

## BRIEF REPORT

# Menopausal symptoms and fertility concerns in premenopausal breast cancer survivors: a comparison to age- and gravidity-matched controls

Kathryn J. Ruddy, MD, MPH,<sup>1</sup> Shari Gelber, MSW,<sup>1</sup> Elizabeth S. Ginsburg, MD,<sup>2</sup> Lidia Schapira, MD,<sup>3</sup> Mary E. Abusief, MD,<sup>2</sup> Meghan E. Meyer, BS,<sup>1</sup> and Ann H. Partridge, MD, MPH<sup>1</sup>

### Abstract

**Objective:** Many young breast cancer survivors experience menopausal symptoms and feel concerned about infertility due to oncologic treatment. However, there has been little research to date comparing young survivors' concerns and symptoms with those of young women of the same age and gravidity in the general population.

**Methods:** We surveyed breast cancer survivors with regular menses after adjuvant chemotherapy and compared them with age-matched, gravidity-matched controls as part of a study to evaluate the effects of chemotherapy on ovarian reserve. All survivors were 1 year or more from diagnosis of early-stage breast cancer, without evidence of recurrence. The survey assessed menopausal symptoms and infertility concerns.

**Results:** The study was stopped after a planned interim analysis of the first 20 matched pairs revealed significantly diminished measures of ovarian reserve in survivors compared with controls. Mean age was 37 years for both groups (range, 31-43 y). Eighty percent of survivors and 25% of controls expressed some concern regarding fertility at the time of the survey ( $P = 0.001$ ). Survivors were more likely to report bothersome menopausal symptoms than were controls ( $P = 0.05$ ). An exploratory analysis revealed that menopausal symptoms were greatest in the survivors taking tamoxifen.

**Conclusions:** Young women who remained premenopausal after breast cancer chemotherapy expressed greater concern about fertility and reported more menopausal symptoms than did age- and gravidity-matched controls. This may have been due to cancer diagnosis or treatment, or it may reflect other differences between the survivors and controls in this study. Additional research is warranted to determine how to most effectively address fertility concerns and reduce symptom burden in this population.

**Key Words:** Hot flashes – Menopause, premature – Infertility – Anxiety.

Premenopausal women with breast cancer are at risk for developing infertility and burdensome menopausal symptoms, both of which may affect quality of life and contribute to distress.<sup>1</sup> Treatments for breast cancer can impair fertility and induce menopausal symptoms by two mechanisms: (1) standard chemotherapy damages the ovaries and (2) standard antiestrogen therapy (eg, tamoxifen) causes menopausal symptoms including hot flashes<sup>2</sup> and requires delay of

childbearing as pregnancy is contraindicated during treatment, allowing natural waning of ovarian function over time. The physical consequences of estrogen deprivation due to ovarian damage from chemotherapy and/or estrogen blockade due to tamoxifen may be particularly burdensome for young breast cancer survivors.<sup>3</sup>

Compared with older survivors, younger women experience greater psychosocial distress and more difficulty with adjustment to the diagnosis and treatment of breast cancer, which may partly result from anxiety about future infertility and the development of menopausal symptoms and premature menopause.<sup>4</sup> Fertility is known to be a major concern for many young women with breast cancer.<sup>5-7</sup> Potential infertility may have an impact on a woman's self-perceived sexuality and self-esteem and may cause emotional distress.<sup>8</sup> However, the psychosocial consequences of the concurrent experience of cancer survivorship and infertility have received little previous attention. Furthermore, the available literature is also limited regarding how fertility concerns and menopausal symptoms in cancer patients compare to those of the general population.

Received April 8, 2010; revised and accepted June 28, 2010.

From the <sup>1</sup>Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; <sup>2</sup>Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, MA; and <sup>3</sup>Medical Oncology, Massachusetts General Hospital, Boston, MA.

Funding/support: Funding for this study was provided by the Lance Armstrong Foundation.

Financial disclosure/conflicts of interest: None reported.

