6
3		268	13.3
4		67	3.3
Don't know		88	4.4
Menopausal status	66		
Yes		1,689	83.6
No		177	8.8
Unsure		154	7.6
Endocrine therapy			
Tamoxifen		715	34.3
Anastrozole		757	36.3
Exemestane		203	9.7
Letrozole		411	19.7
ET history	18		
Switched from another ET in the previous 12 months		219	10.6
Switched from another ET more than 12 months ago		468	22.6
No		1,381	66.8

Abbreviation: ET, endocrine therapy.

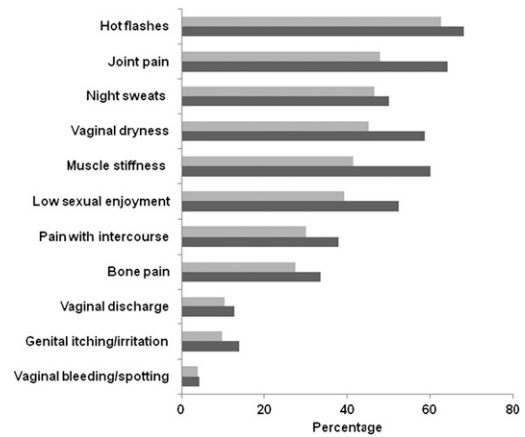


Figure 1. Prevalence of documented endocrine therapy (ET) symptoms (*n* = 2,035). ■, symptoms attributed to endocrine therapy; ■, any symptoms reported.

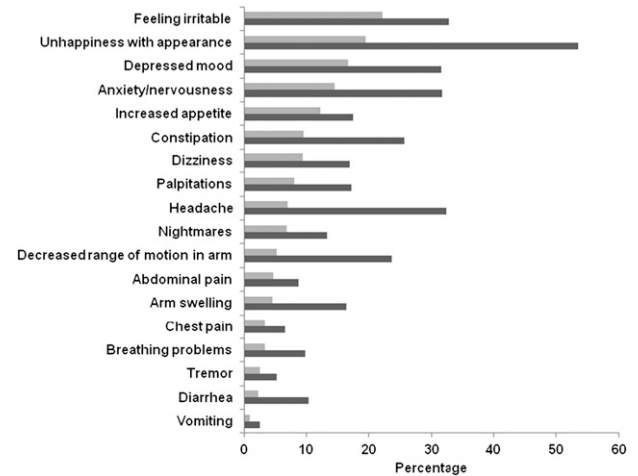


Figure 2. Prevalence of misattributed endocrine therapy (ET) symptoms (*n* = 2,035). ■, symptoms misattributed to endocrine therapy; ■, any symptoms reported.

DISCUSSION

Because women who perceive their symptoms as a consequence of ET might be less likely to adhere to treatment, there is potential value in distinguishing between symptoms attributed to ET, symptoms misattributed to ET, and symptoms that might be prevalent but are infrequently perceived or attributed as being related to ET. Other research has examined factors associated with symptom burden in ET users, including one study in which older women (aged 75 years and older vs. aged 55–64 years) and women with lower levels of emotional distress were less likely to report side effects of tamoxifen [24] and another study that found no association between AI side effect burden and fear of recurrence after adjusting for several breast cancer-related health beliefs and perceptions [15]. Little information is available, however, about patterns of symptom attribution in breast cancer survivors on ET.

