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Menses resumption after cancer treatment-induced amenorrhea occurs early or not at all

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Abstract

Objective—To identify factors associated with cancer treatment-induced amenorrhea and time to return of menses.

Design—Population-based cohort study

Setting—Georgia

Patients—Female cancer survivors who were diagnosed with cancer between the ages of 20–35 and were at least 2 years post-diagnosis at the time of recruitment (median=7 years, interquartile range= 5–11).

Intervention(s)—None

Main Outcome Measure(s)—Amenorrhea (≥ 6 months without menses) and resumption of menses.

Results—After excluding women with hysterectomies prior to cancer diagnosis, 1,043 women were eligible for analysis. Amenorrhea occurred in 31.6% of women. Among women treated with chemotherapy (n=596), older age at diagnosis (30–35 versus 20–24 years: adjusted odds ratio (aOR)=2.37, 95% confidence interval (CI): 1.30, 4.30) and nulligravidity (versus gravid: aOR=1.50, 95% CI: 1.02, 2.21) were risk factors for amenorrhea. Among amenorrheic women,

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menses resumed in most (70.0%), and resumption occurred within 2 years of treatment for 90.0% of women. Survivors of breast cancer were more likely resume menses at times greater than one year compared with lymphoma and pelvic-area cancers. Women diagnosed at older ages, those exposed to chemotherapy, and those exposed to any radiation experienced longer times to return of menses. Women who were older at diagnosis were more likely to have irregular cycles when menses returned.

Conclusion—Treatment-induced amenorrhea is common in cancer survivors although most women resume menses within 2 years. However, once resumed, older women are more likely to have irregular cycles. Age at diagnosis and pregnancy history affect the risk of amenorrhea.

Keywords

amenorrhea; menstrual function; cancer treatment; cancer survivorship

Introduction

Cancer mortality rates have recently been declining across all age groups, which warrants further attention to the health and quality of life of survivors (1). Of the 810,320 new cancer cases diagnosed annually in women in the United States, approximately 11% are diagnosed at ages less than 45 years (1, 2). This population of reproductive-aged women represents a unique cohort because the short and long-term side effects of cancer treatments on reproductive function have not been fully characterized or understood.

Some cancer therapies adversely affect the reproductive system and may cause secondary amenorrhea. Although amenorrhea is defined inconsistently, it is most widely accepted as at least six months without menses (3). Amenorrhea has been shown to represent menstrual dysfunction, early menopause (4–6), and sexual dysfunction (7). Further, it may serve as a marker for more than just reproductive health (3); recent literature suggests that menstrual function patterns are linked to bone fracture and osteoporosis (8, 9), cardiovascular disease (10, 11) and mortality (12), breast (13) and ovarian cancer (14), diabetes mellitus (15, 16), and decreased lung function (17). It is important to identify women who may be at greater risk of amenorrhea and factors associated with menses return, because this may aid clinicians in counseling their patients on what to expect throughout the course of treatment and the possible long-term sequelae.

Several studies suggest that women who receive certain types of chemotherapy such as alkylating agents, those older than 40 years, and those treated with Tamoxifen are more likely to experience amenorrhea and earlier menopause (18, 19). These studies have mostly focused on breast cancer survivors with relatively short follow-up times after cancer diagnosis (median=3.1 years). Therefore, although chemotherapy-induced amenorrhea has been identified in breast cancer survivors, it is unclear how transient the absence of menstruation is, and whether it occurs in women with other cancer types and treatments. The purpose of this study was to identify factors associated with the occurrence and length of amenorrhea after cancer treatment. Further, among women who lost their period during treatment, we sought to identify factors associated with the time to return of menses.

Methods

This study utilized data from The Furthering Understanding of Cancer, Health, and Survivorship in Adult (FUCHSIA) Women's Study, a study of reproductive health in young female cancer survivors. Cancer survivors were identified in the Georgia Cancer Registry (GCR), which is a statewide, population-based tumor registry that includes all reportable malignant cancers (20) diagnosed among Georgia residents. In order to be eligible for the FUCHSIA Women's Study, women had to be diagnosed with their first primary cancer between the ages of 20–35 and be between the ages of 22–45 at interview. In addition, women had to be diagnosed with a malignant cancer or ductal carcinoma in situ at least two years before participating in the study. Eligible cancer survivors were identified and contacted by the GCR, introduced to the FUCHSIA Women's Study, and asked if they were willing to be contacted by the study. Women who agreed were subsequently invited to participate in an interview. Informed consent was obtained over the phone before administration of the interview. The Institutional Review Boards of Emory University and the Georgia Department of Health approved this study.