Address correspondence to: Kathryn J. Ruddy, MD, MPH, Dana-Farber Cancer Institute, 44 Binney St, Boston, MA 02115. E-mail: kruddy@partners.org

## METHODS

## Selection and description of study participants

We conducted an evaluation of menopausal symptoms and fertility concerns as part of a cross-sectional study evaluating the objective measures of ovarian reserve in young breast cancer survivors compared with controls.<sup>9</sup> Women with a history of chemotherapy treatment for stage I-IIIa breast cancer who remained premenopausal were compared with healthy age-matched (paired within 18 mo), gravidity-matched (paired by 0 vs  $\geq 1$  pregnancy) controls. Eligibility requirements included reported menses at least every 2 months, no current use of hormonal contraception, absence of significant comorbidity likely to affect fertility, and age younger than 43 years at enrollment. This age cutoff at the time of enrollment was used because many specialists do not recommend standard reproductive technologies to women 43 years or older because of concerns about safety and efficacy. Breast cancer survivors were required to be 40 years or younger at diagnosis, without a history of infertility or infertility treatment at diagnosis, at least 1 year from diagnosis, not receiving gonadotropin-releasing hormone-agonist therapy, and without evidence of recurrence at the time of the study. This age cutoff was used because women 40 years or younger at diagnosis are more likely to have fertility concerns and have an increased risk of psychosocial distress in follow-up. Controls were required to be without a history of invasive cancer, previous cytotoxic chemotherapy, tamoxifen use, or known infertility or infertility treatment. Survivors were recruited from the patient population of the Breast Oncology Center at the Dana-Farber Cancer Institute and affiliated Faulkner Breast Center, Beth Israel-Deaconess Medical Center, and Massachusetts General Hospital. Controls were recruited using advertisements in print and online. This research study received human subjects research approval from the Dana-Farber/Harvard Cancer Center Institutional Review Board.

## Technical information

Eligible participants signed an informed consent form and then underwent study procedures on days 2 to 4 of a menstrual cycle. At enrollment, women completed a questionnaire that was returned in person or by mail. The questionnaire included the Fertility Issues Survey, which was developed in a large previous study and further refined for this evaluation,<sup>6</sup> as well as a modified version of the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (P1) 43-item menopausal symptoms checklist.<sup>10</sup> The modified checklist measures the presence and degree of bother of each of 41 symptoms during the previous 4 weeks, with possible responses ranging from 0 ("not at all") to 4 ("extremely"). As in the P1, we summed the number of symptoms of any severity (1-4) reported by each woman to obtain a symptom score. For breast cancer survivor participants only, a medical chart review was performed for details of the medical history, including cancer treatment received. The questionnaire and ovarian reserve measures (blood work and ovarian ultrasound) were all completed within 6 months of enrollment.<sup>9</sup> The trial was designed to enroll 39 controls and 39 patients to have the

power to detect group differences in the primary endpoint of the overall study, antral follicle count, a measure of ovarian reserve. However, a planned interim analysis resulted in cessation of the study after 20 women were matched from each group because the differences between the groups in objective measures of ovarian reserve met the early stopping rule.

## Statistics

The McNemar test (two groups) and the Marginal Homogeneity test (three or more categories) were used to test for differences in women and tumor characteristics between the matched pairs of controls and survivors. Concern regarding fertility was dichotomized a priori based on clinical significance ("not at all" vs "a little," "somewhat," or "very"). Comparisons between the matched pairs with regard to fertility concerns were also evaluated with the McNemar test. The Wilcoxon signed rank test was used to evaluate pairwise differences in the total number of reported symptoms for controls and survivors. Comparisons not based on the pairing were performed with Fisher's exact test (eg, differences in desire for more children among women who expressed fertility concerns). Descriptive statistics were used to summarize data on symptoms in survivors on tamoxifen or off tamoxifen and controls.

