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Chemotherapy-Related Amenorrhea after Adjuvant Paclitaxel-Trastuzumab (APT Trial)

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Abstract

Purpose—Chemotherapy-related amenorrhea (CRA) is associated with infertility and menopausal symptoms. Learning how frequently paclitaxel and trastuzumab cause amenorrhea is important. Most other adjuvant breast cancer therapies induce CRA in approximately 50% of all premenopausal recipients [1].

Methods—410 patients enrolled on the APT Trial, a single-arm phase 2 adjuvant study of 12 weeks of paclitaxel and trastuzumab followed by nine months of trastuzumab monotherapy. Eligible patients had ≤3cm node-negative HER2+ breast cancers. Premenopausal enrollees were asked to complete menstrual surveys every 3-12 months for 72 months. Women who responded to at least one survey at least 15 months after chemotherapy initiation (and who did not undergo hysterectomy and/or bilateral oophorectomy or receive ovarian suppressing medications prior to 15 months) were included in this analysis. A participant was defined as having amenorrhea in follow-up if her self-reported last menstrual period at last follow-up was greater than 12 months prior to the survey.

Results—Among the 64 women in the evaluable population (median age at study entry 44 years, range 27-52 years), the median time between chemotherapy initiation and last menstrual survey

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was 51 months (range 16-79). 18 of 64 women (28%, 95% CI 18-41%) were amenorrheic at that time point.

Conclusions—Amenorrhea rates among premenopausal women treated with adjuvant paclitaxel and trastuzumab for early stage breast cancer appear lower than those seen historically with standard alkylator-based breast cancer regimens. Future studies are needed to understand the impact of this regimen on related issues of fertility and menopausal symptoms.

Keywords

breast cancer; chemotherapy; fertility; premenopausal

Introduction

Approximately one quarter of all breast cancers diagnosed in the United States occur in premenopausal women. Standard chemotherapies for breast cancer may damage the ovaries, causing temporary or permanent loss of menses (chemotherapy-related amenorrhea) in many young women. Chemotherapy-related amenorrhea (CRA) is associated with reduced ovarian function and fertility. This is a concern for women who wish to conceive and bear biological children after their breast cancer treatments are finished. Importantly, CRA also is associated with improved prognosis in women with estrogen receptor-positive (ER+) tumors [2,3]. Thus, when premenopausal women are deciding between multiple options for chemotherapy for early stage breast cancer, understanding the likelihood of CRA may contribute to individualized clinical recommendations. Specifically, knowledge of a young woman's likelihood of experiencing CRA could guide decision-making about breast cancer treatments (e.g., whether to receive chemotherapy for a small estimated reduction in risk of recurrence) and fertility preservation techniques (e.g., whether to undergo oocyte or embryo cryopreservation prior to chemotherapy). Older age and higher doses of alkylating agents are known to be associated with more CRA [4,5], but the risk of CRA with certain chemotherapy regimens is less well established.

Doxorubicin-cyclophosphamide followed by paclitaxel-trastuzumab, a common adjuvant regimen for Her2-positive breast cancer, has been shown to induce CRA in approximately 50% of all premenopausal recipients [1]. Although data are mixed and inconclusive [6-9,4], many studies show that rates of amenorrhea differ only minimally if at all with or without a taxane or with or without trastuzumab after anthracycline-based chemotherapy [10,11,1]. No study to date has reported on the risk of CRA after a taxane in the absence of other gonadotoxic treatments. Rates of CRA were examined in a phase 2 single-arm trial of adjuvant paclitaxel-trastuzumab (APT trial) [12].

Methods

410 patients were enrolled on a single-arm phase 2 adjuvant chemotherapy study of 12 weeks of paclitaxel-trastuzumab followed by nine months of trastuzumab monotherapy for patients with ≤3cm of node-negative Her2+ breast cancer (APT Trial). The study was activated on October 9, 2007 and closed to enrollment on September 3, 2010. Menses assessment data were extracted on November 5, 2014.

