Sequelae of Breast Cancer and the Influence of Menopausal Status at Diagnosis Among Rural Breast Cancer Survivors

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Abstract

Background: Rural women are among the largest medically underserved groups in the nation, yet few studies have evaluated the sequelae of breast cancer in this population. The purpose of this study was to examine the physical and psychosocial effects of breast cancer experienced by rural survivors at the time of treatment and currently and to examine differences in these effects between younger and older rural survivors based on menopausal status at diagnosis.

Methods: Women treated for breast cancer within the past 6 years at one of three rural cancer centers were mailed a survey with a cover letter from their oncology provider.

Results: Survey respondents ($n=918$, 83% response rate) were 67 ± 13 years old, on average 3.2 years from treatment, 22% were premenopausal at the time of breast cancer diagnosis, and 95% were postmenopausal at the time of the survey. Women who were premenopausal at diagnosis were significantly more likely to experience numerous symptoms at the time of treatment and currently, including higher rates of hot flashes, vaginal dryness, loss of sexual desire, and weight gain ($p \leq 0.001$). The most common psychosocial concerns were fear of recurrence and change in body image, and women premenopausal at diagnosis were significantly more likely than postmenopausal women to report experiencing these concerns (68% vs. 47%, and 43% vs. 27%, respectively, $p \leq 0.001$).

Conclusions: Negative physical and psychosocial sequelae of breast cancer were common in this rural sample and were significantly worse for premenopausal women. Research and resources are needed for delivering targeted survivorship care to rural women, particularly younger rural women.

Introduction

WITH ADVANCES IN DIAGNOSIS AND TREATMENT of breast cancer, there have been significant improvements in survival, with 5-year survival rates for local disease now $>98\%$.¹ Current estimates indicate that there are >2.5 million breast cancer survivors living within the United States.² Most research in breast cancer survivors has focused on physical and psychosocial late effects,³⁻⁶ but few studies have evaluated the sequelae of late effects in rural breast cancer survivors.⁷ With nearly 20% of the U.S. population living in a rural setting, this is one of the largest medically underserved groups in the nation.⁸

Previous research in rural breast cancer survivors has been largely limited to small-scale studies and has focused on two primary themes: (1) access to cancer care and (2) quality of life and unmet psychosocial needs.^{7,9} Access to quality cancer care has been identified as an issue both in achieving a timely diagnosis and in options for management and treatment.¹⁰⁻¹² Rural women are less likely to have staged tumors and stage-

specific treatment,¹¹ and some data indicate they are more likely to be diagnosed at an advanced stage.¹³ In addition, surgical management trends comparing the use of mastectomy vs. breast conservation indicate much higher rates of mastectomy in the rural setting.^{10,14} This is likely in part because of the lack of resources, that is, radiation oncology, dedicated breast surgeons or specialists, within rural communities and greater travel distance to treatment facilities.¹⁵ These treatment differences combined with greater travel burden may influence the physical and psychosocial effects of breast cancer among rural women.

Regarding psychosocial needs, some research indicates worse social and family role functioning¹⁶ and mental health functioning¹⁷ and poorer overall quality of life^{18,19} in rural compared to nonrural breast cancer survivors. Other research has shown that these two populations report similar levels of quality of life.^{20,21} For example, a recent survey study conducted in Australia showed clinically similar scores for quality of life domains (physical, functional, social, and emotional domains) between rural and nonrural breast cancer

survivors, with one exception: rural women showed worse scores for treatment-related breast cancer concerns, such as pain, lymphedema, body image, and sexuality.²²

Survivorship issues experienced by rural breast cancer survivors diagnosed at a younger age have not been a target of previous studies. Younger women often demonstrate greater changes in body image, sexuality, and mood, often as a result of treatment-related menopause, compared to older breast cancer survivors.^{23,24} Younger women who are premenopausal at diagnosis report increased rates of menopausal side effects as well as more pronounced deficits in emotional and social functioning and cognitive performance.²⁵ However, little information is available about younger premenopausal breast cancer survivors within a rural setting where the general population is older²⁶ and supportive care resources are limited.⁹

The purpose of the present study was (1) to examine the physical and psychosocial effects experienced by rural breast cancer survivors both during treatment and currently (at the time of the survey, 3 months to 6 years since treatment) and (2) to examine differences in these breast cancer sequelae between younger and older rural breast cancer survivors based on menopausal status at diagnosis. Identifying survivorship needs will provide the necessary information to develop and deliver targeted breast cancer survivorship care²⁸ within the rural setting.