TABLE 1. Total cohort sociodemographics

|                            | Survivors<br>(n = 20) | Controls<br>(n = 20) | Total<br>(N = 40) | P <sup>a</sup> |
|----------------------------|-----------------------|----------------------|-------------------|----------------|
| Age, mean (range), y       | 36.8 (31-43)          | 36.9 (32-43)         | 36.8 (31-43)      |                |
| Ethnicity                  |                       |                      |                   | 0.65           |
| White                      | 16 (80)               | 10 (50)              | 26 (65.0)         |                |
| African American/<br>black | 1 (5)                 | 4 (20)               | 5 (12.5)          |                |
| Asian                      | 2 (10)                | 1 (5)                | 3 (7.5)           |                |
| Hispanic                   | 0                     | 4 (20)               | 4 (10.0)          |                |
| Other: Latina              | 0                     | 1 (5)                | 1 (2.5)           |                |
| Other: West Indian         | 1 (5)                 | 0                    | 1 (2.5)           |                |
| Education                  |                       |                      |                   | 0.01           |
| Postcollege graduate       | 11 (55)               | 4 (20)               | 15 (37.5)         |                |
| College graduate           | 6 (30)                | 8 (40)               | 14 (35)           |                |
| Some college               | 1 (5)                 | 5 (25)               | 6 (15.0)          |                |
| Technical/vocational       | 0                     | 2 (10)               | 2 (5.0)           |                |
| High school graduate       | 2 (10)                | 1 (5)                | 3 (7.5)           |                |
| Pregnancies                |                       |                      |                   | 0.67           |
| 0                          | 7 (35)                | 8 (40)               | 15 (37.5)         |                |
| 1                          | 5 (25)                | 6 (30)               | 11 (27.5)         |                |
| 2                          | 6 (30)                | 3 (15)               | 9 (22.5)          |                |
| 3                          | 1 (5)                 | 0                    | 1 (2.5)           |                |
| 4                          | 1 (5)                 | 2 (10)               | 3 (7.5)           |                |
| 8                          | 0                     | 1 (5)                | 1 (2.5)           |                |
| Marital status             |                       |                      |                   | 0.001          |
| Divorced or separated      | 1 (5)                 | 1 (5)                | 2 (5)             |                |
| Married                    | 13 (65)               | 5 (25)               | 18 (45)           |                |
| Living as married          | 2 (10)                | 0                    | 2 (5)             |                |
| Never married              | 4 (20)                | 14 (70)              | 18 (45)           |                |
| Menstrual frequency        |                       |                      |                   | 0.06           |
| Once every month           | 15 (75)               | 20 (100)             | 35 (87.5)         |                |
| Two times per month        | 1 (5)                 | 0                    | 1 (2.5)           |                |
| Once every 2 mo            | 4 (20)                | 0                    | 4 (10)            |                |

Data are presented as no. (%), unless otherwise indicated.

<sup>a</sup>McNemar test and Marginal Homogeneity test P values with the following groups combined for the analysis because of sparse data: white ethnicity versus others combined, graduate degree versus other levels of education combined, and none versus one versus two versus three or more pregnancies.

## RESULTS

## Participant characteristics

For this analysis, we included the 20 breast cancer survivors and 20 controls who were matched in age (within 18 mo) and gravidity (0 vs  $\geq 1$  pregnancy). There was one pair that was mismatched on gravidity (control had actually had two pregnancies rather than the 0 she initially reported). We performed a sensitivity analysis removing the discordant pair, and the results were consistent with those from all 20 pairs. Therefore, we included that pair in our analysis. Mean age was 37 years for both groups (range, 31-42 y). Demographics are presented in Table 1. Fifty-five percent of the survivors had been diagnosed 3 or more years previously, 55% had stage 2 tumors, 90% had no comorbidities, 45% had mastectomy, 70% had radiotherapy, 45% received doxorubicin-cyclophosphamide alone and 45% received doxorubicin-cyclophosphamide followed by a taxane. Thirty percent reported that they had taken steps to minimize infertility, and 80% reported that chemotherapy had interrupted their menses.

## Differences in fertility concern between groups

Survivors expressed greater concern about fertility compared with controls. Among survivors, 80% (16/20) expressed some level of concern regarding fertility (2 "a little," 9 "somewhat," and 5 "very"), compared with 25% (5/20) of the controls (4 "a little" and 1 "somewhat";  $P = 0.001$ ). Sixteen survivors and 10 controls desired a future child. The desire to have a child in the future was associated with greater fertility concern in both survivors and controls, although this trend was statistically significant only in survivors. Of the 16 survivors who expressed concerns about fertility, 15 reported that they wanted a future child (or were unsure) and 1 reported that she did not ( $P = 0.01$ ). Of the five controls with fertility concerns, four reported that they wanted a future child and one reported that she did not ( $P = 0.30$ ). Among the women in both groups who desired a future child, survivors were more likely to express concerns about fertility ( $P = 0.005$ ).