The interview included questions about cancer diagnoses and treatments, various health outcomes, menstrual function, pregnancy history, desire for children, and demographic information. Women were asked if they lost their period during cancer treatment, and if so, for how long. Among women who answered yes, amenorrhea was defined as at least six months without menses when not pregnant or using hormonal contraceptives, which is the most commonly used definition (3). Women were not eligible for this analysis if they reported a hysterectomy or bilateral oophorectomy before or in the same year as cancer diagnosis.

Information on cancer type and age at diagnosis were available from the GCR. We used the GCR cancer diagnosis date as a proxy for the start of treatment. If women specified that they lost their period during treatment, it was assumed to occur within the same year as diagnosis. Treatment types (ever-use of chemotherapy and ever-use of radiation) were reported in the interview.

Statistical Analysis

Descriptive statistics were used to examine the characteristics of the study population, stratified by amenorrheic status and treatment type. We fit logistic regression models to identify factors that influenced menstrual function in women treated with chemotherapy. Covariates hypothesized to be associated with amenorrhea based on the literature were included in the model: treatment type (18, 21, 22), age at diagnosis (6, 22–24), self-reported race (21, 22), gravidity (25), age at menarche (21, 25, 26), body mass index (BMI) (21, 22, 25), and cancer type (3, 6). Cancer types were collapsed into the following groups for analysis: breast, pelvic-area (colon, uterine, cervical, and ovarian), Hodgkin lymphoma (nodal), non-Hodgkin lymphoma (nodal and extranodal) and other (brain (n=25), thyroid (n=116), melanoma (n=100), and other carcinomas (n=195)).

We fit Cox proportional hazards models to estimate hazard ratios (HR) for factors associated with the time to return of menses among those who stopped menstruating for at least one

month during treatment. Women were followed from when they reported losing their period until menses returned or until they were censored due to surgical menopause (i.e., hysterectomy or bilateral oophorectomy), initiation of hormone therapy (i.e., estrogens, progestins, or androgens), or the end of follow-up (i.e., time of interview). The proportional hazards assumption was checked for all covariates using visual inspection of log-log survival curves and testing of Schoenfeld residuals and covariate-by-time interaction terms.

We also performed several sensitivity analyses. We evaluated the sensitivity of our logistic and Cox models to the use of adjuvant hormone therapies (i.e., Tamoxifen), other hormone therapies (i.e., estrogens) and hormonal contraceptives both by excluding women who used any hormonal medications and then by including them in the model but adjusting for the use of hormonal medications. These analyses involved 209 women who used adjuvant hormone therapy (191 breast cancer), 32 women who used other hormone therapies (10 breast cancer) and 809 women who ever-used hormonal contraception (277 breast cancer). In addition, we assessed whether results changed depending on the data source of the treatment information (self-report vs. GCR). Finally, we evaluated the sensitivity of the Cox model results to women reporting extremely late return of menses by censoring them at 2.5 years (resumption of menses was rare after that time). This truncated analysis is reported here.

All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

Results

There were 5,137 potentially eligible women identified in the GCR of whom 60% were successfully contacted by the registry. Of these, 78% agreed to release their name to the study. We successfully contacted 74% of those who released their names, and 73% of them completed the interview. The distribution of demographic characteristics (age, race, and residence) was similar among participants and those in the registry who were initially identified.

Interviews were conducted a median of 7 years after cancer diagnosis (interquartile range: 5–11). Of the 1,282 cancer survivors who completed the interview, 189 had hysterectomies before or in the same year as their cancer diagnosis, and an additional 4 women did not have a hysterectomy but had both ovaries removed at or before diagnosis. There were 46 women who refused to answer (n=1) or did not know whether they lost their period during treatment (n=45). Thus, 1,043 women were included in the analysis.

