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Differences in symptom clusters before and twelve months after breast cancer surgery

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ABSTRACT

Purpose: Given the inter-relatedness among symptoms, research efforts are focused on an evaluation of symptom clusters. The purposes of this study were to evaluate for differences in the number and types of menopausal-related symptom clusters assessed prior to and at 12-months after surgery using ratings of occurrence and severity and to evaluate for changes in these symptom clusters over time.

Methods: Prior to and at 12 months after surgery, 392 women with breast cancer completed the Menopausal Symptoms Scale. Exploratory factor analyses were used to identify the symptom clusters.

Results: Of the 392 women evaluated, the mean number of symptoms (out of 46) was 13.2 (± 8.5) at enrollment and 10.9 (± 8.2) at 12 months after surgery. Using occurrence and severity, three symptom clusters were identified prior to surgery. Five symptom clusters were identified at 12 months following surgery. Two symptom clusters (i.e., pain/discomfort and hormonal) were relatively stable across both dimensions and time points. Two symptom clusters were relatively stable across both dimensions either prior to surgery (i.e., sleep/psychological/cognitive) or at 12 months after surgery (i.e., sleep). The other four clusters (i.e., irritability, psychological/cognitive, cognitive, psychological) were identified at one time point using a single dimension.

Conclusions: While some menopausal-related symptom clusters were consistent across time and dimensions, the majority of symptoms clustered together differently depending on whether they were evaluated prior to or at 12 months after breast cancer surgery. An increased understanding of how symptom clusters change over time may assist clinicians to focus their symptom assessments and management strategies.

1. Introduction

Prior to and following breast cancer treatment women experience multiple co-occurring menopausal-related symptoms (Barton and Ganz, 2015; Howard-Anderson et al., 2012). Most of this research has focused on descriptions of single menopausal-related symptoms (e.g., hot flashes) during or after chemotherapy (CTX) and/or endocrine therapy (ET) in breast cancer survivors. Given the inter-relatedness among symptoms, current research efforts are focused on an evaluation of symptom clusters (Glaus et al., 2006; Marshall et al., 2016; Seib et al., 2017).

A symptom cluster is defined as a group of two (Kim et al., 2005) or more (Dodd et al., 2001) concurrent symptoms that are related to one another through a common etiology, mechanism, variance, or outcome (Barsevick, 2016; Miaskowski et al., 2007, 2017). The identification of differences in the number and types of menopausal-related symptom clusters before and after breast cancer treatment may assist clinicians to focus both their assessments and management strategies. For example, rather than treating a single symptom, clinicians may be able to target several symptoms within a cluster (Kwekkeboom et al., 2012) and minimize the need for women to take multiple medications. For example, in a recent study (Lengacher et al., 2017), a mindfulness-based stress reduction intervention improved the severity of several symptoms within a psychological/cognitive symptom cluster. Given that relative to single symptoms, symptoms clusters are associated with poorer functional status and quality of life (QOL) (Kim et al., 2012), management of several symptoms within a cluster may improve patient outcomes. Moreover, the identification of menopausal-related symptom

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clusters may suggest a common etiology for symptoms within a cluster.

In women with breast cancer, the majority of the research on symptom clusters has evaluated common symptoms associated with cancer treatment using instruments like the Memorial Symptom Assessment Scale (MSAS) (Portenoy et al., 1994) or the MD Anderson Symptom Inventory (MDASI) (Cleeland et al., 2000) (for review see (Nguyen et al., 2011). While both the MSAS and MDASI include some symptoms that would be found on a menopausal symptom inventory like the Menopausal Symptom Scale (MSS) (Radtke et al., 2011), neither instrument assess for hot flashes, the most commonly reported menopausal-related symptom in women with (Gupta et al., 2006) and without (Woods and Mitchell, 2005) breast cancer.

In studies of individual symptoms, breast cancer patients reported bothersome symptoms prior to and following surgery and that these symptoms had a negative impact on their QOL (Denieffe et al., 2014). Yet, with the major focus on the identification of symptom clusters during treatment, no studies were identified that evaluated for menopausal-related symptom clusters prior to breast cancer surgery. Only three cross-sectional studies (Glaus et al., 2006; Marshall et al., 2016; Seib et al., 2017) evaluated for menopausal-related symptom clusters following breast cancer treatment (Supplementary Table 1). In the first study that evaluated breast cancer patients on ET, a single symptom cluster was found using symptom occurrence rates from the Clinical Checklist for Patients with Endocrine Therapy (C-PET) (Glaus et al., 2006). This single 'menopausal' cluster included: hot flashes, weight-gain, tiredness, reduced sexual interest, and vaginal dryness.

In the second study that evaluated breast cancer survivors 8 months after their cancer diagnosis (Marshall et al., 2016), menopausal-related symptom clusters were derived from the Women's Health Initiative Checklist. Five clusters were identified using dichotomous ratings of severity. These five clusters varied slightly depending on whether moderate and severe (i.e., menopausal, pain, fatigue/sleep/gastrointestinal (GI), psychological, increased weight/appetite) or severe (i.e., menopausal, pain, fatigue/psychological/GI, GI, increased weight/appetite) symptoms were evaluated. In addition, menopausal-related symptom clusters were evaluated using symptom data derived from messages on a breast cancer forum. The four clusters identified from the social media data were: pain/fatigue, menopausal/psychological, GI, and miscellaneous.

The third study compared menopausal-related symptom clusters in women with and without breast cancer (Seib et al., 2017). The symptom clusters were using the severity scores from the Greene Climacteric Scale. In the women with breast cancer, the following symptom clusters were identified: psychological, vasoactive, sensory somatic, peripheral somatic, nervous tension, and general somatic. With the exception of the general somatic symptom cluster, the same clusters were identified in women without breast cancer. However, the specific symptoms within each of the five clusters varied between these two groups of women. Across these three studies of breast cancer survivors (Glaus et al., 2006; Marshall et al., 2016; Seib et al., 2017), the menopausal-related cluster was the only consistent symptom cluster identified in patients with breast cancer. Within this cluster, hot flashes was the only consistent symptom.

While these three studies provide preliminary evidence of menopausal-related symptom clusters in breast cancer survivors (Glaus et al., 2006; Marshall et al., 2016; Seib et al., 2017), several limitations warrant consideration. The instruments and dimensions used to evaluate for symptom clusters were not consistent. In addition, all three studies evaluated for symptom clusters using only a single dimension of the symptom experience (i.e., occurrence (Glaus et al., 2006) or severity (Marshall et al., 2016; Seib et al., 2017)). Finally, time since cancer diagnosis (Glaus et al., 2006; Marshall et al., 2016; Seib et al., 2017), demographic and clinical characteristics (Marshall et al., 2016), and specific cancer treatments (Seib et al., 2017) were not reported. These limitations make it difficult to compare findings across these three studies.