## Differences in symptom scores between groups

Survivors had a higher mean symptom score than did matched controls (11.40 vs 6.05, respectively;  $P = 0.05$ ). In an exploratory analysis, we found that survivors on tamoxifen had a higher mean symptom score (17.40) than did survivors not on tamoxifen (5.40). The frequency of each symptom in each group of participants (survivors on tamoxifen, survivors off tamoxifen, and controls) is presented in Table 2. Numerically, the following symptoms were reported more frequently by the survivors currently on tamoxifen than by either of the other two groups: hot flashes, night sweats, pain with intercourse, vaginal discharge, vaginal dryness, avoidance of social affairs, difficulty concentrating, easy distraction, forgetfulness, general aches and pains, joint pains, muscle stiffness, numbness, and/or tingling. For example, hot flashes, numbness/tingling, and pain with intercourse were each reported by 60% of survivors on tamoxifen, 10% of survivors off tamoxifen,

TABLE 2. Menopausal symptoms

| Symptom                       | Survivors on TAM (n = 10) | Survivors off TAM (n = 10) | Controls (n = 20) |
|-------------------------------|---------------------------|----------------------------|-------------------|
| Hot flashes                   | 6 (60%)                   | 1 (10%)                    | 1 (5%)            |
| Bladder control with laughing | 3 (30%)                   | 0                          | 1 (5%)            |
| Bladder control otherwise     | 3 (30%)                   | 0                          | 2 (10%)           |
| Vaginal discharge             | 8 (80%)                   | 2 (20%)                    | 4 (20%)           |
| Genital itching               | 3 (30%)                   | 1 (10%)                    | 2 (10%)           |
| Vaginal dryness               | 6 (60%)                   | 2 (20%)                    | 1 (5%)            |
| Pain with intercourse         | 6 (60%)                   | 1 (10%)                    | 1 (5%)            |
| Breast tenderness             | 6 (60%)                   | 2 (20%)                    | 9 (45%)           |
| Weight gain                   | 7 (70%)                   | 1 (10%)                    | 9 (45%)           |
| Unhappy with appearance       | 7 (70%)                   | 5 (50%)                    | 10 (50%)          |
| Forgetfulness                 | 8 (80%)                   | 2 (20%)                    | 4 (20%)           |
| Tendency to take naps         | 6 (60%)                   | 3 (30%)                    | 3 (15%)           |
| Night sweats                  | 7 (70%)                   | 2 (20%)                    | 3 (15%)           |
| Difficulty concentrating      | 7 (70%)                   | 2 (20%)                    | 5 (25%)           |
| Easily distracted             | 7 (70%)                   | 2 (20%)                    | 5 (25%)           |
| Early awakening               | 5 (50%)                   | 1 (10%)                    | 5 (25%)           |
| Headaches                     | 4 (40%)                   | 4 (40%)                    | 6 (30%)           |
| Fuzzy vision/blind spots      | 3 (30%)                   | 0                          | 2 (10%)           |
| Nausea                        | 3 (30%)                   | 2 (20%)                    | 0                 |
| Vomiting                      | 0                         | 0                          | 0                 |
| Diarrhea                      | 2 (20%)                   | 1 (10%)                    | 0                 |
| Constipation                  | 3 (30%)                   | 1 (10%)                    | 5 (25%)           |
| Vaginal bleeding              | 1 (10%)                   | 2 (20%)                    | 3 (15%)           |
| Cramps                        | 8 (80%)                   | 6 (60%)                    | 9 (45%)           |
| ringing in ears               | 1 (10%)                   | 0                          | 1 (5%)            |
| General aches and pains       | 8 (80%)                   | 1 (10%)                    | 4 (20%)           |
| Joint pains                   | 6 (60%)                   | 1 (10%)                    | 4 (20%)           |
| Chest pains                   | 3 (30%)                   | 0                          | 0                 |
| Swelling of hands and feet    | 2 (20%)                   | 1 (10%)                    | 1 (5%)            |
| Muscle stiffness              | 6 (60%)                   | 0                          | 5 (25%)           |
| Difficulty breathing          | 2 (20%)                   | 0                          | 0                 |
| Dry mouth                     | 2 (20%)                   | 0                          | 2 (10%)           |
| Weight loss                   | 0                         | 1 (10%)                    | 2 (10%)           |
| Decreased appetite            | 0                         | 0                          | 1 (5%)            |
| Excitability                  | 3 (30%)                   | 0                          | 1 (5%)            |
| Short temper                  | 5 (50%)                   | 3 (30%)                    | 4 (20%)           |
| Cold sweats                   | 0                         | 0                          | 0                 |
| Accident proneness            | 3 (30%)                   | 0                          | 2 (10%)           |
| Avoids social affairs         | 5 (50%)                   | 1 (10%)                    | 2 (10%)           |
| Dizziness/faintness           | 3 (30%)                   | 2 (20%)                    | 1 (5%)            |
| Numbness/tingling             | 6 (60%)                   | 1 (10%)                    | 1 (5%)            |

