Acute Menopausal Symptoms in Young Cancer Survivors Immediately following Chemotherapy

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Keywords

Chemotherapy · Menopause · Survivorship · Measures of ovarian reserve

Abstract

Purpose: The aim of this study was to evaluate the prevalence of menopausal symptoms in young cancer survivors immediately following the completion of chemotherapy.

Methods: This prospective cohort study followed 124 young females with a new diagnosis of cancer requiring chemotherapy to assess symptoms of menopause before treatment and immediately following chemotherapy. Symptoms were compared before and after treatment using the McNemar test and between cancer patients and 133 similar-aged healthy controls using Pearson χ^2 and Fisher's exact tests.

Results: Participants undergoing cancer therapy reported more menopausal symptoms compared to controls prior to

the initiation of any treatment (hot flashes or night sweats 33 vs. 7%, $p < 0.01$, trouble sleeping 57 vs. 31%, $p < 0.01$, headaches 50 vs. 35%, $p = 0.02$, and decreased libido 36 vs. 16%, $p < 0.01$) and also reported a greater prevalence of symptoms immediately after cancer therapy compared to pretreatment prevalence (vasomotor symptoms, $p < 0.01$, vaginal dryness, $p < 0.01$, decreased concentration, $p < 0.01$, and body aches, $p = 0.01$). Cancer patients with lower anti-Müllerian hormone (AMH) levels after treatment (< 0.10 ng/mL) had an increased risk of vasomotor symptoms (OR 2.2, $p = 0.04$), mood swings (OR 2.4, $p = 0.03$), feeling sad (OR 2.2, $p = 0.04$), trouble sleeping (OR 2.7, $p = 0.02$), and decreased libido (OR 3.0, $p = 0.03$) when controlled for age and cancer type, and the incidence of these symptoms was not affected by the use of systemic hormones or psychiatric medications. Treatment length, use of alkylating agents, pelvic radiation, and marital status were also not associated with the prevalence of menopausal symptoms. **Conclusions:** Premeno-

pausal women with a new cancer diagnosis have more menopausal symptoms than females of similar age before and after cancer treatment, the effects of which are not mitigated by systemic hormone use. Decreased AMH levels were associated with an increased likelihood of reporting physiologic symptoms after therapy. **Implications for Cancer Survivors:** This information is imperative for counseling; ultimately, improved symptom management during and after cancer therapies will improve quality of life in young cancer survivors.

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Introduction

With improvements in the ability to diagnose and treat many types of cancer, the mortality rate from cancer for both children and adult women has steadily decreased [1, 2]. Today, children and adolescents diagnosed with cancer have an expected long-term survival of approximately 80% [3]. Of the estimated 18 million cancer survivors predicted by 2022 [3], many will be young, premenopausal women. The short-term side effects and long-term reproductive sequelae of cancer treatments on this population are becoming increasingly important. For these survivors, menopausal symptoms and concerns about infertility are common and have a negative impact on quality of life [4–7].

Large retrospective cohort studies have assessed resumption of menstrual function after chemotherapy and have clearly demonstrated that cancer survivors are at risk for both acute and long-term ovarian failure [8–10]. In addition to the temporary or permanent cessation of menses after cancer treatment, women can also experience classic symptoms of natural reproductive aging and the menopausal transition, such as vasomotor symptoms, sleep disturbances, changes in sexual function, and changes in mood [10].

Several studies have examined menopausal symptoms in breast cancer survivors remote from treatment and have shown that, years later, survivors report more symptoms than women without a history of cancer [5, 11–17]. Subjects in the majority of these studies were menopausal or perimenopausal at the time of diagnosis and treatment, and assessment of symptoms occurred remote from treatment. There is limited literature describing menopausal symptoms in very young postmenarcheal women with cancer immediately after therapy.

The purpose of this study was to determine the prevalence and risk factors for menopausal symptoms in young

reproductive-age women undergoing cancer treatment compared to healthy controls. We hypothesize that survivors will experience bothersome symptoms after treatment and that these symptoms will be reduced in those using estrogen-containing hormones.

Materials and Methods

Participants were enrolled as part of an ongoing cohort study conducted by the University of Pennsylvania (Penn) in collaboration with the Children's Hospital of Philadelphia (CHOP), Ann & Robert H. Lurie Children's Hospital of Chicago (formerly Children's Memorial Hospital in Chicago [CMH]), the University of North Carolina at Chapel Hill (UNC), and the University of California San Diego (UCSD). Institutional review board approval was obtained at each site, and informed consent was obtained from all participants.