Materials and Methods

Participants and procedures

Participants were recruited for a cross-sectional survey study in collaboration with three cancer centers located in rural Kansas. Registrars at each cancer center created mailing lists of all patients treated for breast cancer within the past 6 years, excluding those who were known to be deceased. Across the three sites, 98% of treated patients resided in a rural area and received the survey. Conducting the survey across three settings was feasible, and the anticipated sample size (approximately 300 respondents, assuming a 30%–40% response rate) was sufficient for determining the proportion who reported a symptom, with a 5% margin of error and a 90% confidence level. Rural designation (large rural core to isolated rural) was defined by the ZIP code approximation of the Rural Urban Commuting Area (RUCA) codes developed by the U.S. Department of Agriculture, Economic Research Service.²⁹ RUCA codes are based on commuting patterns in and around urbanized areas and urban clusters as defined by the census tract. For large rural cores and other large rural, the primary flow is within or to (respectively) an urban cluster of 10,000–49,999. For small rural cores and other small rural, the primary flow is within or to an urban cluster of 2,500–9,999. For isolated rural, the primary flow is outside any urban cluster.

The mailed survey included a cover letter from the patient's oncology provider, an introduction letter from the research team that addressed voluntary participation and confidentiality, the questionnaire, a prepaid return envelope, and a \$5 incentive. Two weeks after the initial mailing, nonresponders were mailed a reminder postcard, and 1 month after the postcard mailing, nonresponders were sent a replacement survey packet excluding the incentive. The study was approved by the institutional review board at the University of

Kansas Medical Center and by the institutional review boards at each of the three rural Cancer Centers.

Measures

The survey assessed demographics, breast cancer diagnosis (stage, estrogen receptor [ER] status), treatment history (surgery, radiation, chemotherapy, antihormone therapy), treatment and menopause-related symptoms, and psychosocial factors impacted by breast cancer. Ten items assessed physical symptoms of breast cancer treatment (e.g., lymphedema, fatigue, hot flashes) (Table 2) based on the Breast Cancer Prevention Trial Symptom Checklist (BCPT).³⁰ Participants were asked which symptoms (yes/no) they experienced "at the time of your treatment for breast cancer and/or the subsequent few months" and which symptoms (yes/no) they were "still currently experiencing." Psychosocial factors related to adjustment to breast cancer were assessed (yes/no) by asking: Which of the following experiences have impacted you as a survivor? Items included fear of recurrence, fear of death, diminished physical strength, change in body image, change in relationships, and financial stress. Psychosocial factors were chosen based on key elements of major reports,⁶ and reviews specific to a breast cancer population.²⁷ The domains assessed were similar to domains included in longer measures,^{31,32} and the checklist format was modeled after the BCPT.³² Longer measures with reliability and validity data were not used in order to keep participant burden low and thereby maximize the response rate while minimizing selection bias toward potential factors characterizing respondents who are willing to complete longer measures. We pilot tested these items with 12 breast cancer survivors before implementing this study to help ensure their content validity. Self-defined menopausal status at present and at the time of diagnosis were assessed by asking: Have you gone through menopause? and Did you go through menopause prior to treatment for breast cancer? Respondents also reported the date of their last period, and menopausal status was cross-checked and defined as no menstrual cycle within the previous 12 months.³³ Finally, respondents rated their overall satisfaction with the management of their breast cancer symptoms on a scale from 1 (very unsatisfied) to 5 (very satisfied).

