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Relationship Between Reproductive History, Anthropometrics, Lifestyle Factors, and the Likelihood of Persistent Chemotherapy-Related Amenorrhea in Women with Premenopausal Breast Cancer

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Abstract

Objective—To determine the association between patient characteristics at diagnosis of premenopausal breast cancer including gravidity, parity, age at menarche, age at first birth, alcohol use, smoking history, weight, height, and body mass index (BMI) with the development of persistent chemotherapy-related amenorrhea (CRA) in follow-up.

Design—Retrospective Cohort

Setting—Dana Farber Cancer Institute (DFCI) and Brigham and Women's Hospital (BWH)

Patients—Premenopausal women with breast cancer

Methods—We identified all premenopausal women who received standard adjuvant chemotherapy from 1997-2005 for whom menstrual data were available. Multivariable logistic regression models evaluating persistent amenorrhea at ≥ 6 month after completing chemotherapy were conducted.

Results—431 women met eligibility criteria and had ≥ 6 month follow-up. Women with older (age >13 years) versus younger (12-13 years) age at menarche were more than twice as likely to remain amenorreheic (p-value, test for linear trend = 0.03). Current smokers had 2.4 greater odds of CRA versus never smokers, although this association was not statistically significant (95% CI=0.86-6.75).

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Discussion—Few identifiable factors contribute to the variability in CRA among premenopausal women following adjuvant chemotherapy for breast cancer. Further research to improve the prediction of CRA, premature menopause and infertility in young breast cancer survivors is warranted.

Keywords

Chemotherapy-related amenorrhea; breast cancer; gravidity; parity; lifestyle factors; premature menopause

INTRODUCTION

Disruption of menstrual function and loss of reproductive potential in breast cancer survivors is a frequent side effect of breast cancer treatment(1-9) Of the nearly 180,000 new cases of breast cancer diagnosed annually in the United States, approximately 25% occur in premenopausal women(10, 11). Adjuvant chemotherapy, while clearly beneficial to survival(12), may result in short or long term CRA, early menopause and loss of reproductive potential leading to profound physical and emotional ramifications.(3) In some settings, however, CRA may be a welcome event, given evolving evidence for its association with survival in this population.(13) Thus, improved understanding of the risk of CRA may have important implications for women with breast cancer.

Although previous studies have evaluated the association between reproductive history, anthropometrics, lifestyle factors and timing of natural menopause(14-24), the relation of these factors to CRA has not been evaluated, with the exception of one study that exploring CRA and weight gain during chemotherapy.(25) We sought to evaluate whether reproductive history (gravidity, parity, age at menarche, age at first birth), anthropometrics (weight, height, BMI), or lifestyle factors (alcohol use and smoking history) at the time of diagnosis are associated with CRA in premenopausal women with breast cancer.

MATERIALS and METHODS

Study Population

Newly diagnosed breast cancer patients treated at DFCI are asked to participate in a disease registry that includes baseline and longitudinal information regarding clinical characteristics, treatment, and outcomes (90% participation). The registry and this analysis, were approved by the IRB of Dana-Farber/Harvard Cancer Center. Eligibility criteria for this analysis included: premenopausal status at time of diagnosis of early stage breast cancer; no prior chemotherapy; treatment with adjuvant adriamycin/cyclophosphamide (AC) chemotherapy without ovarian ablation at DFCI between 1997 and 2005; menstrual function information; and an intact uterus for a minimum of 6 months following treatment cessation. AC chemotherapy included doxorubicin 60 mg/m^2 and cyclophosphamide 600mg/m^2 every 2 (dose-dense, or DD) or 3 weeks (q3wk) for four cycles, with or without paclitaxel (T) (4 cycles of at 175 mg/m2 administered weekly at 80 mg/m^2 [AC-T]) or T and trastuzumab (H) (12 weeks of weekly T at 80 mg/m^2 and weekly H (at 2mg/kg with an initial loading dose of 4mg/kg), (T + H). Eligible subjects could receive adjuvant tamoxifen (TAM) but not other hormonal agents.