Descriptive statistics

In this cohort, 437 of 1,043 (41.9%) women reported losing their period during cancer treatment. Of these, 430 lost their period for at least one month, and 7 (1.6%) had missing data on the length of time without a period. Three-hundred thirty (31.6%) were considered amenorrheic because they went at least six months without menstruating (Table 1). Of the 330 amenorrheic women, 231 (70.0%) had menses return by the date of their interview (temporary amenorrhea) and 99 (30.0%) did not resume menses by this time. Women who experienced temporary amenorrhea lost their period for a median of 9 months (IQR=7–13

months) and most of these women resumed menses within 2 or 3 years (90.0% and 94.4%, respectively).

Among women treated with any chemotherapy (with or without radiation), 51.7% experienced amenorrhea, and for 71.1% of them, it was temporary. Among women treated with any radiation therapy (with or without chemotherapy), 40.5% experienced amenorrhea, and for 67.2% of them, it was temporary. However, this varied by cancer type, and all of the women who received radiation to the pelvis experienced amenorrhea, although few eligible women had this treatment (n=11).

Overall, breast cancer (50.6%) and non-Hodgkin lymphoma survivors (41.1%) were the most likely to experience amenorrhea, and women diagnosed with other cancers were the least likely (14.9%) (Table 1). Breast cancer (56.2%) and non-Hodgkin lymphoma survivors (51.3%) were also the most likely to receive chemotherapy and radiation together (Supplemental Table 1). White women were less likely to experience amenorrhea (27.4%) than black women (40.4%) or women of other races (43.5%), which was partly due to the greater frequency of melanoma and thyroid cancer diagnoses among white women. When these cancers were excluded (n=100 and n=116, respectively), 36.3% of white women experienced amenorrhea, compared with 43.4% of black women and 54.1% of women of other races.

Risk factors for amenorrhea among women treated with chemotherapy

In models restricted to women treated with chemotherapy, those diagnosed at older ages were more likely to experience amenorrhea (vs. no amenorrhea) compared with women aged 20–24 years (25–29 years: adjusted odds ratio (aOR)=1.59, 95% confidence interval (CI): 0.90, 2.82; 30–35 years: aOR=2.37, 95% CI: 1.30, 4.30) although results were not statistically significant for women aged 25–29 (Table 2 and Supplemental Figure 1). Black women were also more likely to experience amenorrhea compared with white women (aOR=1.35, 95% CI: 0.92, 2.00), although the estimate did not reach statistical significance, and nulligravid women were at an increased risk for amenorrhea compared with gravid women (aOR=1.50, 95% CI: 1.02, 2.21). Treatment with radiation to areas other than the pelvis, age at menarche, and BMI did not appear to be related to the risk of amenorrhea. The model results did not change in sensitivity analyses where we controlled for any hormonal medication use or where we excluded those who ever took any hormonal medications (data not shown).

Menses resumption

Those who reported losing their period for at least one month during cancer treatment (n=430) were included in our analysis of time to return of menses. The 100 women who never resumed menstruating were censored; 11 at the time of hysterectomy, 7 at the time of oophorectomy, 3 at the time of hormone therapy initiation, and 79 at the time of the interview. The time to return of menses differed by cancer type (Figure 1). Overall, breast cancer (76.9%) and lymphoma survivors (81.3%) were more likely to resume menses than survivors of pelvic-area cancers (44.4%). Among survivors of pelvic-area cancers (n=27) and lymphomas (n=91) who lost their period during treatment, the vast majority reported

that menses resumed within one year, and very few experienced return after that time (0.0% and 3.3%, respectively). Patterns of menses resumption did not differ between Hodgkin and non-Hodgkin lymphoma survivors: overall, 82.3% and 79.3% resumed bleeding, respectively, and for both, this was driven by resumption within the first year. However, among breast cancer survivors who lost their period during treatment (n=232), most reported that menses resumed within one year, but a substantial proportion resumed after that time (11.4%).

Adjuvant hormone therapy use affected the frequency of breast cancer survivors who resumed menses. Among breast cancer survivors who lost their period, 122 (51.5%) took Tamoxifen and 44 (18.6%) took Lupron (N=30 (12.6%) took both). Overall, 88.5% of breast cancer survivors without a history of Tamoxifen or Lupron resumed menses compared with 67.2% of those who took Tamoxifen and 52.1% of those who took Lupron. However, the patterns of menses return were not different among those who took these medications and those who did not. Most of these women resumed menses within the first year, but a nontrivial proportion reported return after that time (data not shown).

