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SHORT COMMUNICATION

Depression and vasomotor symptoms in young breast cancer survivors: the mediating role of sleep disturbance

Eynav E. Accortt · Julienne E. Bower · Annette L. Stanton · Patricia A. Ganz

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Abstract Depression, sleep disturbance, and vasomotor symptoms are common in breast cancer survivors (BCS), especially in younger women diagnosed before menopause. Risk factors and mechanisms for depression in this population are relatively unexplored. In 163 young BCS, vasomotor symptoms were significantly associated with higher depressive symptoms (β=0.26, p=0.001) and 64 % of the total effect was mediated through sleep disturbance (beta for specific indirect effect=1.296, 95 % CI 0.591–2.212). Treatments reducing vasomotor symptoms might alleviate sleep disturbance and depression in this population.

Keywords Depression · Vasomotor · Sleep disturbance · Young breast cancer survivor

Introduction

Incidence rates of breast cancer have stabilized in women aged 50 years and older but continue to increase in younger women, with over 25 % of breast cancer cases occurring in premenopausal women (DeSantis et al. 2014). Younger breast cancer survivors (BCS) are at elevated risk for depression (Howard-Anderson et al. 2012); indeed, their levels of depressive symptoms are approximately twice as high as those of older women in the months after diagnosis (Avis et al. 2013). Although depressive symptoms typically improve over time, younger survivors continue to report higher levels of depression in the months and years after diagnosis, with negative consequences for quality of life, medical adherence, and potentially for recurrence and survival (Avis et al. 2013). However, the factors that contribute to elevated depression in younger women, particularly in longer-term survivors, have not been determined. Two key factors that may be linked to depression in younger BCS are menopausal symptoms and sleep disturbance. Younger women are at risk for premature menopause as a result of cancer treatment, which may precipitate an abrupt onset of vasomotor symptoms (Mortimer and Behrendt 2013), which include hot flashes and night sweats. Indeed, vasomotor symptoms affect up to 85 % of breast cancer survivors and are more severe in younger women (Knobf 2006). Younger BCS are also at elevated risk for sleep problems, with over 50 % reporting insomnia symptoms that persist even 4 years after diagnosis (Savard et al. 2001). Both vasomotor symptoms and sleep disturbance are known to be linked to depression, and investigators have hypothesized that mood symptoms among naturally menopausal women (i.e., non-cancer patients) are due to disturbed sleep secondary to vasomotor symptoms (Thurston et al. 2006). This hypothesis may also be relevant for younger BCS, who have elevated levels of all three symptoms, but has not been tested.

The goal of this study was to identify associations among vasomotor symptoms, sleep disturbance, and depressive symptoms in a sample of young BCS. We hypothesized that

E. E. Accortt (✉) · J. E. Bower (✉) · A. L. Stanton
Department of Psychology, University of California Los Angeles (UCLA), 1285, Franz Hall, Box 951563, Los Angeles, CA 90095-1563, USA
e-mail: eaccortt@gmail.com
e-mail: jbower@ucla.edu

J. E. Bower · A. L. Stanton
Department of Psychiatry, UCLA, Los Angeles, CA, USA

P. A. Ganz
UCLA Fielding School of Public Health, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

vasomotor symptoms would be associated with depressive symptoms over and above demographic and medical variables, and that sleep disturbance would mediate the relationship between vasomotor symptoms and depression. Investigation of these relationships in younger BCS is critical, as findings may inform treatments specific to this vulnerable group.

Methods

Participants and recruitment

Recruitment for the study spanned January 2009 to February 2010, using the UCLA Health System tumor registry to identify potentially eligible breast cancer patients diagnosed between 2003 and 2007. Eligibility criteria were the following: diagnosis with early-stage (I–III) breast cancer at or before age 50, currently disease free, >1 year postdiagnosis and >6 months posttreatment (i.e., completed chemotherapy and/or radiation but could be receiving endocrine therapy), and ability to read and write English.

Invitation letters were mailed to potential participants, and interested women returned a mailed response form. Trained research staff screened interested participants via telephone. Eligible participants were mailed consent forms and questionnaire packets to complete and return in postage paid envelopes. Participants who did not return questionnaires were prompted with reminder phone calls. The study was approved by the UCLA Institutional Review Board with written consent.