Subjects

Participants

Postmenarcheal, premenopausal participants with a new cancer diagnosis were enrolled from the 5 participating sites (Penn, CHOP, CMH, UNC, and UCSD). Participants were required to be between 11 and 42 years of age, to have a uterus and 2 ovaries, and to be preparing for treatment with chemotherapy (with or without radiation). Participants were excluded if they had been pregnant or lactating within 3 months of enrollment or if they had ever received chemotherapy or radiation treatment prior to enrollment.

Participants were enrolled at a baseline visit that occurred after the diagnosis of cancer but before initiation of cancer therapy and were then seen for a follow-up visit within 3 months after the cessation of cancer therapy.

Controls

Unexposed controls were obtained at Penn and were identified through health practices affiliated with Penn and through advertising. Controls were required to be postmenarcheal, with regular menstrual cycles (21–35 days), a uterus, and both ovaries. Exclusion criteria included history of cancer and pregnancy or lactation within 3 months.

Each control's study visit occurred on days 1–4 of the menstrual cycle. Control participants were required to stop exogenous hormones for at least 4 weeks prior to the study visit and were seen during the subsequent menstrual cycle.

Examinations

Questionnaires

Both participants and controls underwent structured interviews, which included detailed information on demographics, medical history, menstrual characteristics, pregnancies, infertility history, contraception, medications, and substance use. Use of exogenous hormones was recorded at each visit, including hormonal contraceptives, tamoxifen, gonadotropin-releasing hormone agonists, and hormone replacement therapy. Participants were considered to be on systemic hormones if they were receiving oral contraceptives, Depo-Provera, hormonal patch, NuvaRing, or

hormone replacement therapy. Participants were considered to be on psychiatric medication if they reported taking a medication for depression, anxiety, or sleep disturbances.

Menopausal Symptoms

A symptom list that has been validated to assess menopausal symptoms in late reproductive-age women was asked to all participants by structured interview [18]. As part of this symptom list, participants and controls answered questions about the occurrence of hot flashes, night sweats, vaginal dryness or discomfort, concentration/memory problems, irritability, mood swings, feeling sad/down/blue, feeling anxious/on-edge/nervous, trouble sleeping, aches, joint pain/stiffness, headaches, and decreased libido or interest in sex. Participants and controls were asked about the frequency and severity of these symptoms. For purposes of analysis, hot flashes and night sweats were combined into one vasomotor variable, “hot flashes or night sweats.”

Cancer Therapy

Diagnosis and treatment exposure data were obtained by reviewing medical records. Treatment was summarized with chemotherapeutic type, duration, cumulative dose, radiation dose, and location recorded. Alkylating agent dose scores were determined by assigning a value ranging from 1 to 3 for each agent received and then summing values for all agents [19].

Hormone Analysis

Blood samples were obtained at each study visit to determine levels of follicle-stimulating hormone (FSH) and anti-Müllerian hormone (AMH). All hormone assays were measured at Penn's Clinical Translational Research Center using FSH Coat-A-Count kits (Diagnostic Products Corporation) and AMH enzyme-linked immunosorbent assay (ELISA) kits (DSL Gen II). The FSH immunoradiometric assay's range is 1.5–100 mIU/mL, with a sensitivity of 0.7 mIU/mL and interassay and intra-assay coefficients of variation of <6 and 4%, respectively. The AMH ELISA's range is 0.050–10.0 ng/mL, with a sensitivity of 0.025 ng/mL and interassay and intra-assay coefficients of variation of <8% and 5%, respectively.

Data Analysis

Baseline characteristics and reported symptoms were summarized before and after treatment for participants and at enrollment for controls. A subgroup analysis comparing women with breast cancer to women with other cancer diagnoses was also completed. Pearson χ^2 analyses, Fisher's exact tests, and *t* tests were performed to compare independent groups (cancer participants and healthy controls). Paired *t* tests and McNemar test were used to examine pre- versus posttreatment outcomes in the cancer participants.

Risk factors of interest for menopausal symptoms included age, treatment length, systemic hormone use, alkylator use, pelvic radiation, psychiatric medication use, cancer type (breast or non-breast), and geometric means of FSH and AMH, and were included in multivariable logistic regression models. For some analyses, median cut points were used to dichotomously analyze the continuous variables AMH and FSH.

Study data were collected and managed using REDCap electronic data capture tools at the Penn. Statistical analysis was performed using Stata 12.0 (StataCorp).