All participants enrolled in the APT Trial were asked to complete menstrual surveys at baseline. Each participant was asked 1) whether she menstruated in the past 6 months; 2) menstrual frequency if she menstruated in the past 6 months; 3) the first day of her last menstrual period; 4) whether she considered herself pre-menopausal at that time; 5) whether she took any hormonal agents in the past 6 months. Participants were deemed premenopausal at baseline if they met all of the following criteria: 1) age less than 55 years; 2) at least one menstrual period in the prior 6 months with menstrual frequency at least every 2 months; and 3) considered themselves pre-menopausal at baseline. If a participant was deemed premenopausal at baseline by these three criteria, she was asked to complete menstrual surveys at 12 weeks as well as at 6, 12, 18, 24, 30, 36, 48, 60 and 72 months after initiation of protocol treatment. In the current paper, we do not report on the 12 week, 6 month, or 12 month surveys because the loss of menses during and soon after chemotherapy is very common and does not necessarily imply poor long-term ovarian function (which is more relevant for future fertility). The first survey we report on is from approximately 18 months after chemotherapy initiation because amenorrhea for the one year after chemotherapy ended has been the most common endpoint in other studies of chemotherapy-related amenorrhea after standard breast cancer regimens [13]. However, later time points were also considered important because menstruation later may be more reflective of long-term ovarian function and fertility potential.

A participant was included in this analysis if she was premenopausal at baseline, responded to at least one follow-up menstrual survey at least 15 months after her first dose of chemotherapy, did not undergo surgical menopause or receive ovarian suppression before 15 months after chemotherapy initiation, was not diagnosed with disease recurrence or new primary cancer within 15 months after starting chemotherapy, and did not withdraw study consent within 15 months after starting chemotherapy.

For each participant, the last informative follow-up survey (i.e., the latest survey on which the menstrual data were thought to reflect post-treatment ovarian function) was used to determine the amenorrhea status after treatment, with the definition of “informative” explained in the below paragraph. If a participant underwent surgically-induced menopause or received ovarian suppressing medication, and the date of that surgery or initial dose of medication was more than 15 months after her first dose of chemotherapy, the last survey prior to ovarian surgery date or initiation of ovarian suppression was used. If a participant was diagnosed with disease recurrence or a new primary cancer at least 15 months after her first dose of chemotherapy, the last survey prior to the diagnosis date was used. If participant withdrew study consent at least 15 months after her first dose of chemotherapy, the last survey prior to the date she withdrew study consent was used. If participant experienced more than one of the events listed above, the event that occurred earliest was used to determine which follow-up survey would be used, and surveys at protocol-specified time points after the event date were deemed “not applicable”. When a survey was missed prior to the last informative survey, the menstrual status at the missed time point was deemed “not assessed.” Participants were categorized as amenorrheic if the last menstrual period (LMP) on the most recent informative follow-up survey was more than 12 months prior.

Descriptive statistics were used to summarize patients' baseline characteristics and menstrual status at last informative follow-up survey. Follow-up survey completion status and participants' menstrual status at each protocol-specified time point were tabulated. The association between a patient's demographic/treatment characteristics and menstrual status at the time of her last informative menstrual survey was assessed using two sample t-tests for continous variables [age and body mass index (BMI)], and Fisher's exact tests for categorical variables (race and whether or not she was taking endocrine therapy at the time of her last informative survey). A logarithmic transformation was used for normalization of the BMI data.

Results

Four hundred and ten patients enrolled in the APT trial, and 406 patients started protocol therapy. Seventy six participants (19%) were considered premenopausal at enrollment. Participants were not considered premenopausal for the following reasons (participants were often excluded for more than one reason): 205 (50%) participants were age ≥55 at enrollment; 253 (62%) participants reported no menses in the past 6 months; 15 (4%) participants had had menses but less often than every 2 months in the past 6 months; 12 (3%) participants reported that they had menstruated in the past 6 months but did not know their menstrual frequency; 174 (43%) participants' LMP dates were unknown; 132 (33%) participants considered themselves not premenopausal or were unsure about their menstrual status. Among the participants who were premenopausal at enrollment, 10 underwent surgically-induced menopause within 15 months after their first dose of chemotherapy, and 2 were lost to follow-up for menstrual status (Figure 1). No participants received ovarian function suppression before 15 months after their first dose of chemotherapy. Sixty four participants were included in the analysis (Table 1).

Among these 64 women, median age at study entry was 44 (range 27-52). The median time between first dose of chemotherapy and the last informative menstrual survey was 51 months (range 16-79) and did not vary by menstrual status. During follow-up, 5 (8%) of the 64 went on to experience surgically-induced menopause, 3 (5%) received ovarian suppresing medication, 1 (2%) was diagnosed ipsilateral recurrence, 3 (5%) were diagnosed with new primary contralateral breast cancers, and 2 (3%) withdrew study consent. Surveys after those events were not considered to be informative.