Given these limitations and the paucity of research on menopausal-related symptom clusters in women prior to and following breast cancer surgery, the purposes of this study, in a sample of breast cancer patients, were to: evaluate for differences in the number and types of menopausal-related symptom clusters assessed prior to and at 12-months after surgery using ratings of occurrence and severity and to evaluate for changes in these symptom clusters over time. Given that the occurrence and severity of menopausal-related symptoms vary over the course of treatment (Ganz et al., 2011), we hypothesized that the number and types of symptom clusters would differ over time but not by dimension.

2. Methods

This study is part of a larger descriptive, longitudinal study that evaluated neuropathic pain and lymphedema in women who underwent breast cancer surgery. The methods for this study are described in detail elsewhere (Doong et al., 2015; Kyranou et al., 2013; Langford et al., 2014; McCann et al., 2012; Van Onselen et al., 2013). In brief, patients were recruited from Breast Cancer Centers located in a Comprehensive Cancer Center, two public hospitals, and four community practices. Eligibility criteria included: adult women (≥18 years) who were scheduled for unilateral breast cancer surgery; were able to read, write, and understand English; agreed to participate; and provided written informed consent. Patients were excluded if they had bilateral breast surgery and/or had distant metastases at the time of diagnosis.

2.1. Instruments

The demographic questionnaire obtained information on age, education, ethnicity, marital status, employment status, living situation, and financial status. Menopausal status was determined by the patient's response (yes/no) at the time of enrollment to the question "Have you gone through menopause yet (stopped having your menstrual cycle)?". Patients were asked to indicate if they exercised on a regular basis (yes/no). The Karnofsky Performance Status (KPS) scale was used to evaluate functional status. Patients rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms). The KPS scale has well established validity and reliability (Karnofsky et al., 1948).

The Self-Administered Comorbidity Questionnaire (SCQ) is a short and easily understood instrument that was developed to measure comorbidity in clinical and health service research settings (Sangha et al., 2003). The questionnaire consists of 13 common medical conditions that were simplified into language that could be understood without any prior medical knowledge. Patients indicated if they had the condition; if they received treatment for it (proxy for disease severity); and if it limited their activities (indication of functional limitations). SCQ scores can range from 0 to 39. The SCQ has well established validity and reliability and has been used in studies of patients with a variety of chronic conditions (Brunner et al., 2008; Cieza et al., 2006).

The Menopausal Symptoms Scale (MSS) was modified from the Seattle Women's Health Study questionnaire (Woods et al., 1999). The MSS evaluated the occurrence, severity, and distress of 46 menopausal-related symptoms. Patients were asked to indicate whether they experienced each symptom during the past week (i.e., symptom occurrence). If they experienced the symptom, they were asked to rate its severity and distress. Symptom severity was rated using a 0 (none) to 10 (intolerable) numeric rating scale (NRS). The MSS has well established validity and reliability (Woods et al., 2014).

2.2. Study procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional

Review Boards at each of the study sites. A clinician explained the study and determined patient's willingness to participate during her scheduled preoperative visit. After the visit, the clinician introduced the patient to the research nurse who met with the woman, determined eligibility, and obtained written informed consent. Then, patients completed the enrollment questionnaires an average of four days prior to surgery. For the current study, data from prior to and 12 months after surgery were analyzed. Medical records were reviewed for disease and treatment information.

2.3. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences 23 (SPSS, 2015) and MPlus Version 7.3 (Muthén, 1989; Muthén and Muthén, 1998–2015). Descriptive statistics and frequency distributions were calculated for the demographic and clinical characteristics. As part of the evaluation of symptom occurrence and severity, occurrence rates were generated for each symptom and mean severity scores were calculated for patients who reported the symptom (without zeros) and for all of the patients (with zeros included).

2.3.1. Creation of symptom clusters using exploratory factor analysis (EFA)

Four separate EFAs were done to evaluate for symptom clusters using the dichotomous ratings of symptom occurrence and ordinal ratings of symptom severity obtained prior to and at 12 months after breast cancer surgery. Factor analysis aims to identify whether correlations between a set of observed variables can be explained by a few latent, unobserved variables (i.e., factors) (Brown, 2015). The “factors” in the current study are referred to as symptom clusters (Kim et al., 2009; Miaskowski et al., 2004).

For each EFA, factor loadings were considered meaningful if the loading had an absolute value of ≥0.40 (Browne, 2001; Muthén, 1989; Muthén and Muthén, 1998–2015). While it is common to require that each item load strongly on only one factor, in this study, items that loaded with an absolute value of ≥0.40 on two factors (i.e., cross loaded), were retained and used to define both factors. The cross loading of symptoms on more than one factor may be beneficial in the interpretation of potential causal mechanisms, especially when oblique rotation is employed (Brown, 2015; Browne, 2001; Miaskowski and Aouizerat, 2007).

EFA was used to identify symptom clusters from the occurrence rates and the severity ratings of 24 out of the 46 MSS symptoms. In order to have sufficient variation and covariation to perform the EFAs, only symptoms that were present in > 18% and < 80% of the patients at both time points were included in these analyses. The Cronbach's alphas ranged from good to excellent with all 46 symptoms after and before surgery (i.e., α = .909 and .920) and with 24 symptoms before and after surgery (i.e., α = .896 and .880). Twenty-two symptoms on the MSS were excluded from the analyses due to insufficient variation in the occurrence of these symptoms. These excluded symptoms were tearful/crying spells, nervousness, panic feelings, lost sexual interest, constipation, urinary frequency, loss of interest in things, loss of appetite, heart races/pounds, abdominal bloating, diarrhea, nausea/upset stomach, swollen hands/feet, eating more than usual, indigestion, shortness of breath, skin breakout/acne, hostility, cramps, dizziness, alcohol cravings, increased sexual desire.

The occurrence items were evaluated as dichotomous variables (i.e., had versus did not have the symptom). For these EFAs, tetrachoric correlations were used to create the matrix of associations. In order to provide better estimation of the results, the 0 to 10 severity scores were recoded into: 0 (none), 1 (mild = 1 to 3), 2 (moderate = 4 to 6), and 3 (severe ≥ 7). This approach was used because the distribution of the scores on the 0 to 10 continuous scale were positively skewed, violating the bivariate normality assumption. Reducing the number of ordinal points through recoding better captured the meaning of the scale and allowed for better estimation of the covariance structure for the EFAs. For the rescored severity EFAs, polychoric correlations were used to create the matrix of associations (Muthén, 1989; Muthén and Muthén, 1998–2015).