Women treated with chemotherapy were less likely to resume menses (HR=0.73, 95% CI: 0.47, 1.11) than women not treated with chemotherapy, especially during the first year (Table 3 and Supplemental Figure 2). Women exposed to any radiation therapy who lost their period were also less likely to resume menses (HR=0.80, 95%CI: 0.63, 1.02) compared with women not exposed to radiation. Menses resumed later for women who were older at cancer diagnosis compared with women aged 20–24 years (25–29 years: HR=0.78, 95% CI: 0.52, 1.16; 30–35 years: HR=0.67, 95% CI: 0.44, 1.00) (Table 3 and Supplemental Figure 3). These results remained consistent when we conducted several sensitivity analyses. Excluding women who reported using any hormonal medications from the analysis or controlling for hormonal medication use in models did not affect the results, nor did using GCR data on treatment modality instead of self-report (data not shown). Lastly, these results did not change when we allowed for menses resumption after 2.5 years. Among the 330 women who resumed menstruating, only 6.1% (n=20) reported a time greater than 2.5 years after treatment (maximum=8 years).

Of the 330 women who resumed menstruating, 136 (41.2%) reported that approximately six months after their periods returned, cycle length stayed the same as before treatment. Among women aged 30–35 at diagnosis whose period returned (n=201), only 35.8% reported that their cycle length stayed the same as before treatment in contrast to 49.6% among women aged 20–29 years (n=129). These proportions were statistically significantly different (chi-square test, p-value=0.01). Among women aged 30–35 at diagnosis, 25.9% reported that their cycles were more irregular when they returned than before treatment in contrast to 18.6% among women aged 20–29 (p-value=0.11). Among women who had not met their desired family size at the time of cancer diagnosis, women who had irregular menses after treatment-induced amenorrhea were less likely to have a child after cancer than women who had regular menses after treatment-induced amenorrhea after adjusting for age (OR=0.47, 95% CI 0.24–0.94).

Discussion

We found that amenorrhea was common in women who underwent cancer treatment, especially in those who received chemotherapy. Among women treated with chemotherapy, those who were diagnosed in their thirties (vs. younger women), who were black (vs. white), and who had never been pregnant (vs. gravid) were more likely to experience amenorrhea. Among women who stopped menstruating during treatment, menses usually resumed within 2 years of cancer diagnosis or not at all. Amenorrhea lasted longer in older women compared with younger women. Women treated with chemotherapy as well as those treated with any radiation therapy were also more likely to experience a longer time to return of menses.

Although the FUCHSIA Women's Study collected data a median of 7 years after cancer diagnosis, our results are similar to those of a study that collected menstrual function data prospectively (21). Sukumvanich et al. found that 41% of breast cancer survivors experienced amenorrhea during treatment, but menses returned by 3 years after chemotherapy for 48% of them. In our study, 31.6% of cancer survivors experienced amenorrhea, and menses returned by 3 years after treatment for 66.1% of them. The slight differences in these findings are likely due to our population being comprised of women with different cancer types and treatments, whereas the Sukumvanich study was of breast cancer survivors all exposed to chemotherapy.

Previous studies have reported that older age at diagnosis increases the risk of amenorrhea and acute ovarian failure (6, 23). Our study also found that women diagnosed at older ages were more likely to experience amenorrhea and to experience amenorrhea that lasted longer than younger women. Further, women diagnosed at older ages were more likely to report irregular cycles after treatment-induced amenorrhea than younger women, which is consistent with what Horning et al. reported in a study of Hodgkin's disease survivors (27). It has been postulated that irregular cycles after cancer treatment among older women may reflect a reduced quantity of ovarian follicles and subsequent accelerated follicular atresia (27, 28).

We also identified pregnancy history as a predictor of amenorrhea. To our knowledge, this is the first study to observe this in cancer survivors although this finding is compatible with other studies that have reported that nulligravid women experience natural menopause earlier than gravid women (25, 29, 30).

This study has several strengths. First, our study had ample follow-up time after cancer diagnosis, which allowed us to determine the potential menses recovery window. Our results confirm that the menses recovery time frame is short, which suggests other studies with short follow-up may have had adequate time to observe whether menses resumed for most women. Although some amenorrheic women in our study did report return of menses after 2.5 years, it is likely that prolonged temporary amenorrhea may have been due to use of hormonal medications or recall error. We conducted a sensitivity analysis to assess the potential bias introduced by incorrect timing information, but the results did not change. Second, this cohort was population-based and included women with different types of

cancer, including cancers that have seldom been studied. We found that time to return of menses varied by cancer type, which may be due to differences in treatment regimens. Third, we were able to assess the quality of menses after temporary amenorrhea as a possible marker of unrecognized subfertility.

