Title

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DIFFERENCES IN SYMPTOM CLUSTERS IDENTIFIED USING SYMPTOM OCCURRENCE RATES VERSUS SEVERITY RATINGS IN PATIENTS WITH BREAST CANCER UNDERGOING CHEMOTHERAPY

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Abstract

Purpose—One of the unanswered questions in symptom clusters research is whether the number and types of symptom clusters vary based on the dimension of the symptom experience used to create the clusters. Given that patients with breast cancer receiving chemotherapy (CTX), report between 10 and 32 concurrent symptoms and studies of symptom clusters in these patients are limited, the purpose of this study, in breast cancer patients undergoing CTX (n=515), was to identify whether the number and types of symptom clusters differed based on whether symptom occurrence rates or symptom severity ratings were used to create the clusters.

Methods—A modified version of the Memorial Symptom Assessment Scale was used to assess for the occurrence and severity of 38 symptoms, one week after the administration of CTX. Exploratory factor analysis was used to extract the symptom clusters.

Results—Both the number and types of symptom clusters were similar using symptom occurrence rates or symptom severity ratings. Five symptom clusters were identified using symptom occurrence rates (i.e., *psychological, hormonal, nutritional, gastrointestinal, epithelial*). Six symptom clusters (i.e., *psychological, hormonal, nutritional, gastrointestinal, epithelial, chemotherapy neuropathy*) were identified using symptom severity ratings. Across the two dimensions, the specific symptoms within each of the symptom clusters were similar.

Conclusions—Identification of symptom clusters in patients with breast cancer may be useful in guiding symptom management interventions. Future studies are warranted to determine if symptom clusters remain stable over a cycle of CTX in patients with breast cancer.

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Keywords

symptoms; symptom clusters; breast cancer; chemotherapy; exploratory factor analysis; symptom occurrence; symptom severity

INTRODUCTION

Chemotherapy (CTX) is one of the main treatments for primary and metastatic breast cancer. Previous studies found that patients with breast cancer who receive neoadjuvant or adjuvant CTX reported between 10 (Miaskowski et al., 2014) and 32 (Suwisith et al., 2008) concurrent symptoms. This wide variation in occurrence rates demonstrates the significant inter-individual variability in patients' symptom experiences (Miaskowski et al., 2014). This variability may be due to a number of factors including: the patients' stage of disease, types of treatment, the presence of comorbidities, the symptom assessment instrument used, or the timing of the symptom assessment.

Rather than evaluate single symptoms, current research is focused on an evaluation of symptom clusters in oncology patients (Miaskowski, 2016; Miaskowski et al., 2007; Miaskowski et al., 2017). Symptom clusters are defined as *"two or more symptoms that are related to each other, occur together, composed of stable groups of symptoms, are independent of other clusters and may reveal specific underlying concepts of symptoms"* [p. 278] (Kim et al., 2005). An evaluation of symptom clusters in patients with breast cancer may assist with the identification of symptoms that share a common etiology as well as lead to the development of more tailored treatment regimens.

While research on symptom clusters in oncology patients is progressing (Miaskowski, 2016; Miaskowski et al., 2017), several important questions remain unanswered. One question is whether the number and types of symptom clusters differ depending on the dimensions used to create the clusters. In addition, since most of the studies of symptom clusters were done using samples of patients who were heterogeneous, in terms of their cancer diagnoses and/or cancer treatments (Chen and Lin, 2007; Chen and Tseng, 2006; Karabulut et al., 2010; Molassiotis et al., 2010; Skerman et al., 2012; Yamagishi et al., 2009), research is needed on symptom clusters in patients with a single cancer diagnosis (i.e., breast cancer) and a specific cancer treatment (i.e., CTX).

Only six studies were identified that evaluated symptom clusters in patients with breast cancer (Albusoul et al., 2017; Bender et al., 2005; Kim et al., 2008; Lengacher et al., 2012; Phligbua et al., 2013; Suwisith et al., 2008). However, only one of these studies used a multidimensional symptom inventory (i.e., Memorial Symptom Assessment Scale (MSAS) (Portenoy et al., 1994b) to evaluate for differences in the number and types of symptom clusters in Thai women undergoing CTX for breast cancer (Suwisith et al., 2008). When severity scores were used in an exploratory factor analysis (EFA) (Suwisith et al., 2008), four symptom clusters (i.e., emotions related symptoms, gastrointestinal (GI) and fatigue related symptoms, image related cutaneous symptoms, pain related discomfort symptoms) were identified. The number of symptoms within these clusters ranged from 3 (i.e., numbness/tingling, pain, dry mouth) to 9 (i.e., feeling sad, worrying, feeling irritable, feeling

nervous, “I don't look like myself”, difficulty concentrating, sleeping difficulty, sweating, constipation). When distress ratings were used in the EFA, only three symptom clusters (i.e., emotions and pain related discomfort symptoms, GI symptoms, image related cutaneous symptoms) were identified. The number of symptoms within these clusters ranged from 6 (i.e., nausea, vomiting, lack of appetite, lack of energy, dizziness, feeling drowsy) to 11 (i.e., feeling nervous, difficulty concentrating, worrying, feeling sad, numbness/tingling, feeling irritable, sleeping difficulty, shortness of breath, feeling bloated, sweating, pain). The authors suggested that the lack of concordance in the number of symptom clusters, as well as differences in the specific symptoms within each cluster might be related to theoretical differences in patients’ perceptions of severity and distress.