We found that several potentially modifiable factors were related to the degree of symptom attribution. Higher perceived ET necessity and ET-related negative emotions were associated

Table 2. Factors associated with more symptoms attributed to ET ($n = 1,653$)

Factor	Univariable		Multivariable	
	Parameter estimate	<i>p</i> value	Parameter estimate	<i>p</i> value
Age	-0.10	<.0001	-0.04	.03
Time since diagnosis	-0.19	<.0001	-0.12	.002
ET type (AI vs. tamoxifen)	0.06	.87	1.32	<.0001
Anxiety	0.65	<.0001	0.14	.004
Depression	0.95	<.0001	0.52	<.0001
Positive emotions toward ET	-0.66	<.0001	-0.05	.44
Negative emotions toward ET	1.35	<.0001	0.84	<.0001
Emotional impact of BC diagnosis and treatment	0.76	<.0001	0.07	.30
Concern about BC diagnosis and treatment	0.52	<.0001	0.02	.73
Concern about long-term ET use	0.71	<.0001	0.26	<.0001
Perceived ET necessity	-0.18	.03	0.26	.005
Worry about BC recurrence	0.43	<.0001	-0.02	.74
Perceived ET effectiveness in BC recurrence risk reduction	-0.34	<.0001	0.05	.59

Abbreviations: AI, aromatase inhibitor; BC, breast cancer; ET, endocrine therapy.

Table 3. Multivariable analysis of factors associated with attribution of documented ET symptoms (among women who did not misattribute any symptoms) vs. misattribution of any symptom (among all women)

Factor	Odds ratio (95% confidence interval)	
	Attribution of any documented symptom ($n = 811$)	Misattribution of any symptom ($n = 1,653$)
Age	0.99 (0.97-1.02)	0.98 (0.96-0.99)
Time since diagnosis	0.98 (0.94-1.02)	0.95 (0.92-0.98)
ET type (AI vs. tamoxifen)	1.03 (0.70-1.52)	1.13 (0.88-1.46)
Anxiety	0.98 (0.92-1.04)	1.02 (0.99-1.07)
Depression	1.06 (0.97-1.16)	1.16 (1.11-1.22)
Positive emotions toward ET	0.99 (0.92-1.06)	1.00 (0.95-1.05)
Negative emotions toward ET	1.21 (1.07-1.38)	1.23 (1.15-1.31)
Emotional impact of BC diagnosis and treatment	1.02 (0.95-1.10)	1.03 (0.98-1.08)
Concern about BC diagnosis and treatment	1.01 (0.94-1.08)	1.01 (0.96-1.06)
Concern about long-term ET use	1.03 (0.97-1.10)	1.06 (1.02-1.11)
Perceived ET necessity	1.16 (1.04-1.29)	1.03 (0.96-1.10)
Worry about BC recurrence	1.00 (0.93-1.06)	1.02 (0.98-1.07)
Perceived ET effectiveness in BC recurrence risk reduction	1.02 (0.92-1.14)	1.04 (0.97-1.12)

Abbreviations: AI, aromatase inhibitor; BC, breast cancer; ET, endocrine therapy.

with more attributed symptoms and might indicate that this group of patients, despite a high symptom burden attributed to ET, chooses to remain on treatment because they recognize the importance of ET for survival. Additionally, women who had higher levels of anxiety and depressive symptoms and more concern about long-term ET use attributed a greater overall number of symptoms to their ET. If targeted appropriately, these factors are potentially modifiable and suggest an important role for providers in effectively communicating that adherence to ETs for the duration of treatment is an essential part of ensuring optimal breast cancer outcomes. Educational tools can potentially be useful in this setting by helping women understand the risks and benefits of ET, as well as by providing accurate information regarding side effects associated with ET [25]. Our analysis of a subsample of women ($n = 1,371$) from the present research who completed a self-reported ET adherence

measure 2 weeks after the initial assessment revealed high rates of adherence [26]. Whereas symptoms that women attributed and did not attribute to ET did not predict adherence over and above the contribution of other potentially modifiable factors (e.g., perceived ET necessity, ET-related negative emotions, perceived quality of the relationship with the oncologist), these are promising factors to target in interventions [26].

Many of the most common symptoms reported by study participants have been documented as possible or probable ET side effects. However, 53% of the sample also misattributed at least one symptom to their ET despite a lack of evidence from randomized controlled trials that these symptoms are more common in women on ET compared with placebo controls [18-23]. Although some women attributed them to their ET, complaints like headaches, gastrointestinal problems, and

other nonspecific side effects are frequently reported by individuals who have an unremarkable health history [27–29]. Interestingly, we found that women who had more depressive symptoms and ET-related negative emotions had higher odds of symptom misattribution, which is supported by findings of other research that symptom misattribution is related to greater emotional distress [30].