The simple structures for the occurrence and severity EFAs were estimated using the method of unweighted least squares with geomin (i.e., oblique) rotation. The geomin rotation method was used to identify the model with the best fit (i.e., optimum number of factors using the criteria for simple structure described above). Adopting this rotational method provided an improved representation of how the factors were correlated and improved the interpretability of each factor solution (Muthén, 1989; Muthén and Muthén, 1998–2015). The unweighted least squares estimator (ulsmv: unweighted least squares parameter estimates with standard errors and a mean and variance adjusted (chi-square test using a full weight matrix (Muthén, 1989; Muthén and Muthén, 1998–2015)) was selected in order to achieve more reliable results because the scales for the MSS items were dichotomous (i.e., occurrence) and ordinal (i.e., severity).

Factor solutions were estimated for two through six factors. After examining all of the factor solutions, the factor solution with the greatest interpretability and clinical meaningfulness was selected, given that it met the criteria set for evaluating simple structure (i.e., size of item loadings, number of items on a factor).

2.3.2. Differences in number and types of symptom clusters

To evaluate the agreement among the symptoms within the same cluster using occurrence and severity ratings, within and across each assessment, we used the criteria proposed by Kirkova and Walsh (2007). In their paper, they suggested that to be in agreement with each other, at least 75% of the symptoms in the clusters should be present including the prominent and important symptom, namely the symptom with the greatest weight from the EFAs.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the patients are summarized in Table 1. The mean age of the women was 54.9 ± 11.6 years (range: 29–91 years), 41.9% were married/partnered, 24.2% lived alone, and 64.1% were postmenopausal prior to surgery. The majority of the patients was White (64.4%) and well educated (15.7 ± 2.7 years).

At enrollment, women were 9.5 ± 11.0 weeks from their cancer diagnosis. They had a mean SCQ score of 4.3 ± 2.8, with high blood pressure (30.9%), back pain (28.1%), and depression (21.9%) being the most common comorbidities. The mean KPS score was 93.2 ± 10.3. Approximately 19.9% of the patients had received neoadjuvant CTX. The majority of patients had breast conservation surgery (79.9%), 82.4% had a sentinel lymph node biopsy, and 21.7% had breast reconstruction at time of surgery. During the first 12 months after surgery, 33.5% received adjuvant CTX, 72.5% received external beam radiation therapy (RT), and 63.2% were taking ET.

3.2. Symptom occurrence and severity

The mean number of symptoms (out of 46) was 13.2 ± 8.5 at enrollment and 10.9 ± 8.2 at 12 months after surgery (Table 1). The occurrence and severity scores for the 46 symptoms are summarized in Supplementary Table 2. The severity scores are reported as: ordinal with zero including women who did not report the occurrence of the symptom; ordinal including only women who reported the occurrence of the symptom; and continuous (i.e., 0 to 10 NRS) including only women who reported the occurrence of the symptom. Across the two assessments, the most common and the most severe symptom was wake during the night and lost sexual interest, respectively.

Table 1
Demographic and clinical characteristics of the sample at enrollment (n = 398).

Demographic characteristics	Mean (SD)
Age (years)	54.9 (11.6)
Education (years)	15.7 (2.7)
	% (n)
Ethnicity	
White	64.4 (255)
Non-white	35.6 (141)
Lives alone (% yes)	24.2 (95)
Married/partnered (% yes)	41.9 (165)
Currently working for pay (% yes)	47.8 (189)
Total annual household income	
< $10,000 to $19,999	9.7 (32)
$20,000 to $99,000	52.3 (172)
≥ $100,000	38.0 (125)
Clinical characteristics	Mean (SD)
Body mass index (kg/m^2)	26.8 (6.2)
Karnofsky Performance Status score	93.2 (10.3)
Self-Administered Comorbidity Questionnaire score	4.3 (2.8)
Mean time since diagnosis (weeks)	9.5 (11.0)
Number of menopausal symptoms prior to surgery (out of 46)	13.2 (8.5)
Number of menopausal symptoms 12 months after surgery (out of 46)	10.9 (8.2)
	% (n)
Occurrence of comorbid conditions (% and number of women who reported each comorbid condition from the Self-Administered Comorbidity Questionnaire)	
Heart disease	3.8 (15)
High blood pressure	30.9 (123)
Lung disease	3.0 (12)
Diabetes	7.8 (31)
Ulcer	3.8 (15)
Kidney disease	0.8 (3)
Liver disease	2.5 (10)
Anemia	8.0 (32)
Depression	21.9 (87)
Osteoarthritis	17.3 (69)
Back pain	28.1 (112)
Rheumatoid arthritis	3.5 (14)
Exercise on a regular basis (% yes)	69.6 (275)
Postmenopausal prior to surgery (% yes)	64.1 (248)
Diagnosed with mastitis (% yes)	12.0 (47)
Diagnosed with fibrocystic disease (% yes)	19.1 (73)
Ever breast fed (% yes)	47.0 (186)
Prior hysterectomy (% yes)	13.6 (54)
Prior oophorectomy (% yes)	10.8 (43)
On HRT prior to surgery (% yes)	16.9 (67)
Stage of disease	
Stage 0	16.9 (64)
Stage I	37.7 (143)
Stage IIA and IIB	36.4 (138)
Stage IIIA, IIIB, IIIC, and IV	9.0 (34)
Estrogen receptor positive (% yes)	77.3 (307)
Progesterone receptor positive (% yes)	70.3 (279)
HER2/neu receptor positive (% yes)	16.4 (59)
Received neoadjuvant chemotherapy (% yes)	19.9 (79)
Type of surgery	
Breast conservation	79.9 (318)
Mastectomy	20.1 (80)
Reconstruction at the time of surgery (% yes)	21.7 (86)
Sentinel lymph node biopsy (% yes)	82.4 (328)
Axillary lymph node dissection (% yes)	37.5 (149)
Received adjuvant chemotherapy during the 12 months (% yes)	33.5 (112)
Received external beam radiation therapy during the 12 months (% yes)	72.5 (242)
On endocrine therapy during the 12 months (% yes)	63.2 (211)
BRCA1 and BRCA2 genetic testing	
Positive	2.0 (8)
Negative	10.7 (42)
Not done	87.3 (344)

Abbreviations: BRCA = breast cancer; HER2/neu = human epidermal growth factor receptor 2; HRT = hormone replacement therapy; kg = kilogram; m^2 = meters squared; SD = standard deviation.