As noted above, one of the fundamental questions that remains unanswered in symptom clusters research is which dimension to use to create the symptom cluster (Miaskowski, 2016; Miaskowski et al., 2017). Given the paucity of research in this area, the purpose of this study, in a sample of patients with breast cancer who received CTX (n = 515), was to identify whether the number and types of symptom clusters differed based on whether symptom occurrence rates or severity ratings were used to create the clusters. We hypothesized that the number and types of symptom clusters would be similar using occurrence rates and severity ratings.

METHODS

Patients and Settings

This study is part of a descriptive, longitudinal study that evaluated the symptom experience of oncology outpatients receiving CTX (Kober et al., 2016a; Kober et al., 2016b; Miaskowski et al., 2016; Wright et al., 2015a, b). Eligible patients were ≥18 years of age; had a diagnosis of breast, GI, gynecological, or lung cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran’s Affairs hospital, and four community-based oncology programs.

A total of 2234 patients were approached and 1343 consented to participate (60.1% response rate) in the larger study. The major reason for refusal was that patients were overwhelmed with their cancer treatment. For this study, only patients with a diagnosis of breast cancer were evaluated (n=515).

Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well established validity and reliability (Karnofsky, 1977; Karnofsky et al., 1948). 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) (Ando et al., 2001; Schnadig et al., 2008).

Self-Administered Comorbidity Questionnaire (SCQ) consists of 13 common medical conditions simplified into language that can be understood without prior medical knowledge. (Sangha et al., 2003) 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). For each condition, the patient can receive a maximum of 3 points. The total SCQ score ranges from 0 to 39. The SCQ has well established validity and reliability (Brunner et al., 2008; Cieza et al., 2006).

Alcohol Use Disorders Identification Test (AUDIT) is a 10-item questionnaire that assesses alcohol consumption, alcohol dependence, and the consequences of alcohol abuse in the last 12 months. The AUDIT gives a total score that ranges between 0 and 40. Scores of ≥8 are defined as hazardous use and scores of ≥16 are defined as the use of alcohol that is likely to be harmful to health (Babor et al., 1992; Babor et al., 2001). The AUDIT has well established validity and reliability (Berks and McCormick, 2008; Berner et al., 2007; Reinert and Allen, 2007). In this study, its Cronbach's alpha was 0.63.

A modified version of the MSAS was used to evaluate the occurrence, severity, frequency, and distress of 38 symptoms commonly associated with cancer and its treatment. In addition to the original 32 MSAS symptoms, the following six symptoms were assessed: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain.

The MSAS is a self-report questionnaire designed to measure the multidimensional experience of symptoms. Using the MSAS, patients were asked to indicate whether they had experienced each symptom in the past week (i.e., symptom occurrence). If they had experienced the symptom, they were asked to rate its frequency of occurrence, severity, and distress. Symptom severity was measured using a 4-point Likert scale (i.e., 1 = slight, 2 = moderate, 3 = severe, 4 = very severe). Symptom distress was measured using a 5-point Likert scale (i.e., 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much). The reliability and validity of the MSAS is well established in studies of oncology inpatients and outpatients (Portenoy et al., 1994a; Portenoy et al., 1994b).

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Board at each of the study sites. Eligible patients were approached by a research staff member in the infusion unit to discuss participation in the study. Written informed consent was obtained from all patients. Depending on the length of their CTX cycle, patients completed questionnaires in their homes, six times over two cycles of CTX. For this analysis, the symptom occurrence and severity data from the second assessment, which asked patients to report on their symptom experience one week after receiving CTX (i.e., acute symptoms following the administration of CTX), were analyzed. Medical records were reviewed for disease and treatment information.

Data Analysis

Data were analyzed using IBM SPSS 23 (SPSS, 2015), Stata Release 14 (StataCorp, 2015), and MPlus Version 7.3 (Muthen, 1989; Muthen and Muthen, 1998–2015). Descriptive

statistics and frequency distributions were calculated for the demographic and clinical characteristics.

Creation of symptom clusters using EFA—EFAs were done for the dichotomous (i.e., occurrence) items and for the ordinal (i.e., severity) items. Factor analysis is a generic term used for several procedures that aim to identify whether correlations between a set of observed variables can be explained by a few latent, unobserved variables (i.e., factors) (Brown, 2015). While it is more common to describe the results of an EFA as “factors”, the “factors” in the current study are referred to as symptom clusters (Kim et al., 2005; Miaskowski et al., 2004). All of the EFAs were done using MPlus because the program provides appropriate estimation for EFAs using dichotomous or ordinal items (Muthen, 1989; Muthen and Muthen, 1998–2015).