Results

One-hundred twenty-four women between the ages of 14 and 41 years with a new diagnosis of cancer met criteria for inclusion in this analysis. Eighty-nine women were recruited from Penn, 13 from CHOP, 11 from CMH, 6 from UNC, and 5 from UCSD.

Within the newly diagnosed cancer group, 48 (39%) of the 124 were diagnosed with breast cancer and 48 (39%) were diagnosed with hematological malignancies. The mean age at diagnosis was 27 years. Sixty-nine percent went on to receive therapy with an alkylating agent (mean alkylator score of 1.5, range 1–6) and the remainder with nonalkylating chemotherapy. Chemotherapy regimens for the participants were heterogeneous; the most common breast cancer regimen was ACT (doxorubicin, cyclophosphamide, docetaxel), and the most common hematologic cancer regimen was ABVD (doxorubicin, bleomycin, vincristine, dacarbazine). The median length of cancer therapy was 113 days (range 30–464). Sixty-three women underwent radiation: 40 participants received chest, 9 head, 8 pelvic, 2 abdominal, and 4 total body irradiation.

One-hundred thirty-seven healthy controls between the ages of 14 and 38 years were included in the control group. Demographics for all participants are shown in Table 1. Baseline characteristics were similar between the cancer participants and unexposed controls, with the exception of smoking status (1.6% of cancer participants smoked compared to 9.8% of healthy controls, $p < 0.01$), and marital status (78% of exposed participants were single compared to 88% of unexposed controls, $p = 0.03$).

The pretreatment levels of AMH in the exposed participants were lower than in the controls (geometric mean 1.8 vs. 2.5 ng/mL, $p < 0.01$). Conversely, levels of FSH were lower in the exposed participants than in the controls (geometric mean 5.2 vs. 7.0 mIU/mL, $p < 0.01$). There was no difference in AMH levels between participants diagnosed with cancer who were using systemic hormones compared to those who were not (1.78 vs. 1.81 ng/mL, $p = 0.94$) in analyses controlled for age and body mass index.

Analysis of Exposed Participants

Table 2 presents menopausal symptoms in the exposed group and the control group at baseline and (for the exposed group) at a study visit within 3 months of cancer therapy completion. At baseline, the exposed group had significantly higher rates of hot flashes or night sweats (33 vs. 7%, $p < 0.01$), trouble sleeping (57 vs. 31%,

Table 1. Patient characteristics

	Participants with cancer (<i>n</i> = 124)	Controls (<i>n</i> = 137)	<i>p</i> value
Age, years	26.9 (25.7–28.2)	26.1 (25.1–26.9)	0.23
BMI	24.0 (22.9–25.0)	25.0 (23.7–26.3)	0.22
Race			0.55
Caucasian	76.6 (95/124)	81.0 (111/137)	
African American	10.5 (13/124)	10.2 (14/137)	
Other	12.9 (16/124)	8.8 (12/137)	
Education: college graduate, or greater	59.4 (73/123)	69.9 (93/133)	0.08
Current smoker	1.6 (2/123)	9.8 (13/133)	<0.01
Marital status: single	78.2 (97/124)	88.3 (121/137)	0.03
Previous pregnancy	25.4 (30/118)	34.6 (46/133)	0.12
Cancer type			
Breast	38.7 (48/124)		
Leukemia	7.3 (9/124)		
Lymphoma	31.4 (39/124)		
Sarcoma	8.9 (11/124)		
Brain	2.4 (3/124)		
Germ cell	3.2 (4/124)		
Other	8.0 (10/124)		
Alkylating agent use	69.4 (86/124)		
Mean alkylator score (range) ^a	1.5 (1–6)		
Pelvic radiation	6.5 (8/124)		
Birth control use at baseline ^b			
None	34.7 (43/124)		
IUD	4.0 (5/124)		
Barrier method	29.8 (37/124)		
Rhythm or withdrawal	12.1 (15/124)		
Systemic hormones	49.2 (61/124)		
Combined oral contraceptives	80.3 (49/61)		
Progestin only oral contraceptive	4.9 (3/61)		
Depo Provera	4.9 (3/61)		
Patch	3.3 (2/61)		
Ring	6.6 (4/61)		

Values are means (95% confidence intervals) or % (*n*/*N*) unless otherwise indicated. Italics indicate statistical significance. BMI, body mass index; IUD, intrauterine device. ^a For patients receiving alkylator agents. ^b May be using more than 1 method.