Data analyses

Descriptive analyses were performed for demographics, cancer history, symptom-related variables, and psychosocial factors. Logistic regression analyses were used to compare symptoms and psychosocial factors by women who were premenopausal and postmenopausal at diagnosis. These analyses controlled for time since diagnosis, chemotherapy, and antihormone therapy. Analyses excluded women with missing data for metastatic status and menopausal status and those with self-reported metastatic disease (16% of sample). Missing data were treated as missing, and no data were imputed. Given the large number of statistical tests, alpha was set at $p < 0.01$.

Results

Of the 1191 surveys that were mailed, 80 were returned because of undeliverable addresses, and 11 were returned by

family members indicating the patient was recently deceased. Of the remaining 1100 surveys that were delivered, 918 were returned, for a response rate of 83% of delivered surveys and 77% including undelivered surveys. The frequencies of RUCA rurality categories of respondents were as follows: 42% large rural core/other large rural, 29% small rural core/other small rural, and 29% isolated rural. Of the 918 returned surveys, 105 reported having metastatic disease, 54 did not report their metastatic status, and another 5 did not report their menopausal status at diagnosis. The remaining 770 respondents were included in the analyses.

Table 1 shows demographic and cancer-related characteristics for the total sample and by menopausal status at diagnosis. The vast majority (97%) were white non-Hispanic women, consistent with the rural breast cancer patient population in the state of Kansas.³⁴ Respondents were on average 3.2 ± 2.5 years from treatment, and at the time of the survey, 95% were postmenopausal.

Twenty-two percent ($n=170$) of the sample were premenopausal at the time of diagnosis. Compared to women postmenopausal at diagnosis, premenopausal women were significantly younger, more likely to be married/less likely to be widowed, more likely to be employed full-time, and had higher education levels (all $p < 0.001$). Differences in treatment also existed, with premenopausal women being more likely to receive radiation and chemotherapy. Among the women who were premenopausal at diagnosis, 76% were postmenopausal and 11% were perimenopausal at the time of the survey, in-

dicating 87% went through a menopausal transition between the time of diagnosis and completing the survey.

Table 2 displays the percentage of women who experienced breast cancer-related symptoms both at the time of treatment and currently. For 9 of the 10 symptoms, $\geq 25\%$ of respondents endorsed experiencing the symptom at the time of treatment. The one exception, lymphedema, was reported by 11% of women. The most commonly experienced symptoms at the time of treatment were hot flashes (45%), fatigue (41%), sleeplessness (34%), loss of sexual desire (33%), and weight gain (33%). Symptoms most commonly experienced currently were hot flashes (35%) and weight gain (31%), and $\geq 20\%$ also reported experiencing late effects of fatigue, vaginal dryness, loss of sexual desire, sleeplessness, neuropathic pain, and memory loss.

Women who were premenopausal at diagnosis were significantly more likely to experience numerous symptoms at the time of treatment, including hot flashes, vaginal dryness, loss of sexual desire, sleeplessness, and weight gain (all $p \leq 0.001$), after controlling for time since diagnosis, chemotherapy treatment, and use of antihormone therapy. For example, among premenopausal women, 71% reported hot flashes and 59% reported loss of sexual desire compared to 38% and 25% of postmenopausal women, respectively. Premenopausal women were also more likely to experience depression (39% vs. 23%) at the time of treatment. At the time of the survey, menopause-related symptoms remained more common among women who were premenopausal at