For the EFA, factor loadings were considered meaningful if the loading was ≥0.40 (Browne, 2001; Muthen, 1989; Muthen and Muthen, 1998–2015). In addition, factors were considered to be adequately defined if at least two items (i.e., symptoms) had loadings (i.e., structure coefficients following rotation) of ≥0.40 (Brown, 2015). While it is common to require that each item load strongly on only one factor, in this study, items that loaded on two factors (i.e., cross loaded) and fell within our pre-set criteria of ≥0.40, were retained and used to define both factors (i.e., the symptom clusters). 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; Miaskowski et al., 2007).

EFA was used to identify symptom clusters from the occurrence rates and the severity ratings of 30 out of the 38 MSAS symptoms assessed. Eight symptoms on the MSAS (i.e., lack of energy, difficulty breathing, difficulty urinating, vomiting, increased appetite, difficulty swallowing, swelling, chest tightness) were excluded from the analyses due to insufficient variation in the occurrence of these symptoms. In order to have sufficient variation and covariation to perform the EFAs, only symptoms that were present in >20% and <80% of the patients were included in these analyses.

The occurrence items were evaluated as dichotomous variables (i.e., had versus did not have the symptom) (Muthen, 1989; Muthen and Muthen, 1998–2015). For this EFA, tetrachoric correlations were used to create the matrix of associations. The severity items were examined as ordinal items. For this EFA, polychoric correlations were used to create the matrix of associations. The simple structure for the occurrence and severity EFAs were estimated using the method of unweighted least squares with geomin (i.e., oblique) rotation. The geomin (i.e., oblique) rotation method was used to create the best fit for the model. Adopting this rotational method provided an improved representation of how the factors were correlated and improved the interpretability of each factor solution (Muthen, 1989; Muthen and Muthen, 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 (Muthen, 1989; Muthen and Muthen, 1998–2015)) was selected in order to achieve more reliable results because the scales for the MSAS items are dichotomous (i.e., occurrence) and ordinal (i.e., severity).

The EFA for severity was done using severity ratings that included a zero (i.e., 0, 1, 2, 3, 4). If the patient indicated that they did not have the symptom (i.e., occurrence), a severity score of zero was assigned. An initial EFA analysis was done using severity ratings that did not include zero (i.e., 1, 2, 3, 4). However, the pairwise missingness (i.e., 1-covariance coverage for each of the item pairs) was over 90% and the estimation failed to converge. Therefore, the EFAs for the severity ratings were estimated including zeros.

Factor solutions were estimated for two through seven 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).

Differences in number and types of symptom clusters—To evaluate the agreement among the symptoms within the same cluster using occurrence and severity ratings, we used the criteria proposed by Kirkova and Walsh (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 factor analyses.

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the patients are summarized in Table 1. Of the total sample of 515 patients, 99.2% were female and 65.9% were married or partnered with a mean age of 53.3 ± 11.6 years (range: 21–90). The majority of the patients was White (66.9%) and well educated (16.5 ± 2.9 years). In terms of clinical characteristics, the patients had an average of 2.2 ± 1.3 comorbid conditions; a KPS score of 80.6 ± 12.2; were 2.5 ± 4.6 years from their cancer diagnosis (median = 0.42 years); and had received 1.7 ± 1.8 prior cancer treatments. While the majority of the patients were receiving adjuvant CTX, 26.0% were receiving neoadjuvant CTX. On average, patients reported 14.7 ± 6.9 symptoms on the MSAS.

Symptom Occurrence

The occurrence and severity ratings for the 38 symptoms from the MSAS are summarized in Table 2. Eight symptoms occurred in ≤20.0% or ≥80.0% of the sample (i.e., increased appetite (19.8%), difficulty breathing (17.1%), chest tightness (16.7%), difficulty swallowing (15.3%), swelling of arms or legs (15.0%), problems with urination (12.2%), vomiting (10.7%), and lack of energy (90.3%)) and were not included in the EFAs. The symptoms that occurred in ≥50% of the patients were: lack of energy (90.3%), difficulty sleeping (72.0%), pain (69.7%), feeling drowsy (65.6%), difficulty concentrating (61.0%), change in the way food tastes (60.8%), nausea (57.9%), hair loss (57.3%), “I don’t look like myself” (50.5%), and feeling sad (50.5%).

Symptom Severity

In terms of the severity ratings, mean scores were calculated in two ways (i.e., with and without zeros). In the "with zeros" analyses, all 515 patients were included and those patients who did not report the symptom were assigned a severity score of zero. When zeros were included in the calculation of the mean severity scores, scores ranged from 0.18 ± 0.62 (vomiting) to 1.98 ± 1.00 (difficulty sleeping). In the "without zeros" analyses, only those patients who reported each symptom were included and had severity scores that ranged from 1 to 4. When zeros were not included in the mean severity scores, the scores ranged from 1.35 ± 0.57 (weight loss) to 2.58 ± 1.14 (hair loss).

As shown in Table 2, when zero was included in the analysis, none of the symptoms had a severity score of ≥2.0. In contrast, when zero was not included in the analysis, the symptoms that had a severity score of ≥2.0 included: hair loss (2.58 ± 1.14), problems with sexual interest or activity (2.51 ± 0.96), change in the way food tastes (2.33 ± 0.93), "I don't look like myself" (2.20 ± 0.98), lack of energy (2.20 ± 0.78), and difficulty sleeping (2.07 ± 0.78).