Measures

The survey assessed demographics, health history, self-reported weight and height, cancer treatments, and several measures related to mental and physical quality of life. Reproductive history and menopausal status were assessed through a series of questions adapted from the Study of Women Across the Nation, used previously in our work (Ganz et al. 2003). These questions ascertained current, precancer, and immediate postcancer menstrual histories and whether menstrual periods stopped as a result of cancer treatments. Depressive symptoms over the past week were assessed using the 20-item Center for Epidemiologic Studies Depression (CES-D) Scale. This scale includes one item assessing sleep disturbance which was removed from analyses to avoid construct overlap. Hot flashes and night sweats were assessed using the 2-item subscale of the Breast Cancer Prevention Trial (BCPT) Symptom Checklist and summed to create a measure of vasomotor symptoms. Subjective sleep disturbance was assessed using the 21-item Pittsburgh Sleep Quality Index (PSQI). See Ventura et al. (2013) for additional details about recruitment and measures.

Statistical analysis

Descriptive statistics were calculated to characterize participants by demographic and psychosocial variables. Linear regression models were fitted to estimate associations between vasomotor symptoms (BCPT), sleep disturbance (PSQI), and depressive symptoms (CES-D). To examine mediation by sleep disturbance, a bootstrapping sampling procedure was applied for assessing indirect effects (Preacher and Hayes 2008).

Results

Recruitment results and patient characteristics

The recruitment flow chart and detailed demographic information have been published (Ventura et al. 2013). Of the 476 women who were sent invitation letters, 320 responded and were screened, 288 were eligible, and 164 completed questionnaires. There were no significant differences in age, race/ethnicity, stage at diagnosis, type of surgery, or tumor characteristics between the responders (N=164) and non-responders (N=312). One woman did not complete the CES-D, for a final sample of 163 women.

Women in the present study (N=163) were on average 47 years of age (range 28–56), and most were Caucasian (72 %). The average time since diagnosis of breast cancer was 3.4 years. Over half of the women received both chemotherapy and radiation, and 61 % were receiving endocrine therapy. The majority of women were postmenopausal at survey and more than half reported that they had become menopausal during cancer treatment. Nearly 40 % were categorized as overweight or obese based on current BMI (BMI≥25). The average level of depressive symptoms (total CES-D including sleep item) in the full sample was 14.1 (range 0–46, SD=10.1).

Participant characteristics were stratified by possible clinical depression (CES-D≥16) for descriptive purposes (see Table 1). In line with rates of clinical depression reported previously in young BCS (Avis et al. 2013; Howard-Anderson et al. 2012), 39 % (N=63) were above threshold for possible clinical depression. Mean vasomotor symptoms and sleep disturbance scores were higher (worse) in women with possible clinical depression compared to the non-depressed sample. The depressed group also had higher rates of menopausal status change and slightly lower rates of current employment. The depressed sample did not differ significantly from the non-depressed on any other characteristic.

Table 1 Baseline characteristics

	Total sample (*N*=163)	CES-D<16 (*N*=100, 61 %)	CES-D>16 (*N*=63, 39 %)	*p* value
Age (years)	47.6±5.6	47.8±5.4	47.2±5.9	0.57
Years since diagnosis	3.4±1.5	3.4±1.5	3.4±1.5	0.88
Current BMI	25.2±5.5	24.8±5.2	25.9±5.9	0.20
Married	122	71 (71 %)	51 (81 %)	0.11
Employed	115	76 (76 %)	39 (62 %)	*0.04*
Ethnicity				0.27
White	117	75 (75 %)	42 (67 %)	
African-American	9	7 (7 %)	2 (3 %)	
Asian	23	11 (11 %)	12 (19 %)	
Other	14	7 (7 %)	7 (11 %)	
Young children in home	12	8 (8 %)	4 (6 %)	0.48
Cancer treatments received				
Chemotherapy only	40	22 (22 %)	18 (29 %)	0.22
Radiation therapy only	15	11 (11 %)	4 (6 %)	0.24
Both	87	51 (51 %)	36 (57 %)	0.27
Neither	21	16 (16 %)	5 (8 %)	0.10
Surgery type				0.68
Lumpectomy only	61	35 (35 %)	26 (41 %)	
Mastectomy only	101	64 (64 %)	37 (59 %)	
Current endocrine therapy	98	60 (60 %)	38 (60 %)	0.55
Menopausal status change (pre to post)	77	44 (52 %)	33 (69 %)	*0.04*
Vasomotor symptoms	1.4±1.3	1.2±1.2	1.8±1.3	*<0.01*
PSQI	7.8±4.1	6.2±3.4	10.1±4.1	*<0.01*
CES-D	14.1±10.1	7.5±4.3	24.5±7.6	*<0.01*