Four (6%) of the 64 participants had discontinued protocol treatment during either the chemotherapy portion or the trastuzumab monotherapy portion. Three discontinued protocol treatment for a protocol-specified toxicity (grade 3 ALT/SGPT elevation at 4 weeks, grade 2 sensory neuropathy at 6 weeks, and grade 2 dyspnea at 28 weeks), and one discontinued due to another toxicity (grade 2 anxiety at 24 weeks). All of these participants were included in our analyses of amenorrhea rates.

Of the 64, 18 (28%, 95% CI 18-41%) were amenorrheic (had not menstruated for at least 12 months) and 46 (72%, 95% CI 59-82%) were not amenorrheic (had menstruated within the prior 12 months) at the time of their last available menstrual survey. At the time of that survey, 39 reported that they were receiving endocrine therapy (34 tamoxifen, 5 aromatase

inhibitor), and 25 reported that they were not receiving endocrine therapy. Eighty-two percent of respondents to the 24 month survey and 73% of respondents to the 36 month survey were non-amenorrheic at that time (Figure 2). Data are missing in 3-19% of eligible participants at each time point over 72 months of follow-up. The menstrual status at protocol-specified time points are tabulated in Table 2.

The median age at study entry for participants who were non-amenorrheic at the time of the last informative menstrual survey was 42 years (range:27-49), and 49 years (range: 40-52) for participants who were amenorrheric. Older participants were more likely to be amenorrheic after protocol therapy ($p<0.001$), as were patients receiving endocrine therapy ($p=0.03$) (Table 3). Seventy eight percent of participants who were amenorrheic at the time of last available menstrual survey were aged 45 or above. In contrast, only 33% of participants who were not amenorrheic at the time of last available menstrual survey were 45 years or older (Table 3). Of the 11 patients who were diagnosed at or under age 40, only a single patient (9%) was amenorrheic at the time of last available menstrual survey (Table 3). Race and body mass index were not found to be associated with amenorrhea after paclitaxel-trastuzumab ($p= 0.82$ and 0.23, respectively). It was not possible to assess for an association between amenorrhea and prognosis because there have been so few recurrences on this trial.

Conclusions

Among premenopausal women who received adjuvant paclitaxel and trastuzumab (median age 44 at chemotherapy initiation), we found a 28% (95% CI 18-41%) rate of long-term (median 4 years after chemotherapy initiation) amenorrhea. This is lower than the approximately 50% amenorrhea rate 36 months after a breast cancer diagnosis in premenopausal women aged 40 or older (median age 46) who received no adjuvant therapy on IBCSG VIII [14], and also lower than would be expected with standard adjuvant cytotoxic breast cancer regimens, after which the majority of premenopausal women experience prolonged amenorrhea [15,16,3]. For example, Petrek and colleagues found that approximately 55% of women who received anthracycline-based and/or alkylating agent-based chemotherapy for early stage breast cancer before the age of 45 were amenorrheic three years after diagnosis, and approximately 65% were amenorrheic at five years. Amongst those diagnosed between age 40-45 in that study, the CRA rate was approximately 80% at three years, while the rate in those aged 35-39 was approximately 50%, and the rate in those under 35 was only 10% [4].

As in studies of other chemotherapy regimens, CRA appears highly age-dependent after therapy with paclitaxel and trastuzumab, consistent with evidence that age-associated declines in ovarian reserve increase the likelihood of prolonged loss of ovarian function after chemotherapy [17]. Not suprisingly given previous research showing that tamoxifen increases the rate of amenorrhea after chemotherapy [13,4,18,19], we also found that endocrine therapy use was associated with amenorrhea. The limited number of premenopausal patients on this study did not allow a precise estimate of the association between race and body mass index and CRA, and was underpowered to detect differences as statistically significant.

This study is limited by incomplete data collection (not all patients responded to menstrual surveys at all time points) and a single-arm design. A larger study with more complete menstrual follow-up and with a matched control group will be needed to confirm and clarify these findings.