TABLE 1. PARTICIPANT CHARACTERISTICS FOR TOTAL SAMPLE AND BY MENOPAUSAL STATUS AT DIAGNOSIS

Participant characteristic	Total sample (n=770) Mean $\pm$ SD or n (%)	Premenopausal (n=170) Mean $\pm$ SD or n (%)	Postmenopausal (n=600) Mean $\pm$ SD or n (%)
Age***	66.6 $\pm$ 13.0	51.7 $\pm$ 7.7	70.1 $\pm$ 10.9
Race, % white	750 (97)	161 (95)	584 (97)
Marital status***			
Married	511 (66)	131 (78)	377 (63)
Divorced/separated/single	109 (14)	32 (19)	75 (12)
Widowed	153 (20)	5 (3)	148 (25)
Education level***			
High school diploma or less	309 (40)	46 (27)	261 (44)
Some college	283 (37)	78 (46)	203 (34)
Bachelor's degree	112 (14)	33 (19)	79 (13)
Graduate degree	67 (9)	13 (8)	53 (9)
Employment status***			
Full-time	244 (32)	117 (69)	122 (20)
Part-time	82 (11)	19 (11)	63 (11)
Retired	381 (50)	16 (9)	365 (61)
Unemployed	61 (8)	17 (10)	61 (8)
Years since diagnosis	3.2 $\pm$ 2.5	3.7 $\pm$ 3.7	3.1 $\pm$ 2.0
Treatment received			
Surgery	738 (95)	163 (96)	570 (95)
Radiation**	483 (63)	124 (73)	358 (60)
Chemotherapy***	298 (38)	104 (61)	190 (32)
Antihormone therapy	382 (52)	87 (52)	293 (52)
Menopausal status at time of survey***			
Postmenopausal	730 (95)	128 (76)	599 (100)
Perimenopausal	20 (3)	19 (11)	0
Premenopausal	21 (3)	21 (13)	0

Note: Some variables have missing values.

** $p < 0.01$; *** $p < 0.001$.

SD, standard deviation.

TABLE 2. BREAST CANCER-RELATED SYMPTOMS AT TIME OF TREATMENT AND CURRENTLY AMONG TOTAL SAMPLE AND BY PREMENOPAUSAL AND POSTMENOPAUSAL STATUS AT DIAGNOSIS

Symptom	Symptom within few months of treatment				Symptom currently			
	Total sample n (%)	Premenopausal n (%)	Postmenopausal n (%)	p value ^a	Total sample n (%)	Premenopausal n (%)	Postmenopausal n (%)	p value ^a
Lymphedema	86 (11)	31 (18)	55 (9)	0.05	59 (8)	20 (12)	39 (7)	0.18
Sleeplessness	265 (34)	88 (52)	176 (30)	<0.001	168 (22)	48 (28)	119 (20)	0.03
Fatigue	316 (41)	93 (55)	222 (37)	0.05	194 (25)	46 (27)	147 (25)	0.75
Memory loss	200 (26)	70 (41)	129 (22)	0.02	153 (20)	46 (27)	106 (18)	0.24
Hot flashes	349 (45)	121 (71)	226 (38)	<0.001	274 (35)	102 (60)	169 (28)	<0.001
Neuropathy, pain	234 (30)	74 (44)	159 (27)	0.04	175 (23)	48 (28)	126 (21)	0.64
Vaginal dryness	210 (27)	69 (41)	139 (23)	0.001	190 (25)	65 (38)	123 (21)	<0.001
Depression	203 (26)	66 (39)	136 (23)	<0.001	121 (16)	36 (21)	84 (14)	0.02
Loss of sexual desire	253 (33)	100 (59)	151 (25)	<0.001	201 (26)	83 (49)	117 (20)	<0.001
Weight gain	252 (33)	90 (53)	161 (27)	<0.001	239 (31)	74 (44)	163 (27)	0.001

^ap for difference between premenopausal and postmenopausal, controlling for antihormone therapy, chemotherapy, and time since diagnosis.

diagnosis, with higher current rates of hot flashes, vaginal dryness, loss of sexual desire, and weight gain ($p \leq 0.001$). Of note, 60% of women premenopausal at diagnosis currently experienced hot flashes, and 49% had sustained loss of sexual desire compared to 28% and 20%, respectively, of women postmenopausal at diagnosis.

Table 3 displays the percentage of women who reported experiencing psychosocial factors related to breast cancer survivorship. Across the total sample, the most common concerns were fear of recurrence (52%), diminished physical strength (39%), change in body image (31%), and financial stress (19%). Women premenopausal at diagnosis were significantly more likely than postmenopausal women to report psychosocial factors, including fear of recurrence (68% vs. 47%), fear of death (16% vs. 5%), change in body image (43% vs. 27%), change in relationships (21% vs. 5%), and financial stress (32% vs. 15%), (all $p \leq 0.001$).