Symptom Clusters Based on Symptom Occurrence

As shown in Table 3, the EFA for the dichotomous ratings of symptom occurrence indicated that a 5-factor solution was the best fit for the data. Each factor solution was examined to determine a clinically appropriate name for the symptom cluster. The name of the symptom cluster was based on the majority of the symptoms in the cluster. The five symptoms in factor 1 (i.e., feeling nervous, feeling sad, worrying, feeling irritable, "I don't look like myself") were named the *psychological symptom cluster*. The four symptoms in factor 2 (i.e., hot flashes, difficulty sleeping, sweats, problems with sexual interest or activity) were named the *hormonal symptom cluster*. The seven symptoms in factor 3 (i.e., dry mouth, nausea, lack of appetite, change in the way food tastes, weight loss, abdominal cramps, diarrhea) were named the *nutritional symptom cluster*. The three symptoms in factor 4 (i.e., weight loss, feeling bloated, weight gain) were named the *GI symptom cluster*. The four symptoms in factor 5 (i.e., "I don't look like myself", change in the way food tastes, hair loss, mouth sores) were named the *epithelial symptom cluster*. Within each symptom cluster based on occurrence rates, the number of symptoms ranged from 3 to 7.

Symptom Clusters Based on Symptom Severity

As shown in Table 4, the EFA for the ordinal ratings of symptom severity that included zeros indicated that a 6-factor solution was the best fit for the data. Each factor solution was examined in order to determine a clinically appropriate name for the symptom cluster. The name of the symptom cluster was based on the majority of the symptoms in the cluster. The two symptoms in factor 1 (i.e., hot flashes, sweats) were named the *hormonal symptom cluster*. The four symptoms in factor 2 (i.e., feeling sad, feeling nervous, worrying, feeling irritable) were named the *psychological symptom cluster*. The three symptoms in factor 3 (i.e., feeling drowsy, numbness or tingling in hands/feet, pain) were named the *chemotherapy neuropathy symptom cluster*. The three symptoms in factor 4 (i.e., feeling bloated, abdominal cramps, weight gain) were named the *GI symptom cluster.* The four symptoms in factor 5 (i.e., weight gain, weight loss, nausea, lack of appetite) were named

the *nutritional symptom cluster*. The five symptoms in factor 6 (i.e., hair loss, change in the way food tastes, "I don't look like myself", changes in skin, mouth sores) were named the *epithelial symptom cluster*. Within each symptom cluster based on the severity ratings, the number of symptoms ranged 2 to 5.

Agreement in the types of symptoms within each symptom cluster—Table 5 presents a summary of the percentage agreement among the symptoms within each cluster across the occurrence and severity dimensions. For the psychological symptom cluster, the total number of symptoms ranged from 4 to 5 and the percent agreement ranged from 80.0% to 100.0%. The four symptoms that were included in both the occurrence and severity clusters were: feeling nervous, feeling sad, worrying, and feeling irritable.

For the hormonal symptom cluster, the total number of symptoms ranged from 2 to 4 and the percent agreement ranged from 50.0% to 100%. The two symptoms that were included in both the occurrence and severity clusters were: hot flashes and sweats.

For the nutritional symptom cluster, the total number of symptoms ranged from 4 to 7 and the percent agreement ranged from 50.0 % to 85.7%. The three symptoms that were included in both the occurrence and severity clusters were: nausea, lack of appetite, and weight loss.

For the GI symptom cluster, the total number of symptoms was 3 and the percent agreement was 75.0%. The two symptoms that were included in both the occurrence and severity clusters were: weight gain and feeling bloated

For the epithelial symptom cluster, the total number of symptoms ranged from 4 to 5 and the percent agreement ranged from 80.0% to 100.0%. The four symptoms that were included in both the occurrence and severity clusters were: "I don't look like myself", change in the way food tastes, hair loss, and mouth sores.

For the CTX neuropathy symptom cluster, the total number of symptoms identified using ratings of severity was three.

DISCUSSION

To our knowledge, this study is the first to evaluate for differences in symptom clusters derived using occurrence rates and severity ratings in a relatively large sample of patients with breast cancer in the week following the administration of CTX. Our a priori hypothesis, that the number and types of symptom clusters would be similar using these two dimensions, was partially supported. While five symptom clusters were given identical names based on the EFAs for occurrence and severity, one additional symptom cluster (i.e., *CTX neuropathy*) was identified using severity ratings. In addition, using the criteria proposed by Kirkova and Walsh (2007), the psychological, gastrointestinal, and epithelial symptom clusters had >75% agreement in the symptoms within the clusters derived using ratings of occurrence and severity.