Nevertheless, to our knowledge, this study is the first that documents rates of amenorrhea after paclitaxel with trastuzumab alone. We believe that the relatively low amenorrhea rates seen here in women treated in their mid-40s suggest that this regimen is relatively sparing of ovarian function. Trastuzumab is not believed to cause CRA [1], and these results suggest that it is possible that paclitaxel as a single agent has only a limited effect if any (these rates of amenorrhea may not actually be any higher than would be expected in the general population of women at a median age of 48 who did not receive chemotherapy). These data may increase the appeal of this approach (and of other regimens that avoid anthracyclines and alkylating agents) for young women who prioritize future fertility. On the other hand, these data may decrease the appeal of this regimen for those who are hoping to reap a potential recurrence reduction benefit from CRA [20]. It will therefore be important to study how these low CRA rates after paclitaxel and trastuzumab may impact related issues of fertility, menopausal symptoms, and prognosis in young women. CRA is known to be associated with worse menopausal symptoms (e.g., hot flashes) [21,22], and reduced fertility [23], both of which may impair quality of life. While it is possible that risk of recurrence may be reduced by CRA after paclitaxel-trastuzumab [20], the event rate in the APT trial was so low (98.7% of participants were disease free at 3 years) that the associated absolute benefit would likely be very minimal.

Moving forward with new clinical trials of novel adjuvant and neoadjuvant breast cancer regimens (e.g., when a platinum is added to standard therapy, or when trastuzumab-emtansine is studied as an alternative treatment for Her2-positive disease), it will be critical to evaluate rates of CRA to facilitate optimal counseling of young women about the risks and benefits of various treatment options. In order to minimize unnecessary burden on patients and cost, learning which chemotherapy regimens are not likely to cause prolonged CRA may be relevant to the understanding of which patients will be most likely to benefit from GNRH agonist injections (which only have been shown to improve prognoses in women who would otherwise be menstruating after chemotherapy).[20]

In conclusion, amenorrhea rates among premenopausal women treated with adjuvant paclitaxel and trastuzumab for early stage breast cancer appear lower than would be expected with standard adjuvant cytoxic breast cancer regimens. These preliminary findings warrant additional study.

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Author Ellis has received remuneration from Pfiser, AstraZeneca, Novartis, and Celgene. He has also held a consultant/advisory role with Nanostring and holds stock ownership with Bioclassifier, LLC.

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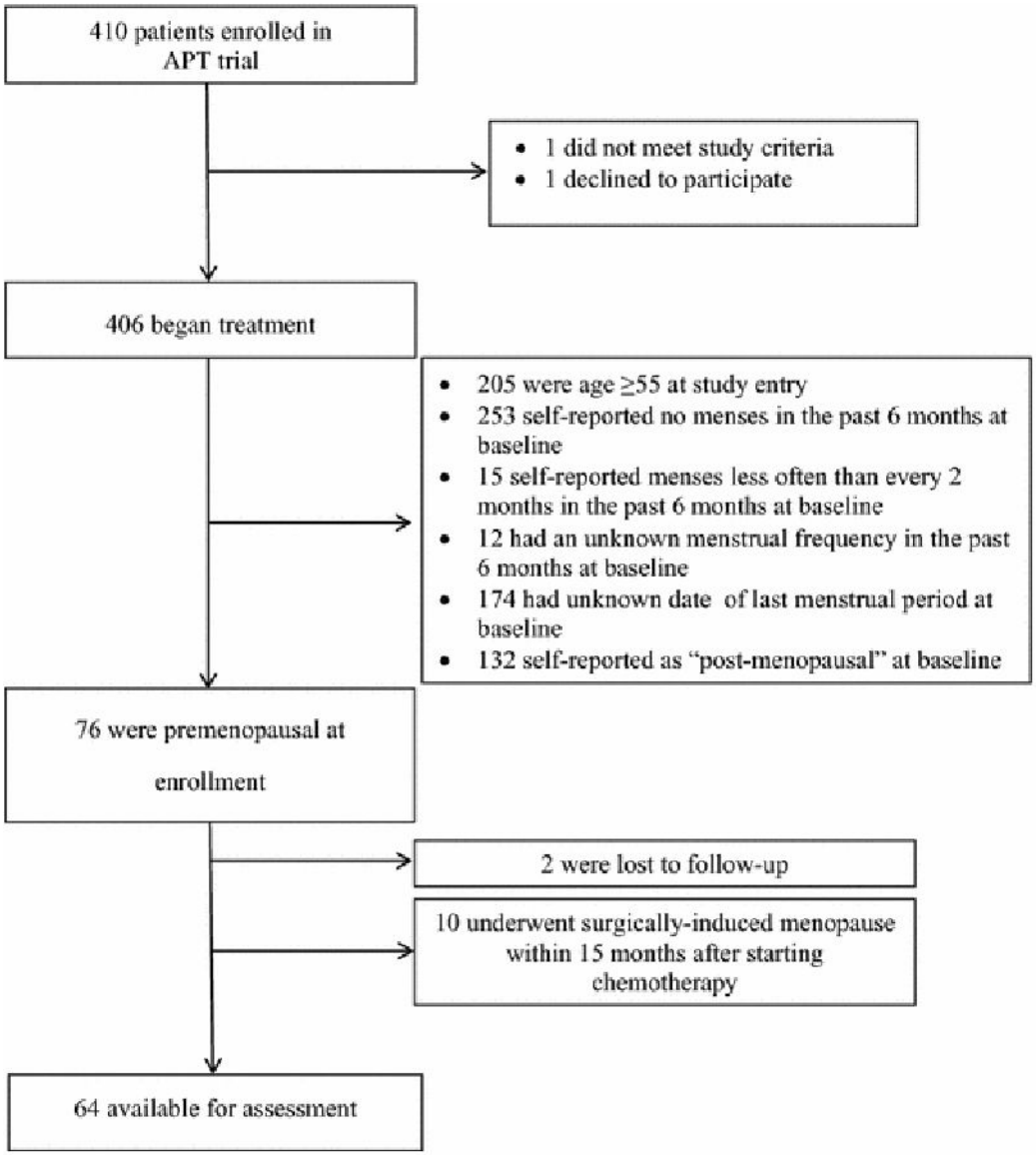