Mean overall satisfaction with symptom management was 3.7 ± 1.5 on a 5-point scale. However, women premenopausal at diagnosis reported significantly lower satisfaction levels (3.4 ± 1.5) compared to women postmenopausal at diagnosis (3.8 ± 1.5) ($p = 0.001$). This difference remained significant after controlling for time since diagnosis, chemotherapy, and antihormone therapy ($p = 0.01$).

Discussion

This study aimed to better understand the issues and challenges experienced by rural breast cancer survivors and to determine if menopausal status at diagnosis was a contributing factor in the sequelae of treatment effects. Our study found that a significant proportion of women across premenopausal and postmenopausal status at diagnosis reported negative physical effects at the time of treatment, and many of these effects extended to the time of this study, on average 3 years posttreatment. The rates of symptoms reported among women in our sample were within the ranges reported in other studies for neuropathy/pain,³⁵ fatigue,³⁶ and menopausal symptoms (hot flashes, vaginal dryness, and loss of sexual desire).²⁴ Of note, lymphedema appears to have been underreported in our sample compared to other studies. Conservative estimates suggest that women approximately 1 year after breast cancer surgery with lymph node removal have a 20%–30% incidence of lymphedema, with some rates as high as 80%, whereas the rate in our sample was only 11%.^{37–39} Although we did not collect whether or not our respondents underwent axillary node dissection, approximately 80% of breast cancer patients do,⁴⁰ and rural women more frequently undergo this procedure compared with urban patients.¹⁰

TABLE 3. PSYCHOSOCIAL FACTORS IMPACTING SURVIVORSHIP FOR TOTAL SAMPLE AND BY PREMENOPAUSAL AND POSTMENOPAUSAL STATUS AT DIAGNOSIS

Psychosocial factor	Total sample n (%)	Premenopausal n (%)	Postmenopausal n (%)	p value ^a
Fear of recurrence	399 (52)	115 (68)	280 (47)	<0.001
Fear of death	59 (8)	28 (16)	31 (5)	<0.001
Diminished physical strength	301 (39)	67 (39)	233 (39)	0.43
Change in body image	239 (31)	74 (43)	164 (27)	<0.001
Change in relationships	67 (9)	36 (21)	29 (5)	<0.001
Financial stress	145 (19)	54 (32)	90 (15)	<0.001

^ap for difference between premenopausal and postmenopausal, controlling for antihormone therapy, chemotherapy, and time since diagnosis.

Moreover, rural women have risk factors for lymphedema, including higher rates of obesity⁴¹ and unprotected or overuse of the arm in which the node dissection was completed.^{42,43} Therefore, it is likely that respondents had not been assessed for lymphedema or were otherwise not knowledgeable about the term and its symptoms. Consistent with this, studies indicate that rural women often lack important cancer and treatment-related knowledge.⁷ Many rural women may not be aware of the potential for late effects, such as lymphedema, and therefore may not practice measures aimed at prevention.

Retrospective report of symptoms at the time of treatment showed a worse profile for premenopausal women at diagnosis across cognitive, physical, and menopausal symptoms. Moreover, women premenopausal at diagnosis had more late effects for menopausal symptoms and weight gain at the time of the survey, consistent with prior studies among mostly urban breast cancer survivors on average 3–6 years after treatment.^{23,24} For example, Ganz²⁴ reported rates of hot flashes ranging from 50% to 70%, vaginal dryness from 48% to 58%, and weight gain from 55% to 60%, with higher rates among women who received both chemotherapy and tamoxifen. Menopausal symptoms exceeded what has been reported by women without breast cancer undergoing menopause, for whom approximately 30% reported experiencing hot flashes and 25% reported vaginal dryness within 1 year of menopause.^{44–47} Women premenopausal at diagnosis also reported significantly higher rates for psychosocial factors, including social functioning (change in relationships), body image, fear of recurrence, fear of death, and financial stress, as well as significantly worse satisfaction with symptom management compared to postmenopausal respondents. These findings replicate previous studies showing higher cancer fear⁴⁵ and worse body image and social functioning²³ among younger survivors. Thus, our results contribute to a growing body of evidence indicating the importance of menopausal status or age at diagnosis when predicting late physical and psychosocial effects of treatment. Our study extends this finding to the rural setting, where the negative effects associated with younger age may be less recognized because the population on average is older and less educated.