While it is reassuring that treatment-induced amenorrhea was temporary for most women, this does not necessarily signify a return to fertility. Women who were over 30 years old at diagnosis were more likely to experience irregular periods after temporary amenorrhea, which may signify damage to the ovaries or perimenopause (31). This is consistent with our observation that these women were also less likely to have a child after cancer treatment. Even if amenorrhea is transient among some women and they experience subsequent resumption of regular menses, this can delay childbearing after cancer and since infertility increases with age, this puts them at additional risk of experiencing infertility. Furthermore, cancer survivors who experience amenorrhea are more likely to reach menopause earlier than those who do not lose their period during treatment (5, 6, 32). Although reproductive capacity is of concern among women who experience amenorrhea, other studies have reported that women who do not cease menstruating during treatment or those who cease menstruating but resume their period after treatment-induced amenorrhea are more likely to have poor prognoses and shorter disease free survival (33, 34). This may be because amenorrhea serves as a marker of chemotherapy efficacy, but the literature is inconsistent (35–37). Taken together, these studies suggest the occurrence of cancer treatment-induced amenorrhea may be an important event for a variety of reasons. Thus, the findings of this study underscore the importance of the clinician-patient consultation during cancer treatment. Clinicians may consider the factors identified in this study as they advise patients about their post-treatment reproductive health and menstrual function.

This study is not without limitations. Although we knew which women used adjuvant hormone therapy and hormonal contraception, we had limited information on the timing of use. However, results did not change meaningfully when women who reported using such medications were excluded from the analyses or when we adjusted for medication use in models. Another limitation is that detailed treatment information such as radiation dose and whether the ovaries were shielded was not available for this analysis. Although we would expect treatment with pelvic radiation (including total body radiation) to have the highest risk of treatment-induced amenorrhea, the scatter from radiation therapy for other cancers may also be associated with an increased risk. Further, radiation to the head and neck region may affect hypothalamic and pituitary function. We report results using self-reported treatment data from the interview because the GCR data on treatment types is restricted to first-course modality and has been shown to be incomplete (38). However, we also fit models using treatment data from GCR to evaluate the sensitivity of our results to possible misclassification of treatment information, and our results did not change substantively regardless of which treatment information was used (data not shown).

Most studies to date on cancer treatment-induced amenorrhea have focused on recently diagnosed breast cancer patients treated with chemotherapy. This study has long-term information on women’s menstrual function after cancer treatment and included women with different cancer types and treatments. These study attributes allowed us to confirm that

after cancer treatment-induced amenorrhea, the potential menses recovery time frame is usually short. Further, the results of this study expand the understanding of this topic because although chemotherapy has been shown to induce amenorrhea, we found that age at diagnosis and pregnancy history also affect this risk. Finally, age at diagnosis affects the duration of amenorrhea and the quality of menses after treatment-induced temporary amenorrhea.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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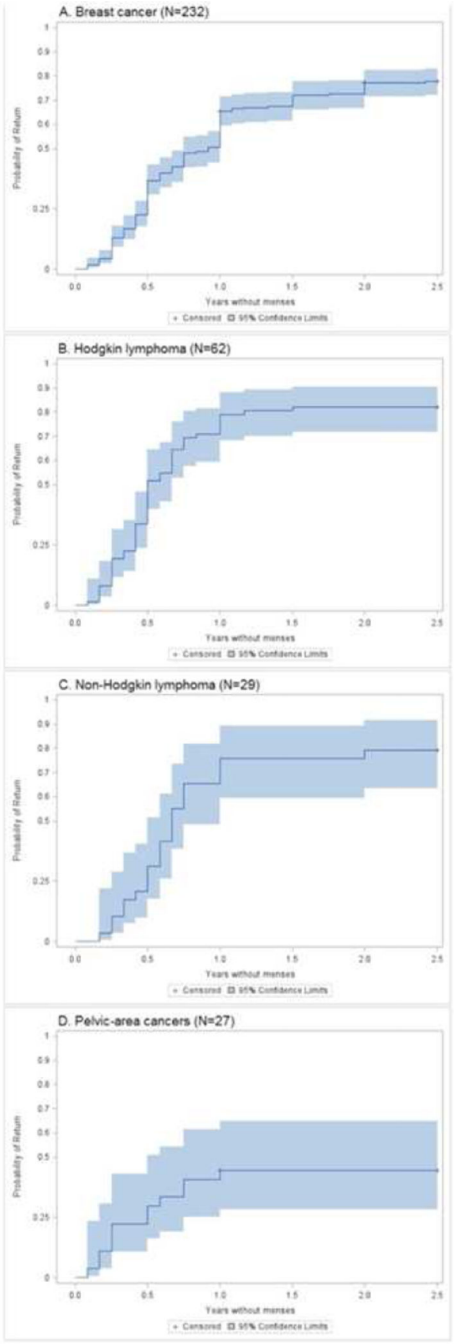