Table 2
Exploratory factor analysis using ratings of symptom occurrence prior to breast cancer surgery.[a]

Symptom	Factor 1	Factor 2	Factor 3	Factor 4
	Irritability Symptom Cluster	Pain/ Discomfort Symptom Cluster	Psychological/ Cognitive/Sleep Symptom Cluster	Hormonal Symptom Cluster
Anger	**0.776**	−0.028	0.021	0.150
Impatience	**0.738**	0.046	0.023	0.291
Irritability	**0.797**	0.020	0.011	0.314
Mood swings	**0.565**	0.106	0.086	0.248
Tension	**0.566**	0.036	**0.453**	−0.121
Backache or neckache	0.332	**0.578**	−0.040	−0.059
General body aches	0.059	**0.973**	−0.111	−0.007
Joint pain or stiffness	−0.064	**0.745**	0.070	0.023
Numbness or tingling	−0.285	**0.675**	0.221	0.164
Painful/tender breasts	0.174	**0.520**	0.090	−0.267
Weight gain	0.061	**0.409**	−0.129	0.302
Anxiety	0.390	−0.050	**0.644**	−0.128
Depression	0.392	−0.001	**0.463**	0.012
Difficulty concentrating	0.385	−0.072	**0.586**	0.123
Difficulty falling asleep	0.022	0.077	**0.737**	0.023
Fatigue or tiredness	0.101	0.373	**0.535**	0.027
Wake during the night	−0.088	0.357	**0.708**	0.076
Waking too early	0.043	0.324	**0.567**	−0.070
Daytime sweats	0.145	−0.022	−0.020	**0.825**
Hot flashes	−0.043	0.008	0.094	**0.939**
Night sweats	0.091	0.043	0.024	**0.839**
Vaginal dryness	−0.044	0.260	0.017	**0.431**
Forgetfulness	0.241	0.145	0.388	0.197
Headache	0.375	0.389	−0.011	0.009
Total number of symptoms in the cluster	5	6	8	4

Rotation method: Geomin (oblique) rotation.
Items in bold are the symptoms that loaded on each factor.
[a] Extraction method: unweighted least squares.

3.3. Symptom clusters based on occurrence rates

As shown in Table 2, prior to surgery, a four factor solution indicated the best fit for the occurrence data. Factor 1 that included five symptoms (i.e., anger, impatience, irritability, mood swings, tension) was named the irritability symptom cluster. Factor 2 that consisted of six symptoms (i.e., backache or neckache, general body aches, joint pain or stiffness, numbness or tingling, painful/tender breasts, weight gain) was named the pain/discomfort symptom cluster. Factor 3 that included eight symptoms (i.e., tension, anxiety, depression, difficulty concentrating, difficulty falling asleep, fatigue or tiredness, wake during the night, waking too early) was named the psychological/cognitive/sleep symptom cluster. Factor 4 that consisted of four symptoms (i.e., daytime sweats, hot flashes, night sweats, vaginal dryness) was named the hormonal symptom cluster. Two symptoms (i.e., forgetfulness and headache) did not load on any factor.

As shown in Table 3, at 12 months after surgery, a four factor solution was the best fit for the occurrence data. Factor 1 that included ten symptoms (i.e., anger, anxiety, depression, difficulty concentrating, fatigue or tiredness, forgetfulness, impatience, irritability, mood swings, tension) was named the psychological/cognitive symptom cluster. Factor 2 that included three symptoms (i.e., daytime sweats,

Table 3
Exploratory factor analysis using ratings of symptom occurrence 12 months after breast cancer surgery.[a]

Symptom	Factor 1	Factor 2	Factor 3	Factor 4
	Psychological/ Cognitive Symptom Cluster	Hormonal Symptom Cluster	Pain/ Discomfort Symptom Cluster	Sleep Symptom Cluster
Anger	**0.823**	0.205	−0.006	−0.183
Anxiety	**0.913**	−0.122	−0.129	0.028
Depression	**0.873**	0.035	−0.095	0.024
Difficulty concentrating	**0.687**	0.091	0.054	0.090
Fatigue or tiredness	**0.510**	−0.033	0.182	0.239
Forgetfulness	**0.587**	0.020	0.189	0.096
Impatience	**0.889**	−0.044	−0.049	−0.024
Irritability	**0.995**	0.030	0.038	−0.268
Mood swings	**0.795**	−0.067	0.011	0.093
Tension	**0.823**	−0.002	0.042	−0.029
Daytime sweats	0.044	**0.922**	0.017	−0.093
Hot flashes	0.003	**0.885**	0.008	0.093
Night sweats	−0.025	**0.872**	−0.040	0.159
Backache or neckache	0.058	0.000	**0.536**	0.113
General body aches	−0.022	0.020	**0.902**	−0.003
Joint pain or stiffness	0.011	−0.032	**0.751**	−0.070
Difficulty falling asleep	0.249	0.130	0.111	**0.505**
Wake during the night	−0.011	0.182	0.080	**0.822**
Waking too early	0.035	−0.013	−0.129	**0.966**
Headache	0.121	0.085	0.383	0.116
Numbness or tingling	0.317	0.145	0.121	0.021
Painful/tender breasts	0.043	0.020	0.238	0.182
Vaginal dryness	0.043	0.020	0.238	0.182
Weight gain	0.143	0.192	0.14	0.174
Total number of symptoms in the cluster	10	3	3	3

Rotation method: Geomin (oblique) rotation.
Items in bold are the symptoms that loaded on each factor.
[a] Extraction method: unweighted least squares.

hot flashes, night sweats) was named the hormonal symptom cluster. Factor 3 that included three symptoms (i.e., backache or neckache, general body aches, joint pain or stiffness) was named the pain/discomfort symptom cluster. Factor 4 that included three symptoms (i.e., difficulty falling asleep, wake during the night, waking too early) was named the sleep symptom cluster. Five symptoms (i.e., headache, numbness or tingling, painful/tender breasts, vaginal dryness, weight gain) did not load on any factor.

3.4. Symptom clusters based on severity ratings

As shown in Table 4, prior to surgery, a three factor solution was the best fit for the severity data. Factor 1 that included fourteen symptoms (i.e., anger, anxiety, depression, difficulty concentrating, difficulty falling asleep, fatigue or tiredness, forgetfulness, headache, impatience, irritability, mood swings, tension, wake during the night, waking too early) was named the psychological/cognitive/sleep symptom cluster. Factor 2 that included seven symptoms (i.e., daytime sweats, general body aches, hot flashes, night sweats, numbness or tingling, vaginal dryness, weight gain) was named the hormonal symptom cluster. Factor 3 that consisted of four symptoms (i.e., general body aches, numbness or tingling, backache or neckache, joint pain or stiffness) was named the pain/discomfort symptom cluster. Only painful/tender breasts did not load on any factor.