Clinical implications for rural setting

Comprehensive survivorship education and planning would be beneficial for rural patients, who may have significant effects posttreatment and limited access to specialists and outlets for intervention. Rural cancer treatment centers may consider targeting limited resources for younger women recognizing their greater needs. Specific education and counseling around menopause and late effects should include discussion of the uncertain risks and benefits of posttreatment therapies. Materials specific to the risks of the patient, such as weight gain, lymphedema, or psychosocial distress, should be provided during the targeted counseling session, with suggested lifestyle changes that may reduce or prevent these issues. Given lower education, health literacy, and general cancer knowledge among many rural survivors, counseling should be targeted to the appropriate literacy level and first address gaps in knowledge.

In addition, there is a need for more continuing medical education (CME) and intervention materials for rural pro-

viders in managing this special population. With the limited access to specialists in the rural setting, primary care is the main source of assessment and management of late and long-term effects of breast cancer. At present, there are limited opportunities for high-quality CME that address these issues and provide empirically supported management strategies. The need for readily accessible CME in the rural setting is essential for providers to care for the ever growing number of breast cancer survivors.

A challenge is providing education and supportive services for hard-to-reach rural areas; therefore, alternative methods, such as the internet, telephone, or video, are possible intervention delivery targets.⁴⁸ Technologic barriers exist as well, however; for example, only 46% of residents have home broadband internet access,⁴⁹ and televideo capacity is often limited to sparsely located clinics. Group phone-based interventions, such as those developed by our group,⁵⁰ hold great promise for adequately reaching remote rural breast cancer survivors while maintaining some of the benefits of group-based education and support.

This cross-sectional study has several limitations. First, we were limited by patient recall regarding symptoms experienced at the time of treatment, and the impact of current symptomology on recall bias is unknown. Prior research has shown that breast cancer survivors can accurately recall their weight at diagnosis and weight gain proximal to treatment up to 5 years later,⁵¹ rendering some support to their ability to recall treatment-related symptoms. In addition, symptom rates during treatment in our sample were largely consistent with the available literature. In addition, potential low health literacy among many respondents was brought to light by inconsistencies in self-reported menopausal status and date of last menstrual period. The impact of low literacy on survey responses is also unknown. Finally, in an effort to keep the survey short to minimize participant burden and enhance response rates, we used simple checklists of symptoms and psychosocial issues, based on the literature, rather than multi-item developed measures. This limits our ability to compare across studies and to a noncancer population. Because of the bimodal response format, the checklists do not capture the full response range and may produce unstable results or more favorable results to the extent that respondents are optimistic when forced to respond yes/no. Given the broad range of factors assessed, however, the findings do provide a snapshot of survivorship across multiple domains. Future studies would be strengthened by a nonrural comparison group. Strengths of the current study include the high response rate and the large sample of rural breast cancer survivors, including a large proportion from isolated rural areas, which are among the most understudied groups.

This study fills a gap in the literature by demonstrating the late effects of breast cancer among younger women living in rural areas. Future studies are needed targeting interventions that address multiple survivorship domains using alternative methods of delivery capable of reaching younger rural breast cancer survivors. Clearly, late effects impact breast cancer survivors regardless of their rural or urban setting. However, because of barriers in healthcare delivery and access to survivorship care for rural women, there is a need for research and resources focused on this large group of underserved patients.

Acknowledgments

We gratefully acknowledge our rural cancer center partners in this project, including registrars and staff at the Tammy Walker Cancer Center at Salina Regional Medical Center located in Salina, KS; Dreiling/Schmidt Cancer Institute at Hays Medical Center located in Hays, KS; and Mt. Carmel Regional Cancer Center located in Pittsburg, KS.

Support was provided by NIH K12 HD052027 and Susan G. Komen for the Cure Foundation.

Disclosure Statement

The authors have no conflicts of interest to report.

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