Number and Types of Symptom Clusters

Only three studies evaluated for differences in the number and types of symptom clusters using the dimensions of occurrence versus severity (Baggott et al., 2012; Kim et al., 2009) or severity versus distress (Suwisith et al., 2008) in oncology patients. In the two studies that compared the number and types of symptom clusters using occurrence and severity ratings (Baggott et al., 2012; Kim et al., 2009), each study identified three similar symptom clusters. In the study that used the dimensions of severity and distress to create the symptom clusters in patients undergoing CTX for breast cancer (Suwisith et al., 2008), four clusters were identified using the MSAS severity ratings and three clusters were identified using the MSAS distress ratings. In addition, the types of symptom clusters as well as the symptoms within the clusters were different. Taken together, based on our current findings and the findings in pediatric oncology patients receiving CTX (Baggott et al., 2012) and patients with breast and prostate cancer undergoing RT (Kim et al., 2009), when the dimensions of occurrence and severity are used, similar symptom clusters are identified. The findings by Suwisith and colleagues (2008) warrant confirmation in future studies. However, given that severity and distress assess different dimensions of the symptom experience (Humphreys et al., 2014; Portenoy et al., 1994a; Portenoy et al., 1994b), it is plausible that different types of symptom clusters would occur.

The remainder of the discussion describes the specific symptom clusters identified in our sample. Our findings are discussed primarily in the context of the four studies that evaluated symptom clusters in patients with breast cancer undergoing CTX (Albusoul et al., 2017; Kim et al., 2008; Phligbua et al., 2013; Suwisith et al., 2008).

Psychological Symptom Cluster

As shown in Table 5, four of the five symptoms in the psychological symptom cluster (i.e., feeling nervous, feeling sad, worrying, feeling irritable) were identical regardless of the dimension used to create the symptom cluster. While the number and specific symptoms found in the psychological symptom cluster varied based on symptom assessment instruments used, all three of the studies of breast cancer patients undergoing CTX (Kim et al., 2008; Phligbua et al., 2013; Suwisith et al., 2008), as well as numerous studies of heterogeneous samples of oncology patients undergoing CTX (e.g., (Chen and Lin, 2007; Yates et al., 2015)), identified this symptom cluster. The ubiquitous nature of this symptom cluster confirms previous reports of the high prevalence rates for anxiety (Burgess et al., 2005; Gold et al., 2016; Lim et al., 2011) and depressive symptoms (Burgess et al., 2005; Dunn et al., 2011; Gold et al., 2016) in oncology patients undergoing cancer treatment.

GI Symptom Cluster

Across the two symptom dimensions, weight gain and feeling bloated were the common symptoms in the GI symptom cluster. In a review of 19 studies that evaluated symptom clusters in oncology patients receiving CTX (Ward Sullivan et al., in review), some type of GI symptom cluster was identified in 14 studies (e.g., Albusoul et al., 2017; Kim et al., 2008; Suwisith et al., 2008). However, the specific symptoms within each of these clusters were highly variable. In many of the previous studies, the symptoms of nausea, lack of appetite, and change in the way food tastes, which loaded on our nutritional symptom cluster

were included in the GI symptom cluster. Reasons for the differences in which symptoms loaded on the GI symptom cluster may be related to differences in the patients' cancer diagnoses, the specific CTX regimen received, the specific GI symptoms included in the symptom assessment inventory, and the method used to create the symptom clusters. Despite these differences, the GI symptom cluster appears to be extremely common in oncology patients receiving CTX.

Nutritional Symptom Cluster

For the nutritional symptom cluster, nausea, lack of appetite, and weight loss were the common symptoms for both the occurrence and severity symptom clusters. It is interesting that in our study, both weight gain and weight loss loaded on both the GI and the nutritional symptom clusters. While weight loss is often associated with a cancer diagnosis (Salzman et al., 2009) and its treatment,(Pedersen et al., 2016) patients with breast cancer report that weight gain can be a significant problem (Nyrop et al., 2016; Wolin et al., 2010). Patients in this study had a BMI of 26.24 (±5.81), which is categorized as overweight by the Centers for Disease Control (Centers et al., 2016). It should be noted that in previous studies that identified a GI or a nutritional symptom cluster (Ward Sullivan et al., in review), weight gain was not an identified symptom because for our study, this symptom was added to the MSAS. Therefore, our two distinct symptom clusters (i.e., GI, nutritional) warrant confirmation in future studies. However, given the importance of nutritional status to the health and well-being of patients with breast cancer, these findings suggest that patients receiving CTX need nutritional counseling and referral to a dietician.

Epithelial Symptom Cluster

While the common symptoms across the two dimensions of the epithelial symptom cluster (i.e., "I don't look like myself", change in the way food tastes, hair loss, mouth sores) represent a rather disparate set of symptoms, three of them are the result of the direct effects of CTX on the epithelium. Mucositis occurs in 20% to 40% of patients receiving CTX (Villa and Sonis, 2016). Concomitant with and distinct from mucositis, CTX is associated with taste changes (Zabernigg et al., 2010). The most common alterations in taste include: loss of appetite, early satiety, decreased saliva production, and overall taste perceptions (Bernhardson et al., 2007, 2008). In addition, hair loss occurs in 65% of oncology patients receiving CTX (Dua et al., 2015). Previous research found that alopecia is associated with significant changes in body image (Dua et al., 2015).

It is not entirely clear why changes in skin loaded only on the severity cluster and what the exact skin changes in our sample were. However, 22% of the patients were receiving a targeted therapy (e.g., bevacizumab, trastuzamab, pertuzamab) which is associated with rashes and other skin changes (Macdonald et al., 2015a, b). Given that 45.2% of the patients reported skin changes of slight to moderate severity and the use of targeted therapies for the treatment of breast cancer is increasing, future studies should obtain more detailed assessments of these skin changes and their effects on patients' body image.