The primary source of menstrual status at diagnosis was patient survey, confirmed through directed chart review. Patients were considered to be premenopausal at diagnosis if they reported menses within the prior six months and were not on hormone replacement therapy. Patients with absent or conflicting information on menstrual status at diagnosis from survey and chart review were classified as postmenopausal if they were 50 years of age or older.

Directed medical record reviews were conducted to determine menstrual status during follow-up. Persistent chemotherapy-related amenorrhea was defined as lack of return of cyclic menstrual bleeding after chemotherapy during the follow-up intervals under consideration (≤6 months, between 6-12 months, >12 months after the completion of chemotherapy). A single, isolated episode of bleeding was not considered as a resumption of menstrual function. Also, a patient who resumed menses at any point during follow-up was not considered as having persistent CRA. Patients who developed cancer recurrence were censored at the time of recurrence. Patients who underwent oophorectomy or hysterectomy in follow-up were censored at that time.

Statistical Methods

The distribution of patient characteristics was quantified among all women and stratified by amenorrheic status throughout follow-up. Unconditional multivariable logistic regression – adjusted for available covariates including age at diagnosis, age at menarche, weight, gravidity, parity, smoking, alcohol consumption, type and regimen of chemotherapy, use of TAM or H and length of follow-up- was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). (74) To evaluate heterogeneous associations with age at diagnosis, we also applied these models to the study population stratified at age 40. Linear trend was evaluated via two-sided Wald test for all ordinal variables with continuous or count structure as is standard epidemiologic practice to assess a “dose-response” association for these variables. Power for intracategory pair-wise comparisons is reduced when evaluating categorical associations while linear trend is evaluated utilizing the entire study population. Therefore, it is often observed that a trend across effect estimates is apparent and the test for linear trend is statistically significant even when individual categorical comparisons include 1.0 within the 95% confidence intervals.

All multivariable Wald statistic p-values are based on two-sided tests. The SAS statistical software (version 9.1, SAS Institute Inc., Cary, NC) was used for all analyses.

RESULTS

Patient Characteristics

We identified 431 premenopausal breast cancer patients who met eligibility criteria. (Table 1) Eight hundred and ninety-one premenopausal women had received AC chemotherapy. However, 460 were excluded for the following reasons: 346 received chemotherapy that deviated from the study criteria, 64 had undergone hysterectomy and/or removal of bilateral ovaries before treatment, 10 underwent hysterectomy after completing chemotherapy but before 6 months of follow-up, 26 had insufficient menstrual status information after follow-up, and 14 received leuprolide or aromatase inhibitors during and/or after chemotherapy.

Among the 431 women included in our analysis of persistence of CRA at 6 months or greater from completion of chemotherapy (Table 1), all participants received AC chemotherapy; some also received H and TAM. The median follow-up time was 33 months (range 6-114 months). There was minimal loss to follow-up due to missing menstrual cycle data; data were available for 100% of patients at the 6-month, 97% at the 6-12, and 96% at the >12 month intervals, respectively. Menses resumed for 192 women (45%) after completion of chemotherapy. Among the women who reported menses, 119 of 192 (62%) menstruated within 6 months of treatment cessation, 60 (31%) resumed menses between 6-12 months, and 13 (7%) resumed menses more than 12 months after chemotherapy cessation.

Associations with CRA

Table 2 presents the unadjusted and adjusted models of the relation between patient characteristics and likelihood of persistent CRA. The proportion of obese women among those who remained amenorrheic was slightly higher than the proportion among those whose menses returned following treatment cessation (p=0.02). Women who consumed more alcohol also appeared to have an increased odds of CRA (p=0.08, test for linear trend). However, both of these relations were attenuated after adjustment for potential confounders.

After adjusting for age, weight, gravidity, parity, age at menarche, smoking, alcohol use, TAM use, type and regimen of chemotherapy, the multivariable model revealed that the likelihood of remaining amenorrheic during follow-up was not significantly associated with nulligravity, nulliparity, or age at first birth. No suggestion of a linear trend was evident. Women whose age at menarche had been after13 years of age were twice as likely to experience CRA compared to those whose first menstrual period was at age 12 or 13 (odds ratio (OR)=2.22, 95% confidence interval (CI)=1.06-4.64; p-value, test for linear trend = 0.03). When analyses of the association with age at menarche were restricted to women aged 40 or older at diagnosis, the observed relation was similar with a slightly stronger linear relation (p-value, test for linear trend = 0.01) (data not shown).