Figure 1. Flow diagram of participants

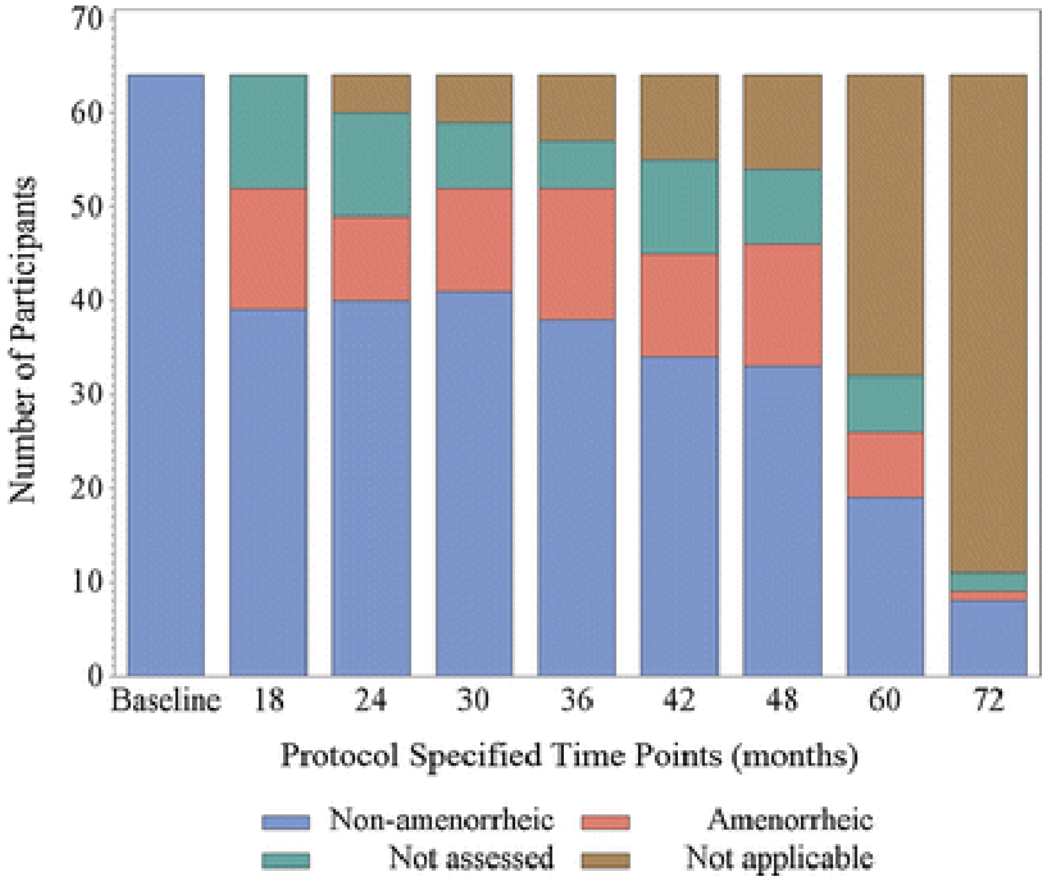

Figure 2. Menstrual status at protocol specified time points

Table 1

Patient Characteristics

	Evaluable premenopausal patients (N=64)		All patients (N=406)	
	N	**%**	**N**	**%**
Age at study entry (years)				
≤40 years	11	17	21	5
41-45 years	24	38	52	13
>45 years	29	45	333	82
Race				
White	59	92	351	86
Black	1	2	28	7
Asian	2	3	11	3
Other	2	3	16	4
Body Mass Index (kg/m^2) at study entry				
<25	41	64	180	44
25-29.9	18	28	129	32
30+	5	8	97	24
Size of primary tumor				
T1mi ≤ 0.1cm	3	5	9	2
T1a 0.1-≤0.5cm	14	22	68	17
T1b 0.5- ≤1.0cm	22	34	124	31
T1c 1.0- ≤2.0cm	22	34	169	42
T2 2.0- ≤3.0cm	3	5	36	9
Histologic grade				
I - Well differentiated	9	14	44	11
II - Moderately differentiated	27	42	131	32
III - Poorly differentiated	28	44	228	56
Unknown	0	0	3	1
ER status				
Positive	23	36	260	64
Negative	40	63	141	35
Borderline	1	2	5	1
PR status				
Positive	27	42	201	50
Negative	36	56	196	48
Borderline	1	2	8	2
Unknown	0	0	1	<1

Table 2

Follow-up status and menstrual status at protocol-specified time points

	Protocol Specified Time Points								
	Baseline	**18 months**	**24 months**	**30 months**	**36 months**	**42 months**	**48 months**	**60 months**	**72 months**
Follow-up status (n=64)									
Assessed [n (%)]	64 (100)	52 (81)	49 (77)	52 (81)	52 (81)	45 (70)	46 (72)	26 (41)	9 (14)
Not assessed[†] [n (%)]	0 (0)	12 (19)	11 (17)	7 (11)	5 (8)	10 (16)	9 (14)	6 (9)	2 (3)