When the symptoms in our epithelial symptom cluster were compared to previous studies of symptom clusters in oncology patients receiving CTX that used the MSAS, three studies

identified an image-related cutaneous symptom cluster (Suwisith et al., 2008) or a body image symptom cluster (Huang et al., 2016; Molassiotis et al., 2010). In the study that included only patients with breast cancer (Suwisith et al., 2008), hair loss, change in the way food tastes, mouth sores, and changes in skin were included in the image-related cutaneous symptom cluster. Given the potential impact that changes in body image can have on breast cancer patients' mood (Moreira and Canavarro, 2012) and social relationships,(Dua et al., 2015; Moreira and Canavarro, 2012) clinicians need to assess for these symptoms and their impact.

Hormonal Symptom Cluster

Given the changes in sex hormones associated with breast cancer treatment (Knobf, 2001, 2006, 2008), it is not surprising that a hormonal symptom cluster was identified in our study. Hot flashes, difficulty sleeping, sweats, and problems with sexual interest or activity are common symptoms associated with the transition to menopause (Kim et al., 2009; Knobf, 2001, 2006, 2008). Given that no information is available on the menopausal status of the female patients in our study, the etiology of these symptoms cannot be determined. However, given that over 30% of the patients in our study reported these symptoms, they warrant more detailed assessment in future studies.

It is interesting to note that in the three studies that evaluated symptom clusters in breast cancer patients undergoing CTX (Kim et al., 2008; Phligbua et al., 2013; Suwisith et al., 2008), only one (Phligbua et al., 2013) found a menopausal symptom cluster that included: sweats, night sweats, hot flashes, mood swings, feeling irritable, and difficulty concentrating. In this study, additional symptoms were added to the MSAS and distress was the dimension used to create the clusters. In the other two studies (Kim et al., 2008; Suwisith et al., 2008), night sweats was included in the psychological symptom cluster. Only one other study that included a heterogeneous sample in terms of cancer diagnoses and treatments identified a hormonal cluster (Yates et al., 2015). The symptoms included in this cluster that were identified in patients <60 years of age but not in patients ≥60 years of age were: sweats, difficulty sleeping, pain, and weight gain. In a study that evaluated patients with ovarian cancer receiving CTX (Huang et al., 2016), a menopausal symptom cluster was identified. However, sweats were the only common symptom included in their hormonal symptom cluster. Additional research is warranted on the specific symptoms that need to be included in a multidimensional symptom inventory to fully capture a hormonal symptom cluster in patients with breast cancer.

CTX Neuropathy Symptom Cluster

Given that patients who are being treated for breast cancer often receive a platinum and/or taxane-based CTX regimen (Addington and Freimer, 2016; Park et al., 2013), it is not surprising that a CTX neuropathy cluster was identified that included: feeling drowsy, numbness/tingling in hands/feet, and pain. Numbness and tingling, the two most common symptoms associated with CTX-induced neuropathy (Park et al., 2013), occurred in 44.3% of the patients in our study and was of slight to moderate intensity. In the other studies of symptom clusters in patients with breast cancer receiving CTX, numbness/tingling was included with a pain (Suwisith et al., 2008) and a discomfort symptom cluster (Phligbua et

al., 2013). In addition, it was included in a neuropathy cluster identified in patients with ovarian cancer (Hwang et al., 2016) and in a hand/foot symptom cluster in a study of patients with a variety of cancer diagnoses treatments (Molassiotis et al., 2010).

Limitations

Several study limitations warrant consideration. Because only a single time point was used to create the symptom clusters, the stability of these clusters over an entire cycle of CTX cycle was not evaluated. Because only a small sample of men with breast cancer was included in this analysis, these findings may not be generalizable to all men with breast cancer. Finally, a number of symptoms with relatively low occurrence rates did not load on any of the factor solutions. Therefore, studies with larger samples sizes may identify additional or slightly different symptom clusters.

Conclusions

Despite these limitations, our findings provide additional evidence that the number and types of symptom clusters derived using symptom occurrence and severity data are relatively similar. In addition, given that these patients reported an average of 15 symptoms, clinicians need to use a multidimensional assessment tool to monitor these patients and initiate appropriate interventions. Future studies of symptom clusters in patients with breast cancer need to evaluate the stability of symptom clusters over time. In addition, research is needed on the number and types of symptom clusters that occur prior to the initiation of CTX. Future studies should evaluate the efficacy of symptom management strategies for specific symptom clusters in patients with breast cancer who are undergoing CTX.

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Highlights

- Following chemotherapy, patients with breast cancer reported an average of 15 symptoms.
- Number and types of symptom clusters were similar using occurrence and severity.
- Identification of symptom clusters can guide symptom management interventions.