Figure 1.

Unadjusted Kaplan-Meier survival curves of time to return of menses by cancer type in a cohort of young adult cancer survivors who stopped menstruating during cancer treatment, truncated at 2.5 years follow-up

Table 1

Characteristics of a Cohort of Young Adult Female Cancer Survivors by Amenorrhea Status

	Eligible Women (n=1,043)		Amenorrhea[a,b] (n=330)		No Amenorrhea[a,c] (n=713)	
	No.	**%**	**No.**	**%**	**No.**	**%**
Treatment[a,d,e]						
Chemotherapy alone	251	24.1	121	48.2	130	51.8
Radiation alone	136	13.0	8	5.9	128	94.1
Chemotherapy and radiation together	345	33.1	187	54.2	158	45.8
Neither chemotherapy or radiation	311	29.8	14	4.5	297	95.5
Age at Diagnosis (years)[f]						
20–24	155	14.9	32	20.6	123	79.4
25–29	337	32.3	90	26.7	247	73.3
30–35	551	52.8	208	37.7	343	62.3
Cancer Type[f]						
Breast	356	34.1	180	50.6	176	49.4
Hodgkin lymphoma	115	11.0	41	35.7	74	64.3
Non-Hodgkin lymphoma	56	5.4	23	41.1	33	58.9
Pelvic-area[g]	80	7.7	21	26.3	59	73.8
Other[h]	436	41.8	65	14.9	371	85.1
BMI[a]						
<18.5	42	4.1	10	23.8	32	76.2
18.5–24.9	617	59.6	195	31.6	422	68.4
25–29.9	210	20.3	65	31.0	145	69.0
>30.0	167	16.1	58	34.7	109	65.3
Missing	7		2		5	
Race[a]						
White	719	69.5	197	27.4	522	72.6
Black	270	26.1	109	40.4	161	59.6

	Eligible Women (n=1,043)		Amenorrhea[a,b] (n=330)		No Amenorrhea[a,c] (n=713)	
	No.	%	No.	%	No.	%
Other	46	4.4	20	43.5	26	56.5
Missing	8		4		4	
Age at Menarche[a]						
<12 years old	251	24.1	87	34.7	164	65.3
12–13 years old	576	55.3	174	30.2	402	69.8
>13 years old	215	20.6	68	31.6	147	68.4
Missing	1		1		0	
Pregnancy History[a]						
Nulligravid	479	45.9	131	27.3	348	72.7
Gravid	564	54.1	199	35.3	365	64.7

[a] Data from interview

[b] Defined as ≥ 6 months without a menstrual period

[c] Defined as no loss of menstrual period or loss of menstrual period for < 6 months

[d] Treatment modalities are mutually exclusive

[e] Ever-use (yes/no)

[f] Data from Georgia Cancer Registry (GCR)

[g] Pelvic-area cancers included ovarian, colon, uterine and cervical cancer

[h] Other cancers included brain, melanoma, thyroid, and other carcinomas

Table 2

Adjusted Odds Ratios (aOR) and 95% Confidence Intervals (CI) of Cohort Characteristics and Amenorrhea[a] in a Cohort of Chemotherapy-Exposed[a,b] Female Cancer Survivors (N=585)[c]