Table 4
Exploratory factor analysis using ratings of symptom severity prior to breast cancer surgery.[a]

Symptom	Factor 1	Factor 2	Factor 3
	Psychological/ Cognitive/Sleep Symptom Cluster	Hormonal Symptom Cluster	Pain/Discomfort Symptom Cluster
Anger	**0.713**	−0.110	0.017
Anxiety	**0.925**	−0.272	−0.125
Depression	**0.773**	−0.097	−0.120
Difficulty concentrating	**0.837**	0.027	−0.132
Difficulty falling asleep	**0.655**	0.068	0.013
Fatigue or tiredness	**0.600**	0.152	0.161
Forgetfulness	**0.557**	0.251	0.002
Headache	**0.411**	0.024	0.280
Impatience	**0.754**	0.015	−0.004
Irritability	**0.729**	0.070	0.019
Mood swings	**0.692**	0.075	0.024
Tension	**0.977**	−0.309	−0.002
Wake during the night	**0.535**	0.304	0.056
Waking too early	**0.569**	0.075	0.089
Daytime sweats	0.036	**0.835**	−0.140
General body aches	0.003	**0.427**	**0.740**
Hot flashes	−0.016	**0.962**	−0.100
Night sweats	0.065	**0.849**	−0.096
Numbness or tingling	−0.048	**0.506**	**0.443**
Vaginal dryness	−0.043	**0.485**	0.118
Weight gain	0.035	**0.413**	0.283
Backache or neckache	0.342	−0.011	**0.507**
Joint pain or stiffness	0.018	0.377	**0.569**
Painful/tender breasts	0.310	−0.092	0.362
Total number of symptoms in the cluster	14	7	4

Rotation method: Geomin (oblique) rotation.
Items in bold are the symptoms that loaded on each factor.
[a] Extraction method: unweighted least squares.

As shown in Table 5, at 12 months after surgery, a five factor solution was the best fit for the severity data. Factor 1 that included seven symptoms (i.e., anger, anxiety, depression, impatience, irritability, mood swings, tension) was named the psychological cluster. Factor 2 that included four symptoms (difficulty concentrating, fatigue or tiredness, forgetfulness, painful/tender breasts) was named the cognitive symptom cluster. Factor 3 that included three symptoms (i.e., daytime sweats, hot flashes, night sweats) was named the hormonal symptom cluster. Factor 4 that included four symptoms (i.e., backache or neckache, general body aches, headache, joint pain or stiffness) was named the pain/discomfort symptom cluster. Factor 5 that included three symptoms (i.e., difficulty falling asleep, wake during the night, wake too early) was named the sleep symptom cluster. Three symptoms (i.e., numbness/tingling, vaginal dryness, and weight gain) did not load on any factor.

3.5. Agreement in the number and types of symptom clusters

Table 6 presents a summary of the factor loadings and percentage agreement among the symptoms within each cluster that were identified regardless of dimension (i.e., occurrence and severity) and time (i.e., prior to surgery, 12 months after surgery). For the pain/discomfort symptom cluster, that was identified for both dimensions and at both time points, the total number of symptoms ranged from three to six and the percent agreement ranged from 42.9% to 85.7%. Across both

Table 5
Exploratory factor analysis using ratings of symptom severity 12 months after breast cancer surgery.[a]

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Psychological Symptom Cluster	Cognitive Symptom Cluster	Hormonal Symptom Cluster	Pain/Discomfort Symptom Cluster	Sleep Symptom Cluster
Anger	**0.881**	−0.070	0.180	0.055	−0.132
Anxiety	**0.879**	−0.028	−0.149	−0.072	0.082
Depression	**0.706**	0.095	0.026	0.001	0.036
Impatience	**0.793**	0.103	0.020	−0.115	0.010
Irritability	**0.946**	0.035	0.026	0.030	−0.137
Mood swings	**0.676**	0.109	−0.016	0.017	0.120
Tension	**0.724**	0.106	−0.049	0.030	0.028
Difficulty concentrating	0.207	**0.678**	0.032	−0.014	0.044
Fatigue or tiredness	0.231	**0.420**	−0.078	0.146	0.199
Forgetfulness	−0.005	**0.981**	0.069	−0.004	−0.065
Painful/tender breasts	0.063	**0.411**	−0.107	0.204	0.004
Daytime sweats	0.111	−0.036	**0.897**	0.059	−0.062
Hot flashes	−0.026	0.150	**0.848**	−0.011	0.106
Night sweats	−0.008	0.018	**0.832**	−0.035	0.189
Backache or neckache	0.123	0.015	−0.042	**0.618**	0.076
General body aches	−0.058	0.016	0.028	**0.897**	0.006
Headache	0.260	−0.069	0.045	**0.466**	0.012
Joint pain or stiffness	0.008	0.118	0.023	**0.625**	−0.020
Difficulty falling asleep	0.132	0.154	0.022	0.084	**0.518**
Wake during the night	0.051	−0.062	0.138	0.021	**0.883**
Waking too early	−0.065	0.043	−0.007	−0.002	**0.891**
Numbness/tingling	0.299	0.077	0.108	0.097	0.071
Vaginal dryness	0.016	0.092	0.037	0.218	0.160
Weight gain	0.019	0.301	0.163	0.131	0.055
Total number of symptoms in the cluster	7	4	3	4	3

Rotation method: Geomin (oblique) rotation.
Items in bold are the symptoms that loaded on each factor.
[a] Extraction method: unweighted least squares.

Table 6
Summary of symptom clusters that were relatively consistent across dimensions and time.

Symptom Cluster	Symptoms Within the Cluster	Occurrence		Severity	
		Time 1	Time 2	Time 1	Time 2
Pain/Discomfort Symptom Cluster	Backache/ neckache	0.578	0.536	0.507	0.618
	General body aches	0.973	0.902	0.740	0.897
	Joint pain or stiffness	0.745	0.751	0.569	0.625
	Numbness or tingling	0.675		0.443	
	Painful/tender breasts	0.520			
	Weight gain	0.409			
	Headache				0.466
	Percent agreement	85.7	42.9	57.1	57.1
Hormonal Symptom Cluster	Daytime sweats	0.825	0.922	0.835	0.897
	Hot flashes	0.939	0.885	0.962	0.848
	Night sweats	0.839	0.872	0.849	0.832
	Vaginal dryness	0.431		0.485	
	General body aches			0.427	
	Numbness or tingling			0.506	
	Weight gain			0.413	
	Percent agreement	57.1	42.9	100.0	42.9

dimensions and assessments, the three symptoms that were included in the pain/discomfort cluster were: backache or neckache, general body aches, and joint pain or stiffness.