Table 1

Demographic and Clinical Characteristics of Patients With Breast Cancer (n=515)

Characteristic	Mean (SD)
Age (years)	53.3 (11.6)
Education (years)	16.5 (2.9)
Body mass index (kilograms/metered squared)	26.3 (5.8)
Karnofsky Performance Status score	80.6 (12.2)
Number of comorbidities	2.2 (1.3)
Self-administered Comorbidity Questionnaire score	5.0 (2.9)
Alcohol Use Disorders Identification Test score	2.8 (2.3)
Time since cancer diagnosis (years)	2.5 (4.6)
Time since diagnosis (median)	0.42
Number of prior cancer treatments (out of 9)	1.7 (1.8)
Number of metastatic sites including lymph node involvement (out of 9)	0.9 (1.2)
Number of metastatic sites excluding lymph node involvement (out of 9)	0.5 (1.0)
Mean number of MSAS symptoms (out of 38)	14.7 (6.9)
	% (N)
Gender	
Female	99.2 (511)
Male	0.8 (4)
Ethnicity	
White	66.9 (337)
Black	6.9 (35)
Asian or Pacific Islander	15.3 (77)
Hispanic Mixed or Other	10.9 (55)
Married or partnered (% yes)	65.9 (333)
Lives alone (% yes)	17.6 (89)
Child care responsibilities (% yes)	30.9 (154)
Care of adult responsibilities (% yes)	7.5 (35)
Currently employed (% yes)	41.0 (209)
Income	

Characteristic	Mean (SD)
< $30,000	14.7 (67)
$30,000 to <$70,000	18.4 (84)
$70,000 to < $100,000	17.5 (80)
> $100,000	49.5 (226)
Specific comorbidities (% yes)	
Heart disease	3.7 (19)
High blood pressure	22.5 (116)
Lung disease	3.9 (20)
Diabetes	6.6 (34)
Ulcer or stomach disease	2.9 (15)
Kidney disease	1.0 (5)
Liver disease	3.9 (20)
Anemia or blood disease	14.6 (75)
Depression	21.6 (111)
Osteoarthritis	11.1 (57)
Back pain	25.2 (130)
Rheumatoid arthritis	2.9 (15)
Exercise on a regular basis (% yes)	75.6 (377)
Current or history of smoking (% yes)	28.0 (143)
Receiving neoadjuvant chemotherapy (% yes)	26.0 (133)
Type of prior cancer treatment	
No prior treatment	27.7 (140)
Only surgery, CTX, or RT	42.1 (213)
Surgery & CTX, or surgery & RT, or CTX & RT	13.6 (69)
Surgery & CTX & RT	16.6 (84)
Sentinel lymph node biopsy (% yes)	53.5 (267)
Axillary lymph node dissection (% yes)	42.4 (211)
Reconstruction to the affected breast (% yes)	23.3 (118)
Type of initial surgery	
Breast conservation	19.8 (67)
Mastectomy	18.6 (63)
Bilateral mastectomy	15.7 (53)
Unknown	0.6 (2)
Not applicable	45.3 (153)
Estrogen receptor (ER) status	
ER positive	67.7 (344)
ER negative	30.9 (157)

Characteristic	Mean (SD)
Progesterone receptor (PR) status	
PR positive	54.5 (277)
PR negative	43.9 (223)
Breast cancer gene 1 (BRCA1) (% positive)	3.9 (20)
Breast cancer gene 2 (BRCA2) (% positive)	2.6 (13)
Human epidermal growth factor receptor (HER)-2 (% negative)	64.6 (328)
On hormone replacement therapy prior to cancer diagnosis	
Yes	8.5 (43)
No	56.3 (286)
Unknown	35.2 (179)

Abbreviations: CTX = chemotherapy; MSAS = Memorial Symptom Assessment Scale, RT = radiation therapy, SD = standard deviation.

Table 2

Symptom Occurrence Rates and Severity Ratings in Patients With Breast Cancer (n = 515)

Symptom[a]	Occurrence % (n)	Severity Ratings with Zero Mean (SD)[b]	Rank Order	Severity Ratings without Zero Mean (SD)[c]	Rank Order
Lack of energy	90.3 (465)	1.98 (1.00)	1	2.20 (0.78)	4
Difficulty sleeping	72.0 (371)	1.47 (1.14)	2	2.06 (0.78)	5
Pain	69.7 (359)	1.36 (1.10)	5	1.99 (0.75)	6
Feeling drowsy	65.6 (338)	1.16 (1.05)	6	1.82 (0.74)	12
Difficulty concentrating	61.0 (314)	1.00 (0.98)	9	1.66 (0.69)	23
Change in the way food tastes	60.8 (313)	1.40 (1.36)	4	2.33 (0.93)	3
Nausea	57.9 (298)	1.05 (1.12)	8	1.87 (0.84)	9
Hair loss	57.3 (295)	1.43 (1.54)	3	2.58 (1.14)	1
“I don’t look like myself”	50.5 (260)	1.09 (1.30)	7	2.20 (0.98)	4
Feeling sad	50.5 (260)	0.86 (1.02)	12	1.75 (0.75)	18
Lack of appetite	49.9 (257)	0.95 (1.14)	10	1.94 (0.84)	7
Dry mouth	48.9 (252)	0.85 (1.04)	13	1.80 (0.79)	14
Worrying	47.6 (245)	0.86 (1.07)	11	1.87 (0.78)	9
Feeling irritable	47.2 (243)	0.79 (0.99)	16	1.71 (0.73)	20
Changes in skin	45.2 (233)	0.81 (1.06)	15	1.85 (0.79)	10
Constipation	44.7 (230)	0.84 (1.09)	14	1.93 (0.77)	8
Numbness/tingling in hands/feet	44.3 (228)	0.78 (1.05)	17	1.83 (0.84)	11
Hot flashes	42.1 (217)	0.74 (1.02)	19	1.81 (0.77)	13
Sweats	33.2 (171)	0.58 (0.94)	20	1.78 (0.74)	16
Dizziness	33.2 (171)	0.50 (0.82)	21	1.54 (0.69)	25
Feeling bloated	32.8 (169)	0.58 (0.94)	20	1.83 (0.72)	11
Feeling nervous	32.6 (168)	0.50 (0.83)	21	1.61 (0.67)	24
Problems with sexual interest or activity	30.3 (156)	0.74 (1.26)	18	2.51 (0.96)	2
Cough	28.0 (144)	0.43 (0.80)	23	1.61 (0.69)	24
Shortness of breath	27.2 (140)	0.43 (0.81)	22	1.67 (0.70)	22
Diarrhea	25.0 (129)	0.42 (0.83)	24	1.74 (0.77)	19