Data are *N* (%) or mean±standard deviation. Comparison between groups was tested with *t* tests or chi-square. Statistically significant *p* values are shown in italics. Information about surgery type was not available for one survivor

Linear regression results

We first examined the association between demographic and medical variables with depressive symptoms or sleep disturbance to determine whether these should be included in the model as potential confounders. The significant association between BMI and sleep disturbance (β=0.18, p<0.01) led to the inclusion of BMI in analyses. Theoretically derived confounding variables included age and endocrine therapy. Regression analyses were conducted to examine whether depressive symptoms were associated with vasomotor symptoms and with sleep disturbance. As expected, both models yielded positive associations; higher levels of vasomotor symptoms were associated with higher levels of depressive symptoms (β=0.260, p=0.001), as were higher levels of sleep disturbance (β=0.545, p<0.001). Finally, as shown in Fig. 1, we observed significant indirect mediating effects through sleep disturbance (beta for specific indirect effect=1.296, 95 % CI 0.591–2.212), indicating that 64 % of the total effect of vasomotor symptoms on depressive symptoms was mediated through sleep disturbance. These findings persisted when additionally controlling for current employment, included due to lower rates of employment in the depressed group.

Discussion

In this sample of young BCS, vasomotor symptoms and sleep disturbance were both associated with higher levels of depressive symptoms, and sleep disturbance mediated the association between vasomotor symptoms and depression. This is the

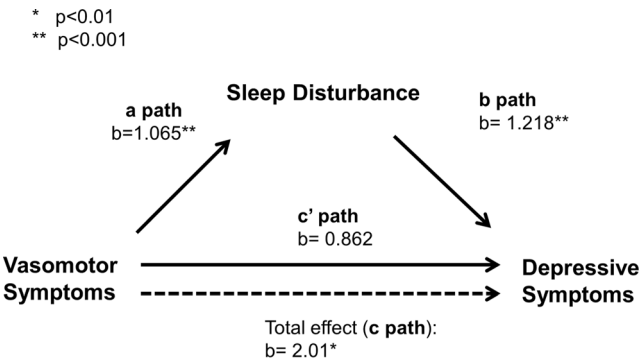

Fig. 1 Mediation model. A bootstrapping sampling procedure was applied for assessing indirect effects (Preacher and Hayes 2008). The indirect effect was significant, and 64 % of the total effect between vasomotor symptoms and depression was mediated through sleep disturbance. Analysis controlled for age, BMI, and endocrine therapy

first study to document these relationships in young BCS, although a limitation is the cross-sectional nature of the data. Additionally, the mean age of the sample was 47 years, placing some in the natural menopause transition range. Thus, it is unclear whether the impact of breast cancer would be the main contributor to vasomotor symptoms (and consequently sleep disturbance and depression) in this sample. However, a large percentage (59 %) of these young BCS experienced a menopausal status change during their cancer treatments, suggesting that treatment did play an important role. Furthermore, nearly 40 % of the sample was overweight or obese, and symptoms worsen as BMI increases, particularly vasomotor symptoms early in the transition to menopause (Bromberger et al. 2011; Thurston et al. 2013). We therefore adjusted all analyses for age and BMI, and results remained significant. Given negative effects of depression on quality of life and overall health, it is critical to understand and reduce the risk for depression in young BCS.

Pharmacological treatments, such as hormone replacement therapies and antidepressants, can alleviate vasomotor symptoms in naturally transitioning women. However, hormone replacement therapy is contraindicated in BCS, potentially placing survivors at risk for cancer recurrence. Therefore, antidepressants, gabapentin, and non-pharmacological treatments (e.g., cognitive behavioral therapy, CBT) aimed at reducing menopausal symptoms (Bordeleau et al. 2007) may be helpful in alleviating depressive symptoms in this population, potentially by improving sleep. Indeed, the growing literature on CBT for hot flashes during natural menopause and after breast cancer treatment shows promise for reducing not only vasomotor symptoms but also symptoms of depression and sleep disturbance. For example, a randomized controlled trial of group CBT for hot flashes and night sweats in BCS found that CBT was effective in reducing levels of all of these symptoms (Mann et al. 2012).

The present study results suggest that improving vasomotor symptoms in young BCS may be helpful for reducing depression in this vulnerable population, in part through improvements in sleep. Clinicians should be aware of the distressing effects that vasomotor symptoms have on the psychological well-being of breast cancer patients, especially those who are young and may be transitioning early into menopause due to cancer treatments.

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