Not applicable[ℊ] [n (%)]	0 (0)	0 (0)	4 (6)	5 (8)	7 (11)	9 (14)	10 (16)	32 (50)	53 (83)
Follow-up time did not reach that time point	0	0	0	0	0	0	1	22	43
Underwent surgical menopause	0	0	1	1	3	4	4	4	4
Received ovarian suppressing medication	0	0	2	2	2	2	2	2	2
Diagnosed with recurrent or new primary breast cancer	0	0	1	1	1	1	1	2	2
Withdrew study consent	0	0	0	1	1	2	2	2	2
Menstrual Status									
Number of patients assessed	64	52	49	52	52	45	46	26	9
Non-amenorrheic [n (%)]	64 (100)	39 (75)	40 (82)	41 (79)	38 (73)	34 (76)	33 (72)	19 (73)	8 (89)
Amenorrheic [n (%)]	0 (0)	13 (25)	9 (18)	11 (21)	14 (27)	11 (24)	13 (28)	7 (27)	1 (11)

[†]Menstrual status was deemed “not assessed” when surveys were not filled prior to the last informative survey

[ℊ]Menstrual status was deemed “no applicable” for all time points after the last informative survey

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Table 3
Clinical characteristics of amenorrheic and non-amenorrheic participants

	Amenorrheic (N= 18)		Non-amenorrheic (N= 46)	
	N	**%**	**N**	**%**
Age at study entry (years)				
≤40 years	1	6	10	22
41-45 years	3	17	21	46
>45 years	14	78	15	33
Race				
White	17	94	42	91
Black	0	0	1	2
Asian	1	6	1	2
Other	0	0	2	4
Body Mass Index (kg/m^2) at study entry				
<25	7	39	34	74
25-29.9	8	44	10	22
30+	3	17	2	4
Taking endocrine therapy at last menstrual survey				
Yes	15	83	24	52
No	3	17	22	48