The likelihood of remaining amenorrheic was not related to the woman's anthropometry – height, weight, or BMI (whether evaluated as a linear relation or categorized as underweight or overweight/obese relative to a healthy BMI). However, while no clear trend across alcohol consumption per week was observed, the data did suggest that current cigarette smokers may be at increased odds of CRA compared to women who never smoked (OR=2.41, 95% CI=0.86-6.75). When analyses of the association with cigarette smoking were restricted to women aged 40 or older at diagnosis, the observed relation increased in magnitude with current smokers observed to be six times more likely to remain amenorrheic compared to never smokers (OR=5.54, 95% CI=1.43-21.5) (data not shown).

A subset analysis of women with at least 12 months of follow-up (N=399), was performed. Only 32 participants were excluded to meet this new restriction. Findings were similar, with cigarette smoking and late age of menses significantly associated with risk of CRA in multivariable analysis. Women age > 13 at menarche were at increased odds of CRA compared with women who underwent menarche at 12-13 (OR=2.55, 95% 1.14-5.70). Current smokers were nearly 4 times more likely to remain amenorrheic compared to never smokers (OR=3.69, 95% 1.18-11.6)(Table 3). Other variables remained non-significant.

DISCUSSION

The average age of natural menopause in the Western World is 50-51.(20, 21, 23, 26) However, premenopausal breast cancer patients treated with chemotherapy are at risk for persistent CRA and early menopause. Although further research is needed to understand the endocrinological relationship between persistent CRA and menopause, symptoms are similar and include side effects of estrogen deficiency and loss of reproductive function. While not all patients receiving chemotherapy experience CRA, the psychological ramifications of early menopause can be devastating, especially for younger breast cancer survivors.(3, 4) Ovarian dysfunction is a well recognized side effect of cytoxic chemotherapeutic agents for breast cancer.(1, 2, 9, 25, 27) While exact mechanisms remain unknown, ovarian function is thought to be compromised by an agent and dose dependent decrease in the number of primordial follicles (9, 25, 28-32) leading to the disruption of normal menstrual cycles and CRA.

Given the important implications of CRA and premature menopause in premenopausal women with breast cancer, improved prediction of this late effect is needed. Unfortunately, we found few additional predictors of persistent CRA. However, the novel finding that women who had later age at menarche and smokers had an increased odds of CRA clearly warrant replication and evaluation of potential mechanisms.

In contrast to our findings, prior population studies demonstrated an increased risk for earlier natural menopause among nulliparous versus parous women or a trend towards a delay in menopause with increasing number of live births.(16, 17, 21, 23, 33-37) Women with continuous ovulatory cycles, uninterrupted by pregnancy, have been hypothesized to experience earlier depletion of their follicular pool leading to earlier menopause.(15) While an interruption in ovulatory cycles may cause a delay in natural menopause, this subtle change in the number of primoridial follicles may not be apparent in women whose reproductive lifespan is truncated by chemotherapeutic agents powerful enough to deplete their entire follicular pool.

The reason for the association between later menarche and CRA is unclear and warrants further investigation. While it is possible that some women with a later onset of menarche may have a smaller original pool of ovarian follicles, increasing their risk of CRA, this has not been supported in the literature. In studies of predictive factors in natural menopause, age at menarche was found to be associated in one study,(38) but not in others(16, 17, 19, 20, 34, 36, 37, 39). It may also be possible that confounding factors, not accounted for in the present study, were present such as menstrual cycle length and oral contraceptive use.