TAM, tamoxifen.

and 5% of controls. Forgetfulness was reported by 80% of survivors on tamoxifen, 20% of survivors off tamoxifen, and 20% of controls. Difficulty concentrating and easy distraction were each reported by 70% of survivors on tamoxifen, 20% of survivors off tamoxifen, and 25% of controls.

## DISCUSSION

To our knowledge, this study provides the first quantitative data regarding fertility concerns and menopausal symptoms in young breast cancer survivors compared with age- and gravidity-matched controls. Breast cancer survivors (half of whom were on tamoxifen at the time of the study) reported more menopausal symptoms than did matched controls. The rates of reported menopausal symptoms found in survivors on tamoxifen in this study are not dissimilar from those previously reported in older breast cancer survivors<sup>11</sup> or in a large population of young breast cancer survivors including some on ovarian suppression.<sup>12</sup>

The data from controls in the current study suggests that some of the symptoms reported by premenopausal breast cancer survivors may be nearly as frequent in the general population of premenopausal women. For example, in this study, 45% of controls reported breast tenderness, weight gain, and cramps, and 50% reported unhappiness with appearance. This finding is concordant with data from the National Surgical Adjuvant Breast and Bowel Project P-1 showing that healthy women receiving placebo in a randomized trial to prevent breast cancer reported substantial symptoms, although not as commonly as did women receiving tamoxifen.<sup>13</sup>

Premenopausal survivors who were not on tamoxifen seemed to have a similar symptom burden compared with controls, although our small sample size precluded testing for statistical significance. This finding may be reassuring to young women taking tamoxifen who may assume that their menopausal symptoms reflect poor ovarian function rather than a medication effect.

In this exploratory study, premenopausal women with breast cancer seem to be more concerned about fertility than age- and gravidity-matched controls, even when only the women who desire a future child are analyzed. Interestingly, the fact that nearly half of the healthy controls who desired children expressed concern regarding fertility suggests that these concerns may be quite prevalent even in women without cancer between the ages of 31 and 42 years. This implies that even women without a history of cancer or infertility may benefit from information and counseling regarding reproductive choices.

The differences we found between healthy controls and premenopausal survivors of breast cancer may have important implications for optimal care of these patients at diagnosis and in follow-up. The higher level of concern about fertility among survivors may reflect appropriate education of young breast cancer patients that chemotherapy may have damaged their ovaries and that they are at higher risk of ovarian dysfunction, infertility, and early menopause than others their age, even when they remain premenopausal in early follow-up.<sup>9</sup> Survivors' concerns about possible infertility may also be increased because of apprehension about access to nonbiologic options for parenthood. There is evidence that cancer patients lack adequate information about adoption and also face discrimination in domestic and international adoption procedures.<sup>14</sup>

Our findings should be interpreted with caution in light of the limitations of this work. This study was small and had potential for selection bias. Healthy controls and breast cancer survivors who chose to participate may differ from those who did not with regard to their fertility concerns and menopausal symptoms; it is possible that greater concerns and symptoms would motivate participation in both groups. In addition, controls seemed less likely to be married ( $P = 0.001$ ), less likely to have postgraduate education ( $P = 0.01$ ), and, at trend level, more likely to have a period every month ( $P = 0.06$ ).