For the hormonal symptom cluster, that was identified for both dimensions and at both time points, the total number of symptoms ranged from 3 to 7 and the percent agreement ranged from 42.9% to 100.0%. Across both dimensions and assessments, the three symptoms that were included in the hormonal cluster were: daytime sweats, hot flashes, and night sweats.

3.6. Differences in the number and types of symptom clusters

Table 7 presents a summary of the factor loadings and symptoms within each cluster that were different across time (i.e., prior to surgery, 12 months after surgery). For the psychological/cognitive/sleep symptom cluster that was identified prior to surgery using both dimensions, the total number of symptoms ranged from 8 to 14. The eight symptoms included in this cluster were: tension, anxiety, depression, difficulty concentrating, difficulty falling asleep, fatigue or tiredness, wake during the night, and waking too early.

The irritability cluster was only identified for the occurrence dimension assessed prior to surgery. The five symptoms included in this cluster were: anger, impatience, irritability, mood swings, and tension.

The sleep symptom cluster was identified using both occurrence and severity dimensions assessed at 12 months after surgery. The three symptoms in this cluster were: difficulty falling asleep, wake during the night, and waking too early.

The psychological/cognitive symptom cluster was identified only for the occurrence dimension assessed at 12 months after surgery. The ten symptoms included in this cluster were: anger, anxiety, depression, difficulty concentrating, fatigue or tiredness, forgetfulness, impatience, irritability, mood swings, and tension.

The psychological symptom cluster was identified only for the severity dimension assessed at 12 months after surgery. The seven symptoms included in this cluster were: anger, anxiety, depression, impatience, irritability, mood swings, and tension.

The cognitive symptom cluster was identified only for the severity dimension assessed at 12 months after surgery. The four symptoms

Table 7
Summary of symptom clusters that varied across time.

Symptom Cluster	Occurrence		Severity	
	Symptom	Factor Loading	Symptom	Factor Loading
Time 1 – Prior to Surgery				
Psychological/ Cognitive/ Sleep Symptom Cluster	Tension	0.435	Tension	0.977
	Anxiety	0.644	Anxiety	0.935
	Depression	0.463	Depression	0.733
	Difficulty concentrating	0.586	Difficulty concentrating	0.837
	Difficulty falling asleep	0.737	Difficulty falling asleep	0.655
	Fatigue or tiredness	0.535	Fatigue or tiredness	0.600
	Wake during the night	0.708	Wake during the night	0.535
	Waking too early	0.567	Waking too early	0.569
			Anger	0.713
			Forgetfulness	0.557
			Headache	0.411
			Impatience	0.754
			Irritability	0.729
			Mood swings	0.692
Irritability Symptom Cluster	Anger	0.778	*Not Identified*	
	Impatience	0.738		
	Irritability	0.797		
	Mood swings	0.565		
	Tension	0.566		
Time 2 – 12 Months After Surgery				
Sleep Symptom Cluster	Difficulty falling asleep	0.505	Difficulty falling asleep	0.518
	Wake during the night	0.822	Wake during the night	0.883
	Waking too early	0.966	Waking too early	0.891
Psychological/ Cognitive Symptom Cluster	Anger	0.823	*Not Identified*	
	Anxiety	0.913		
	Depression	0.873		
	Difficulty concentrating	0.687		
	Fatigue or tiredness	0.510		
	Forgetfulness	0.587		
	Impatience	0.889		
	Irritability	0.995		
	Mood swings	0.795		
	Tension	0.823		
Psychological Symptom Cluster	*Not Identified*		Anger	0.881
			Anxiety	0.879
			Depression	0.706
			Impatience	0.793
			Irritability	0.946
			Mood swings	0.676
			Tension	0.724
Cognitive Symptom Cluster	*Not Identified*		Difficulty concentrating	0.678
			Fatigue or tiredness	0.420
			Forgetfulness	0.981
			Painful/tender breasts	0.411

included in this cluster were: difficulty concentrating, fatigue or tiredness, forgetfulness, and painful/tender breasts.

4. Discussion

This study is the first to assess for differences in the number and types of menopausal-related symptom clusters in women before and at 12 months after breast cancer surgery using occurrence rates and severity ratings. Our hypothesis, regarding the consistency in number and types of symptom clusters across dimensions and time points, was only partially supported. While eight distinct symptom clusters were identified across the two dimensions and time points, only two (i.e., pain/discomfort and hormonal) were relatively stable across both dimensions and time points. In addition, two symptom clusters were relatively stable across both dimensions, either prior to surgery (i.e., sleep/psychological/cognitive) or at 12 months after surgery (i.e., sleep). The other four clusters (i.e., irritability, psychological/cognitive, cognitive, psychological) were only identified at one time point using a single dimension. In the remainder of the discussion, the two symptom clusters that were the same across all four EFAs will be discussed first followed by a discussion of the six distinct symptom clusters.

4.1. Consistent symptom clusters

4.1.1. Pain/discomfort symptom cluster

The pain/discomfort cluster was identified using both dimensions and at both assessment times. While the number of symptoms in this cluster ranged from three to six, backache/neckache, general body ache, and joint pain or stiffness were the common symptoms across all four EFAs. This finding is consistent with previous studies of symptom clusters in healthy women (Cray et al., 2013) as well as in women during (Phligbua et al., 2013; Suwith et al., 2008) and after (Fu et al., 2009; Marshall et al., 2016; Roiland and Heidrich, 2011) breast cancer treatment.

While this 'pain-like' cluster had various names (i.e., pain (Cray et al., 2013; Fu et al., 2009; Marshall et al., 2016), pain/discomfort (Suwith et al., 2008), discomfort (Phligbua et al., 2013), musculoskeletal (Roiland and Heidrich, 2011)), backache, joint pain, and headache were the consistent symptoms regardless of whether healthy women (Cray et al., 2013) or women after breast cancer treatment were assessed and regardless of the symptom dimension evaluated (i.e., occurrence (Marshall et al., 2016), severity (Fu et al., 2009), or bother (Roiland and Heidrich, 2011)). In contrast, in studies of patients with breast cancer undergoing CTX or RT, while joint pain (Phligbua et al., 2013) and numbness and tingling (Phligbua et al., 2013; Suwith et al., 2008) were found in the pain cluster, other symptoms in this cluster included: dry mouth, feeling irritable, dizziness, difficulty concentrating, vaginal dryness, worrying, skin changes, and lack of energy. These inconsistent findings may be related to the symptom assessment instrument used and the timing of the assessments.