$p < 0.01$), headaches (50 vs. 35%, $p = 0.02$), and decreased libido (36 vs. 16%, $p < 0.01$) compared to the unexposed group even before the initiation of cancer therapy. These associations were independent of age or marital status. For the 49% of the exposed group who were using systemic hormones at the time of the baseline visit, this did not significantly impact the incidence of vasomotor, mood, or physical symptoms, nor did the use of psychiatric medications.

The exposed participants were seen for a post-treatment study visit at a mean of 31 days after the cessation

of cancer therapy. At this visit, the prevalence of several menopausal symptoms had increased within the exposed group compared to the pretreatment prevalence. Vasomotor symptoms increased significantly from 33 to 52% ($p < 0.01$), vaginal dryness increased significantly from 8 to 23% ($p < 0.01$), difficulty concentrating increased from 25 to 45% ($p < 0.01$), and body aches increased from 38 to 55% ($p = 0.01$). The prevalence of anxiety was decreased at the posttreatment visit compared to baseline, falling from 62 to 55% ($p = 0.04$). In logistic regression models, neither treatment length, alkylator score, nor pelvic ra-

Table 2. Menopausal symptoms

Symptoms	Unexposed controls	Pretreatment		Post-treatment	
		exposed participants	<i>p</i> value*	exposed participants	<i>p</i> value**
Hot flashes or night sweats	6.6 (9/137)	33.1 (41/124)	<i><0.01</i>	52.4 (65/124)	<i><0.01</i>
Vaginal dryness	6.7 (9/134)	7.5 (9/120)	0.81	22.7 (25/110)	<i><0.01</i>
Concentration	29.1 (39/134)	25.0 (30/120)	0.46	45.2 (54/110)	<i><0.01</i>
Irritability	50.0 (67/134)	45.0 (54/120)	0.43	45.5 (50/110)	0.87
Mood swings	38.8 (52/134)	32.8 (39/119)	0.32	40.9 (45/110)	0.19
Feeling sad	51.5 (69/134)	55.8 (67/120)	0.49	52.7 (58/110)	0.43
Feeling anxious	59.0 (79/134)	61.7 (74/120)	0.66	51.8 (57/110)	0.04
Trouble sleeping	30.6 (41/134)	56.7 (68/120)	<i><0.01</i>	60.0 (66/110)	0.62
Aches	34.3 (46/134)	37.8 (45/119)	0.56	54.5 (60/110)	0.01
Headaches	35.1 (47/135)	50.0 (60/120)	0.02	38.1 (42/110)	0.06
Decreased libido (of those sexually active)	16.0 (16/100)	36.1 (30/83)	<i><0.01</i>	48.6 (36/74)	0.16

Values are % (*n*/*N*). Italics indicate statistical significance. * *p* value for unexposed controls compared to exposed participants at baseline. ** *p* value for exposed participants at baseline compared to immediately after cancer therapy.

diation was associated with a significant change in the risk of reporting symptoms within the exposed participants. Reported use of psychiatric medications at the post-treatment visit did not change the risk of reporting mood symptoms ($p = 0.42$), nor did the use of systemic hormones change the risk of reporting vasomotor symptoms, mood symptoms, or physical symptoms after completion of cancer therapy ($p = 0.65$, $p = 0.15$, and $p = 0.22$, respectively).

Levels of AMH decreased after cancer therapy, and lower levels were associated with an increase in the prevalence of many symptoms. The post-treatment mean AMH for the exposed group fell to 0.18 ng/mL from the baseline mean 1.8 ng/mL ($p < 0.01$), with a median of 1.0 ng/mL. Decreased AMH at the post-treatment visit (defined as <0.10 ng/dL) was associated with an increased risk of physiologic, mood, and multi-factorial symptoms, even when controlled for age and cancer type. Participants with decreased AMH experienced an increased risk of vasomotor symptoms (OR 2.2, $p = 0.04$), mood swings (OR 2.4, $p = 0.03$), feeling sad (OR 2.2, $p = 0.04$), trouble sleeping (OR 2.7, $p = 0.02$), and decreased libido (OR 3.0, $p = 0.03$) compared to exposed participants after cancer therapy with AMH levels >0.10 ng/mL. In logistic regression models, when controlled for age and AMH, increased FSH was not independently significantly associated with any increased risk in reporting symptoms.

Twelve cancer survivors reported use of gonadotropin-releasing hormone agonists within 3 months of their

post-treatment visit, and a subsequent sensitivity analysis excluding those individuals found no differences in these associations.