Many of the controls reported graduate school education, probably due, in part, to ease of participation for those who work or study near the university hospital in which the study was run. All of these factors may have contributed to lower levels of fertility concern in controls. Moreover, we performed multiple statistical tests on a small dataset, so some of the apparent associations may be spurious. Furthermore, this was a cross-sectional evaluation, but fertility concerns and menopausal symptoms may change over time in both survivors and controls. Finally, the current study is limited by the absence of a formal evaluation of quality of life and psychologic correlates of reported symptoms and fertility concerns. Ongoing and future studies should clarify these issues.

## CONCLUSIONS

Young breast cancer survivors reported more menopausal symptoms and expressed greater concern about fertility and than did age- and gravidity-matched controls. This study highlights the need for interventions to reduce menopausal symptom burden and fertility-related concerns, as well as to improve fertility preservation options, in the young survivor population.

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# Partnership for Families Program

## Philanthropy for in Vitro Fertilization Patients

James M. Goldfarb, M.D., M.B.A., Nancy Lerner Fisher, J.D., Laura Gillespie, M.D., Cynthia M. Austin, M.D., Hanna Lisbona, M.D., Barry D. Peskin, M.D., and Nina Desai, Ph.D.

**OBJECTIVE:** To describe our Partnership for Families Program, which was established to provide second in vitro fertilization (IVF) cycles for couples who pay for one IVF cycle, do not get pregnant and cannot afford a second IVF cycle. In addition, this program provides funding for fertility-sparing procedures for financially needy cancer patients.

**STUDY DESIGN:** Retrospective description of the Partnership for Families' first 5 years of operation.

**RESULTS:** In its 5 years of operation, the Partnership for Families Program has provided 137 infertile couples with a second IVF cycle, resulting in 68 ongoing or delivered pregnancies. It has also provided funding for 19 fertility-sparing procedures for cancer patients.

**CONCLUSION:** Because of the high costs of IVF, alternative funding sources, specifically philanthropy, must be explored to provide increased access to IVF. The Partnership for Families Program, started by patients in a single practice, has in 5 years provided over 151 infertile and cancer patients IVF or egg-freezing cycles that they otherwise could not have afforded. This is a program that can be emulated by other fertility centers. (J Reprod

Med 2009;54:548–552)

**Keywords:** in vitro fertilization, Partnership for Families Program, philanthropy.

**The success we are having in giving couples a second chance to have the families they so much desire gives us hope that other programs can emulate the Partnership for Families Program.**

In 2002, 7% of married couples surveyed in which the woman was of reproductive age had not conceived despite 12 or more months of unprotected intercourse.<sup>1</sup> In 2006, 426 fertility clinics provided over 138,000 cycles of as-

sisted reproductive technologies (ART).<sup>1</sup> Access to in vitro fertilization (IVF), typically the last option for infertile couples, is severely limited because of the high cost and limited insurance coverage. According to the American Society of Reproductive Medicine Web page, as of October 2005 only 8 states have strong mandates requiring insurance coverage of IVF.<sup>2</sup> There is no consistency among these states that do mandate insurance coverage. Many do not cover it completely and/or greatly limit the coverage. For example, Hawaii provides a "one time only" lifetime benefit for IVF coverage, and Arkansas allows insurers to limit coverage to a life-

From the Cleveland Clinic Beachwood Fertility Center, Beachwood, Ohio.

Address correspondence to: James M. Goldfarb, M.D., M.B.A., Cleveland Clinic Beachwood Fertility Center, 26900 Cedar Road, Suite 220 South, Beachwood, OH 44122 (goldfaj2@ccf.org).

**Financial Disclosure:** The authors have no connection to any companies or products mentioned in this article.