Despite these inconsistencies, a growing body of evidence suggests that a pain cluster (i.e., joint pain, back pain, headache) occurs prior to breast cancer surgery and appears to persist well into survivorship. Of note, in our study, all three symptoms occurred in over 20% of the women and were in the moderate to severe range at both assessments. Given the inter-relationships among symptoms and the high occurrence of joint pain with aromatase inhibitors (Glaus et al., 2006), future studies need to evaluate the underlying mechanisms for the symptoms within this cluster. Clinicians need to assess for the specific types and causes of pain throughout the course of breast cancer treatment.

4.1.2. Hormonal symptom cluster

A hormonal symptom cluster was identified across all four EFAs. The total number of symptoms in this cluster ranged from three to seven. Regardless of dimension or time, daytime sweats, hot flashes, and night sweats were the three vasomotor symptoms included in this cluster. While the names for this cluster varied (i.e., menopausal (Glaus et al., 2006; Huang et al., 2016; Marshall et al., 2016), hormonal (Fu et al., 2009; Roiland and Heidrich, 2011; Yates et al., 2015), vasoactive (Seib et al., 2017), and vasomotor (Cray et al., 2013; Mitchell and Woods, 1996)), similar clusters were identified in healthy women (Avis et al., 2001; Cray et al., 2013) and in women with breast (Cray et al., 2013; Fu et al., 2009; Glaus et al., 2006; Marshall et al., 2016; Mitchell and Woods, 1996; Roiland and Heidrich, 2011; Seib et al., 2017),

ovarian (Huang et al., 2016), or heterogeneous (Yates et al., 2015) cancer diagnoses.

Across these studies, the consistent symptoms included hot flashes (Avis et al., 2001; Cray et al., 2013; Fu et al., 2009; Glaus et al., 2006; Marshall et al., 2016; Mitchell and Woods, 1996; Phligbua et al., 2013; Roiland and Heidrich, 2011; Seib et al., 2017), night sweats (Avis et al., 2001; Marshall et al., 2016; Mitchell and Woods, 1996; Phligbua et al., 2013; Seib et al., 2017), vaginal dryness (Avis et al., 2001; Glaus et al., 2006; Marshall et al., 2016; Roiland and Heidrich, 2011), lost sexual interest (Fu et al., 2009; Glaus et al., 2006; Seib et al., 2017), and weight gain (Glaus et al., 2006; Marshall et al., 2016; Roiland and Heidrich, 2011). While not found in our hormonal cluster, psychological symptoms (i.e., mood swings (Marshall et al., 2016; Phligbua et al., 2013; Roiland and Heidrich, 2011), depression (Marshall et al., 2016; Roiland and Heidrich, 2011), anxiety (Roiland and Heidrich, 2011), irritated (Huang et al., 2016)) were included in this cluster in previous studies. These variable associations between vasomotor and psychological symptoms are well established and may be related to the multiple and complex etiologies for hormonal symptoms (for review see Avis et al., 2005) and differences in the symptoms included on the various assessment instruments.

Consistent with a previous study (Savard et al., 2009), in our study, occurrence rates of and severity ratings for hot flashes and daytime and night sweats increased from before to 12 months after surgery (see Supplemental Table 2). Given that hormonal symptoms are common and severe in women treated for breast cancer, these symptoms need to be added to multidimensional instruments like the MSAS (Portenoy et al., 1994) and MDASI (Cleeland et al., 2000).

4.2. Variable symptom clusters

In our study, psychological, cognitive, and sleep symptoms clustered together differently depending on whether the EFAs were conducted before or at 12 months after surgery. Prior to surgery, regardless of the symptom dimension considered, these symptoms loaded on one factor that was named the psychological/cognitive/sleep cluster. In addition, five psychological symptoms formed a distinct irritation cluster using occurrence ratings prior to surgery. Of note, at 12 months after surgery, these same symptoms formed two (i.e., psychological/cognitive, sleep disturbance) or three (i.e., psychological, cognitive, sleep disturbance) distinct clusters depending on whether occurrence rates or severity ratings were used in the EFAs, respectively.

4.2.1. Clusters with a combination of psychological, cognitive, and sleep symptoms

Symptom clusters that include psychological, cognitive, and sleep symptoms are common in patients with (Bender et al., 2005; Evangelista and Santos, 2012; Fu et al., 2009; Huang et al., 2016; Hwang et al., 2016; Kim et al., 2008; Marshall et al., 2016; Phligbua et al., 2013; Reich et al., 2017; Seib et al., 2017; Suwith et al., 2008) and without (Avis et al., 2001; Cray et al., 2013) cancer. For example, in healthy women across four menopausal stages (Cray et al., 2013), a mood/cognitive/nervous cluster was identified that included six symptoms that were similar to our psychological/cognitive/sleep cluster (i.e., depression, difficulty concentrating, tiredness, forgetfulness, irritability, tension).

Moreover, most ‘psychological’ clusters found in studies of women during treatment for breast (Kim et al., 2008; Phligbua et al., 2013; Suwith et al., 2008) or ovarian (Huang et al., 2016; Hwang et al., 2016) cancer or after breast cancer treatment (Bender et al., 2005; Evangelista and Santos, 2012; Fu et al., 2009; Marshall et al., 2016; Reich et al., 2017; Seib et al., 2017), included cognitive and/or sleep symptoms. For example, a psychoneurological cluster was found in breast cancer patients before, during, and after RT (Kim et al., 2008). Although this cluster consisted of several symptoms that were similar to our psychological/cognitive/sleep cluster (i.e., depressed mood, fatigue, and insomnia (Kim et al., 2008)), it did not vary over time. These inconsistent findings are likely due to differences in the instruments used and the timing of assessments (Kim et al., 2008).

To date, only a limited number of studies have evaluated underlying mechanisms that may contribute to a psychoneurological symptom cluster in cancer patients (for reviews see Miaskowski et al., 2017; Starkweather et al., 2013b). In the two studies that evaluated associations between cytokine levels and this cluster in breast cancer patients, higher symptom burden was associated with several cytokines (e.g., interleukin (IL)3, IL5, IL6, IL7) (Starkweather et al., 2013a) and C-reactive protein (Starkweather et al., 2017). Additional mechanisms that may underlie this cluster include: dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis (Thornton et al., 2010) or stress-induced epigenetic changes in neuroendocrine-immune signaling pathways (Lutgendorf and Sood, 2011). Further research is warranted to confirm these preliminary findings.