Subgroup Analysis of Participants with Breast Cancer

Of the exposed participants, the 39% of women with breast cancer were older (30.6 vs. 24.7 years, $p < 0.01$) and were more likely to be using systemic hormones (71 vs. 45%, $p < 0.01$) or a psychiatric medication (48 vs. 22%, $p = 0.04$) at the baseline visit compared to exposed participants with other types of cancer. When compared to exposed participants with non-breast cancer, participants with a breast cancer diagnosis had a lower risk of aches and headaches at the baseline visit (OR 0.26, $p = 0.01$ and OR 0.41, $p = 0.03$, respectively). After treatment, breast cancer survivors were more likely to report to experience difficulty with concentration (RR 2.7, $p = 0.03$), even when controlling for age and AMH level. Eight survivors reported ongoing tamoxifen use after their initial chemotherapy, and there was no difference in symptom reporting between women on tamoxifen and those not using tamoxifen.

Discussion

Cancer therapies have been shown to impair reproductive function in cancer survivors, but the short-term sequelae of these therapies on menopausal symptoms in young postmenarcheal, premenopausal women are not

well documented. With the increasing number of young women surviving cancer, information about risks for menopausal symptoms and strategies to reduce these symptoms should be important parts of counseling.

This study sought to determine the prevalence of menopausal symptoms in young females undergoing cancer treatments and to assess risk factors associated with those symptoms. This is one of the first studies comparing menopausal symptoms in patients before and after cancer therapy. Comparison of survivors to controls of a similar age revealed that survivors had significantly more symptoms before cancer treatment. Additionally, survivors had significantly more menopausal symptoms after treatment than at baseline, and this appears to be more pronounced in the subgroup with lower AMH levels after therapy, even when controlled for age. In this small study, systemic hormone use or psychiatric medication was not associated with the prevalence of symptoms. Additionally, we did not find that treatment length, alkylator use, or pelvic radiation were associated with the prevalence of symptoms after treatment.

The observation that cancer patients are experiencing more symptoms at baseline compared to controls, before any reproductive insult, is a novel finding. A possible explanation is that increased symptoms at baseline may reflect symptoms due to the disease itself rather than reproductive effects of the treatment. Newly diagnosed cancer patients may have a variety of nonspecific health and emotional symptoms that may overlap with menopause-like complaints. Nonetheless, it is possible that these symptoms may truly be reflecting reproductive dysfunction as they correlate with measures of ovarian reserve. Similar to our finding of decreased AMH levels in the exposed participants before cancer therapy compared to the controls, there is evidence of decreased ovarian reserve in women with a diagnosis of cancer even before exposure to cancer therapy [20, 21], which could possibly be related to the increased prevalence of symptoms at baseline in our cancer population.

This study has several strengths. The use of a validated menopausal symptom list before and after treatment in a population of young cancer participants makes this study unique. Recall bias was minimized by prospective enrollment, and confounding was reduced by restricting the study to nonpregnant, nonlactating females. Valid comparisons were made with an unexposed control population of a similar age. Cancer diagnoses and treatments were validated with medical records to diminish misclassification bias. Unlike other studies looking at menopausal symptoms after cancer treatment, our study included

women with all cancer types and only those who were 42 years of age or younger.

Several limitations should be mentioned. This is a small study, and it should be noted that both null associations and artificial risks are potential problems due to a lack of power and the possibility of chance findings, respectively. Combining hot flashes and night sweats into one question may have biased our results toward finding no association, since night sweats are often nonspecific symptoms of cancer. Timing of the first post-treatment visit varied between participants from the day treatment ended to 3 months after the cessation of treatment, and we were unable to assess menopausal symptoms with more precise time points. Typical of studies involving childhood and young adult cancer survivors, subjects with a variety of diagnoses and treatments were included. Therefore, it was not possible to compare the effects of specific chemotherapeutic regimens on menopausal symptoms. Finally, the menopausal symptom questionnaire used here was initially designed for late reproductive-aged women, and its use in younger women experiencing menopausal symptoms has not been used previously in this population.

Conclusions

Overall, young premenopausal women with a new cancer diagnosis have more menopausal symptoms than controls of a similar age even prior to cancer therapy. The prevalence of these symptoms increases after treatment, and lower levels of AMH are associated with an increased prevalence of symptoms. The use of systemic hormone therapy or psychiatric medications does not ameliorate these symptoms. Additional studies are needed to identify further factors associated with symptoms and to follow these young women longitudinally to determine the persistence of symptoms. This information is imperative for counseling; ultimately, improved symptom management during and after cancer therapies will improve quality of life in young cancer survivors.

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The authors have no conflicts of interest to declare.

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