Assessment of lifestyle factors revealed no clear relation between alcohol consumption per week and CRA. However, cigarette smokers were observed to have greater odds of CRA compared to women who never smoked. These findings are consistent with studies of natural menopause in which cigarette smoking is one of the strongest predictors of early menopause.(16, 19, 22, 40-51) Benzopyrene and other polycyclic aromatic hydrocarbons contained in cigarette smoke have been linked to destruction of primordial follicles in animal models.(52)

The odds of CRA was not found to be related to a woman’s anthropometry – height, weight, or BMI (whether evaluated as a linear relation or categorized as underweight or overweight/obese relative to a healthy BMI). While some prior studies have similarly observed no association between timing of natural menopause and BMI(21, 22), others observed a delayed(48-50, 53), and another observed earlier onset(37)in obese women. One study demonstrated an association between decreased weight as a predictor of earlier menopause(16). In the only prior study assessing the risk of BMI with timing of CRA, baseline weight was not predictive of CRA, however, weight gain during the year after diagnosis was found to be correlated with CRA(25). In many prior studies, confounders such as smoking history were not taken into account and therefore, further study of the relation between BMI and timing of both natural menopause and CRA is warranted.

Limitations of the current study include its retrospective design. Information about oral contraceptive use and post-treatment anthropometrics were not available. Details of alcohol use were also limited. In an ongoing study, prospectively collected data will limit both potential recall bias and errors in data entry.

Our findings may assist in the counseling of premenopausal women with breast cancer. Validation of our findings in additional cohorts of young survivors and future studies using endocrine biomarkers such as follicle stimulation hormone, estradiol, inhibin, and anti-mullerian hormone levels as well and antral follicle counts are warranted to further understand the relation between CRA and ovarian reserve. Such research may improve our

ability to more accurately predicting a patient's ovarian function and reproductive capacity post-treatment.

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Table 1

Study population characteristics by amenorrhea status at end of follow-up after chemotherapy among premenopausal women diagnosed with breast cancer (n = 431).

Variables	N[a]	Median	Minimum	Maximum
Total follow-up time (months)	431	33	6	114
Age at diagnosis (years)	431	43	25	56
Gravidity	429	2	0	12
Parity	425	2	0	12
Age at Menarche (years)	427	13	9	18
Age at first birth (years)	310	29	15	45
Weight (kg)	415	65	42.3	119
Height (inches)	373	163	145	180
BMI (kg/m^2)	370	23.9	15.1	46.6
	N	%		
BMI				
Underweight[b]	47	13		
Overweight/obese[b]	145	39		
Race				
Caucasian	361	94		
Cigarette smoking status				
Never	228	53		
Past	165	38		
Current	38	9		
Alcohol consumption (drinks per week)				
<1	130	45		
1-4	109	38		
5-9	34	12		
10-19	14	5		
Treatment				
AC	228	53		
AC-T				
4 doses	170	39		
12 doses	33	8		
ACT+H				
12 doses	15	4		
52 doses	24	6		
DD	120	28		
TAM	303	70		

[a] Totals may not = 431 due to missing data

[b] underweight = BMI<20.0 kg/m^2; overweight/obese = BMI >24.9 kg/m^2

Table 2

Likelihood of persistent CRA by personal characteristics among premenopausal women diagnosed with breast cancer (N=431).

	Unadjusted			Multivariable[a]		
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Reproductive History						
Nulliparity						
No	1.00	Referent		1.00	Referent	
Yes	0.72	0.46-1.13	0.15	1.34	0.69-2.62	0.39
Nulligravidity						
No		Referent		1.00	Referent	
Yes	0.78	0.47-1.27	0.32	1.15	0.55-2.43	0.71
Age at Menarche						
<12	1.02	0.60-1.76	0.95	0.80	0.36-1.78	0.58
12-13	1.00	Referent		1.00	Referent	
>13	1.31	0.81-2.13	0.27	2.22	1.06-4.64	0.03
	p-value, test for trend = 0.76			p-value, test for trend = 0.03		
Age at first birth						
<25	1.00	Referent		1.00	Referent	
25-29	1.36	0.73-2.55	0.34	1.60	0.60-4.21	0.35
30-34	0.57	0.33-0.99	0.04	0.67	0.30-1.50	0.32
≥35	1.29	0.56-2.99	0.55	1.13	0.33-3.84	0.84
	p-value, test for trend = 0.80			p-value, test for trend = 0.60		
Lifestyle Factors						
Alcohol (drinks per week)						
<1	1.00	Referent		1.00	Referent	
1-4	1.15	0.72-1.84	0.55	0.99	0.49-1.97	0.97
5-9	1.30	0.62-2.71	0.49	0.83	0.28-2.46	0.73
10-19	3.33	0.90-12.3	0.07	2.04	0.31-13.3	0.46
	p-value, test for trend = 0.08			p-value, test for trend = 0.74		
Cigarette Smoking						
Never	1.00	Referent		1.00	Referent	