	Amenorrhea[d] (n=302)		No Amenorrhea[e] (n=283)			
	No.	**%**	**No.**	**%**	**aOR[f]**	**95% CI**
Radiation therapy[a,g]						
Yes	185	54.6	154	45.4	1.16	0.82, 1.65
No[h]	117	47.6	129	52.4	1.00	Referent
Age at Diagnosis (years)[i]						
20–24[h]	31	35.2	57	64.8	1.00	Referent
25–29	79	48.8	83	51.2	1.59	0.90, 2.82
30–35	192	57.3	143	42.7	2.37	1.30, 4.30
BMI[a]						
<18.5	10	47.6	11	52.4	0.89	0.35, 2.24
18.5–24.9[h]	179	51.9	166	48.1	1.00	Referent
25–29.9	63	53.4	55	46.6	0.90	0.58, 1.41
>30.0	50	49.5	51	50.5	0.79	0.49, 1.27
Race[a]						
White[h]	182	48.5	193	51.5	1.00	Referent
Black	102	55.7	81	44.3	1.35	0.92, 2.00
Other	18	66.7	9	33.3	2.09	0.89, 4.93
Age at Menarche[a]						
<12 years old	82	52.6	74	47.4	1.02	0.68, 1.52
12–13 years old[h]	159	50.2	158	49.8	1.00	Referent
>13 years old	61	54.5	51	45.5	1.21	0.77, 1.89
Pregnancy History[a]						
Gravid[h]	181	51.6	170	48.4	1.00	Referent

	Amenorrhea[d] (n=302)		No Amenorrhea[e] (n=283)			
	No.	%	No.	%	aOR[f]	95% CI
Nulligravid	121	51.7	113	48.3	1.50	1.02, 2.21

[a] Data sourced from interview

[b] Ever-use of chemotherapy (yes/no)

[c] 11 subjects were dropped due to missing data on covariates

[d] Defined as ≥ 6 months without a menstrual period

[e] Defined as no loss of menstrual period or loss of menstrual period for less than 6 months

[f] Model controls for age at diagnosis, race, gravidity, radiation, cancer type (breast, pelvic-area, Hodgkin lymphoma, non-Hodgkin lymphoma, other), BMI and age at menarche

[g] Ever-use of radiation (yes/no)

[h] Reference group

[i] Data sourced from Georgia Cancer Registry (GCR)

Table 3

Estimated Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Study Covariates and Time to Return of Menses (truncated at 2.5 years)[a] in a Cohort of Cancer Survivors Who Lost Their Period (N=421)[b]

	Women with return of menses[a] (n=302)		Women with no return of menses[a] (n=119)			
	No.	**%**	**No.**	**%**	**HR[c]**	**95% CI**
Chemotherapy[a,d]						
Yes	276	71.7	109	28.3	0.73	0.47, 1.11
No[e]	26	72.2	10	27.8	1.00	Referent
Radiation therapy[a,f]						
Yes	171	68.4	79	31.6	0.80	0.63, 1.02
No[e]	131	76.6	40	23.4	1.00	Referent
Age at Diagnosis (years)[g]						
20–24[e]	40	76.9	12	23.1	1.00	Referent
25–29	82	74.5	28	25.5	0.78	0.52, 1.16
30–35	180	69.5	79	30.5	0.67	0.44, 1.00
BMI[a]						
<18.5	8	72.7	3	27.3	0.84	0.41, 1.73
18.5–24.9[e]	189	74.4	65	25.6	1.00	Referent
25–29.9	51	64.6	28	35.4	0.84	0.60, 1.17
>30.0	54	70.1	23	29.9	1.10	0.79, 1.52
Race[a]						
White[e]	188	71.2	76	28.8	1.00	Referent
Black	100	73.0	37	27.0	1.02	0.79, 1.32
Other	14	70.0	6	30.0	0.88	0.50, 1.52
Age at Menarche[a]						
<12 years old	80	69.0	36	31.0	0.87	0.66, 1.14
12–13 years old[e]	166	75.5	54	24.5	1.00	Referent
>13 years old	56	65.9	29	34.1	0.82	0.60, 1.12
Pregnancy History[a]						
Gravid[e]	177	68.9	80	31.1	1.00	Referent
Nulligravid	125	76.2	39	23.8	1.00	0.78, 1.29

[a] Data sourced from interview

[b] 16 subjecfts were dropped due to missing data on covariates and/or the outcome

[c] Model additionally controls for radiation, race, cancer type, BMI, age at menarche and gravidity

[d] Ever-use of chemotherapy (yes/no)

[e] Reference group

[f] Ever-use of radiation (yes/no)

[g] Data sourced from Georgia Cancer Registry (GCR)