4.2.2. Clusters of distinct psychological, cognitive, and sleep symptoms

Symptom clusters that contain distinct psychological, cognitive, or sleep symptoms, are less common in the literature. To our knowledge, only four studies identified distinct psychological (Bender et al., 2005; Fu et al., 2009; Reich et al., 2017), cognitive (Bender et al., 2005; Reich et al., 2017; Roiland and Heidrich, 2011), and/or sleep (Roiland and Heidrich, 2011) clusters in women with breast cancer. The consistent symptoms across these three distinct clusters were: anxiety and depression for psychological (Bender et al., 2005; Fu et al., 2009; Reich et al., 2017); memory problems (Bender et al., 2005; Reich et al., 2017; Roiland and Heidrich, 2011) and difficulty concentrating (Bender et al., 2005; Roiland and Heidrich, 2011) for cognitive; and difficulty falling asleep, wake during the night, and waking too early (Roiland and Heidrich, 2011) for sleep.

Of interest and consistent with our study, all of these distinct symptom clusters were identified in women after completion of primary breast cancer treatment (i.e., surgery and adjuvant CTX and/or RT). Moreover, findings from a randomized controlled trial that evaluated the impact of mindfulness based stress reduction (MBSR) on symptom cluster burden in breast cancer survivors (Reich et al., 2017), suggested improvements in the psychological cluster after six weeks of MBSR. Of note, symptom burden associated with the cognitive and physical clusters did not improve. These findings provide initial evidence of distinct cognitive, psychological, and sleep symptom clusters after breast cancer treatment (Bender et al., 2005; Fu et al., 2009; Reich et al., 2017; Roiland and Heidrich, 2011). Additional research is warranted to confirm these findings and to evaluate for common and distinct underlying mechanisms.

4.2.3. Hypotheses to explain these variable symptom clusters

Similar to our study, previous findings suggest that associations between symptoms vary over time. For example, Sanford and colleagues (Sanford et al., 2014) found that while fatigue, anxiety, and depression were strongly correlated before CTX, fatigue and sleep were highly correlated after CTX. In addition, in a study of a pre-specified symptom cluster (i.e., sleep, depression, and fatigue), correlations among these three symptoms varied over the three assessments that were done before and after adjuvant CTX (Ho et al., 2015).

One potential explanation for the differences in the number and types of symptom clusters is that the etiologies and associated mechanisms for these symptoms at the two assessment times are distinct. For example, prior to surgery, women reported a high level of distress and co-occurring psychoneurological symptoms, which negatively impacted their social and emotional functioning and overall QOL (Denieffe et al., 2014; Doong et al., 2015; Kyranou et al., 2013; McCann et al., 2012; Van Onselen et al., 2013). Consistent with these findings, women in our study reported relatively higher occurrence rates and severity scores for these types of symptoms (i.e., fatigue, anxiety, irritability, difficulty concentrating, tension, depression, anger, mood

swings, nervousness) before as compared to after surgery. For example, from before to after surgery, the occurrence rates for anxiety, depression, and difficulty concentrating decreased by 41%, 27%, and 37%, respectively. It is plausible that the increased stress associated with a cancer diagnosis and the impending surgery may contribute to the higher occurrence rates for these co-occurring symptoms as well as to the psychological/cognitive/sleep and irritability clusters found in our study prior to surgery.

However, at one year after surgery, most if not all of these women were cancer survivors. At this time, the majority of the women in our study had completed their adjuvant CTX and/or RT and was on ET. Therefore, it is possible that the etiologies and mechanisms for these symptoms were treatment-related and/or associated with survivorship concerns (e.g., fear of recurrence). For example, cognitive changes after cancer treatment are well documented and may be due to a variety of treatment-related toxicities (e.g., inflammation, peripheral tissue damage, estrogen deprivation) (Merriman et al., 2013). Hence, in this example, the mechanisms that contribute to treatment-related cognitive changes may be different than those that contribute to stress-induced changes prior to surgery. Given that this study is the first to evaluate for differences in the number and types of symptom clusters from before to 12 months after surgery, these findings and hypotheses warrant confirmation in future studies.

4.3. Limitations

Several limitations warrant consideration. Given that the majority of women in our study were diagnosed with stage I and II breast cancer, our findings may not generalize to women with advanced stage disease. Because we used EFA to create the symptom clusters, symptoms with lower occurrence rates could not be included in the analysis. Therefore, it is possible that different clusters would be identified, if these symptoms were included in the EFAs. Of note, in a previous study (Ho et al., 2015), the pre-specified symptom cluster varied based on patients' age, menopausal status, and cancer treatments. Future studies need to evaluate for differences in symptom clusters using a variety of demographic and clinical characteristics. In addition, given that the MSS assesses menopausal-related symptoms, more common symptom clusters (e.g., sickness behavior) may have been missed. While two time points were evaluated, the inclusion of a third assessment, perhaps during treatment would provide additional insights into changes in symptom clusters over time. The primary reason for refusal was being overwhelmed with the cancer diagnosis. Therefore, our findings may underestimate the symptom burden of these women. Lastly, the majority of our sample was White and well educated, which limits the generalizability of our findings.

4.4. Implications for clinical practice and research

Findings from this study confirm that women with breast cancer experience multiple co-occurring menopausal-related symptoms at two distinct points in their cancer treatment trajectory. Of note, the most common and severe symptoms varied depending on whether symptoms were assessed prior to or at 12 months after surgery. In addition, while two clusters were consistent at both assessments, two clusters were time but not dimension dependent. An increased understanding of how symptom clusters change over time may assist clinicians to better focus their symptom assessment and management strategies. For example, in response to a patient's report of a single symptom (e.g., depression), clinicians may assess the occurrence and severity of additional symptoms within the cluster (e.g., difficulty concentrating and difficulty falling asleep). In addition, our findings suggest that comprehensive evaluations of patient-reported outcomes are warranted as part of survivorship care plans. These evaluations should assess multiple dimensions of the symptom experience (e.g., occurrence, severity) and be done at multiple time points across the cancer treatment trajectory. Given the high occurrence rates and severity scores for the psychological, sleep, and cognitive symptoms prior to surgery, referrals to mental health clinicians or social workers may help women better manage these symptoms.

Given that this study is the first to evaluate for menopausal-related symptom clusters in women before and after breast cancer surgery, additional studies are needed to confirm our findings. Research should focus on the identification of symptom clusters at different points across the treatment trajectory. In addition, future studies should evaluate for differences in the number and types of symptom clusters based on individual factors (e.g., menopausal status, age, types of treatment). For example, the occurrence and severity of hot flashes vary across menopausal stages and cancer treatments. Therefore, future studies should evaluate for these characteristics. Finally, associations between phenotypic and genetic characteristics and symptom clusters warrant evaluation. These investigations may support intervention studies that target multiple co-occurring symptoms and symptom clusters.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejon.2017.12.003.

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