	Unadjusted			Multivariable[a]		
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Past	1.04	0.70-1.56	0.84	1.33	0.72-2.45	0.37
Current	1.42	0.70-2.89	0.33	2.41	0.86-6.75	0.09
Anthropometry						
Weight (kg)	1.01	1.00-1.02	0.22	1.01	0.98-1.03	0.66
Height (inches)	1.00	0.97-1.03	0.92	1.02	0.98-1.07	0.32
BMI (kg/m^2)	1.03	0.99-1.07	0.22	1.00	0.94-1.06	0.99
Underweight[b]	0.91	0.48-1.73	0.77	1.19	0.45-3.11	0.73
Healthy	1.00	Referent		1.00	Referent	
Overweight/obese[b]	1.69	1.09-2.64	0.02	1.52	0.79-2.93	0.21

OR = odds ratio, CI = confidence interval,

[a]Multivariable model adjusted for patient age at diagnosis, type and regimen of chemotherapy including AC, T, H, DD and Tam, follow-up time, weight, gravidity, parity, age at menarche, smoking status, and alcohol consumption.

[b]underweight = BMI<20.0 kg/m^2; overweight/obese = BMI >24.9 kg/m^2

Table 3

Likelihood of persistent CRA by personal characteristics among premenopausal women diagnosed with breast cancer with greater than 12 months follow-up (N=399).

	Unadjusted			Multivariable[1]		
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Reproductive History						
Nulliparity						
No	1.00	Referent		1.00	Referent	
Yes	0.68	0.42-1.08	0.10	1.42	0.69-2.94	0.34
Nulligravidity						
No		Referent		1.00	Referent	
Yes	0.78	0.46-1.31	0.35	1.19	0.53-2.69	0.68
Age at Menarche						
<12	1.09	0.62-1.90	0.78	0.91	0.39-2.14	0.83
12-13	1.00	Referent		1.00	Referent	
>13	1.25	0.76-2.06	0.38	2.55	1.14-5.70	0.02
	p-value, test for trend = 0.90			p-value, test for trend = 0.02		
Age at first birth						
<25	1.00	Referent		1.00	Referent	
25-29	1.28	0.68-2.43	0.45	1.47	0.52-4.14	0.47
30-34	0.59	0.33-1.05	0.07	0.67	0.27-1.68	0.40
≥35	1.37	0.58-3.23	0.47	1.01	0.27-3.68	0.99
	p-value, test for trend = 0.72			p-value, test for trend = 0.66		
Lifestyle Factors						
Alcohol (drinks per week)						
<1	1.00	Referent		1.00	Referent	
1-4	1.15	0.71-1.87	0.57	0.74	0.34-1.60	0.44
5-9	1.33	0.62-2.86	0.47	0.55	0.17-1.79	0.32
10-19	2.88	0.76-11.0	0.12	2.19	0.30-16.0	0.44
	p-value, test for trend = 0.12			p-value, test for trend = 0.74		
Cigarette Smoking						

	Unadjusted			Multivariable[1]		
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Never	1.00	Referent		1.00	Referent	
Past	1.16	0.76-1.76	0.50	1.70	0.86-3.34	0.13
Current	1.63	0.79-3.41	0.19	3.69	1.18-11.6	0.03
Anthropometry						
Weight (kg)	1.01	1.00-1.03	0.14	1.01	0.99-1.03	0.33
Height (inches)	1.00	0.97-1.03	0.90	1.03	0.98-1.09	0.24
BMI (kg/m^2)	1.03	1.00-1.08	0.13	1.02	0.95-1.08	0.64
Underweight[2]	0.87	0.45-1.70	0.68	1.21	0.43-3.44	0.72
Healthy	1.00	Referent		1.00	Referent	
Overweight/obese[2]	1.88	1.18-3.00	0.01	1.88	0.91-3.90	0.09