Importantly, we also identified younger age, less time since diagnosis, and taking an AI (vs. tamoxifen) as independently associated with a greater number of symptoms attributed to ET. This information can potentially be used to focus on subsets of the population most at risk for experiencing and perceiving their symptoms as caused by ET. By identifying those women who are more likely to attribute symptoms to the drug, such as younger women, an opportunity exists to promote interventions that help women cope with bothersome symptoms. A wide variety of pharmacological, behavioral, and psychoeducational interventions have been studied in breast cancer survivors, and many have been found to be highly effective in improving the most common side effects, including hot flashes, vaginal dryness, sexual dysfunction, sleep, emotional, and cognitive problems [31–37]. Exercise has also been associated with better QOL outcomes in breast cancer survivors [38] and can help improve bothersome muscle and joint pain symptoms often associated with AI use; pharmacologic options to ameliorate these symptoms include nonsteroidal anti-inflammatories and COX-2 inhibitors [39, 40]. Additional strategies for managing hot flashes and night sweats include dressing in layers, using cold packs, and lowering ambient temperatures. Several nonhormonal options also exist to reduce vaginal dryness and help with dyspareunia, including vaginal lubricants and moisturizers [41]. Sharing such strategies proactively with patients early in the course of their ET may reduce their symptom burden.

Our analysis has several limitations. This was a cross-sectional survey, and the direction of any significant associations must be interpreted cautiously. The sample was recruited from a large, national web-based registry of women who volunteered to be contacted for research purposes and therefore generalizability might be limited. Furthermore,

participants might have been experiencing a larger symptom burden and therefore might have been more likely to participate in the study than women experiencing fewer side effects from ET. In turn, our study might be overestimating the prevalence of certain ET symptoms. Conversely, our analyses only included current ET users and therefore possibly excluded women experiencing the worst side effects who might be the most likely to stop ET early and be off therapy for several years. Future studies to capture the experiences of those high-risk women are warranted, given that their perceptions and emotions about ET and breast cancer risk might differ from women who remain on ET despite having symptoms.

CONCLUSION

Notwithstanding these limitations, our findings that many women attribute a range of symptoms to their ET suggest that implementation of effective approaches to modify negative perceptions and emotions toward ET, together with recognition of and attention to symptoms, even when they are not necessarily caused by ET, may improve symptom burden and associated QOL for breast cancer survivors.

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AUTHOR CONTRIBUTIONS

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Final approval of manuscript: Shoshana M. Rosenberg, Annette L. Stanton, Keith J. Petrie, Ann H. Partridge

DISCLOSURES

The authors indicated no financial relationships.

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Vishal Saggur, Shenhong Wu, Maura N. Dickler et al. Alopecia With Endocrine Therapies in Patients With Cancer. *The Oncologist* 2013;18:1126–1134.

Implications for Practice:

Whereas the frequency of alopecia in the context of cytotoxic chemotherapies has been well described, its incidence with endocrine therapies (i.e., anti-estrogens, aromatase inhibitors) has not been systematically described. This lack of knowledge precludes comprehensive therapeutic decision-making, appropriate pretherapy counseling, and the establishment of interventions for patients who experience alopecia. Moreover, this lack of knowledge has negated the importance of alopecia and its associated psychosocial impact, hindering research endeavors toward its prevention, management, and the identification of individuals at risk. The data presented here reveal that alopecia is a common and likely underreported adverse event of treatment with endocrine therapies for cancer. Data also showed a higher relative risk of alopecia for those treated with selective estrogen receptor modulators than for those treated with aromatase inhibitors. This knowledge represents a step toward a heightened awareness of this condition, which may have an impact on patient adherence and persistence.