Symptom[a]	Occurrence % (n)	Severity Ratings with Zero Mean (SD)[b]	Rank Order	Severity Ratings without Zero Mean (SD)[c]	Rank Order
Weight gain	24.1 (124)	0.38 (0.78)	26	1.67 (0.78)	22
Itching	22.7 (117)	0.38 (0.80)	27	1.76 (0.78)	17
Abdominal cramps	22.7 (117)	0.41 (0.86)	25	1.87 (0.82)	9
Mouth sores	21.9 (113)	0.38 (0.82)	26	1.79 (0.81)	15
Weight loss	21.2 (109)	0.27 (0.60)	29	1.35 (0.57)	27
Increased appetite	19.8 (102)	0.34 (0.76)	28	1.81 (0.71)	13
Difficulty breathing	17.1 (88)	0.26 (0.67)	29	1.69 (0.67)	21
Chest tightness	16.7 (86)	0.23 (0.60)	31	1.51 (0.66)	26
Difficulty swallowing	15.3 (79)	0.25 (0.71)	30	1.80 (0.84)	14
Swelling of arms or legs	15.0 (77)	0.24 (0.69)	30	1.75 (0.93)	18
Problems with urination	12.2 (63)	0.19 (0.58)	32	1.67 (0.71)	22
Vomiting	10.7 (55)	0.18 (0.62)	33	1.79 (0.95)	15

Abbreviations: SD, standard deviation.

[a]Symptoms from the Memorial Symptom Assessment Scale with the addition of the following six symptoms: chest tightness, difficulty breathing, increased appetite, hot flashes, abdominal cramps, weight gain.

[b]Severity ratings: 0 =did not have the symptom, 1=slight, 2=moderate, 3=severe, 4=very severe.

[c]Severity ratings: 1=slight, 2=moderate, 3=severe, 4=very severe.

Table 3

Exploratory Factor Analysis Using Ratings of Symptom Occurrence Approximately One Week After Chemotherapy Administration [a]

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Psychological Symptom Cluster	Hormonal Symptom Cluster	Nutritional Symptom Cluster	Gastrointestinal Symptom Cluster	Epithelial Symptom Cluster
Feeling nervous	**0.818**	0.007	0.046	0.039	−0.051
Feeling sad	**0.805**	0.079	0.000	−0.018	0.018
Worrying	**0.811**	0.154	−0.094	−0.048	0.105
Feeling irritable	**0.501**	0.127	0.047	0.057	0.246
“I don’t look like myself”	**0.417**	−0.008	−0.019	−0.024	**0.523**
Hot flashes	−0.031	**0.880**	−0.023	0.002	−0.249
Difficulty sleeping	0.166	**0.475**	0.113	0.159	0.106
Sweats	0.076	**0.787**	0.028	0.125	−0.175
Problems with sexual interest or activity	0.226	**0.403**	−0.073	0.028	0.159
Dry mouth	−0.008	0.153	**0.448**	0.037	0.031
Nausea	−0.091	0.261	**0.663**	−0.076	−0.152
Lack of appetite	0.018	0.117	**0.728**	−0.372	0.053
Change in the way food tastes	−0.277	0.022	**0.427**	−0.009	**0.410**
Weight loss	0.113	−0.058	**0.479**	**−0.444**	0.140
Abdominal cramps	−0.046	−0.040	**0.583**	0.358	0.048
Diarrhea	0.069	−0.132	**0.474**	0.148	−0.103
Feeling bloated	0.060	0.173	0.274	**0.447**	0.033
Weight gain	0.014	0.035	−0.066	**0.826**	0.146
Hair loss	0.018	−0.018	0.046	0.041	**0.618**
Mouth sores	−0.005	0.084	0.066	0.001	**0.464**
Feeling drowsy	0.388	0.169	0.255	−0.045	−0.015
Numbness/tingling in hands/feet	0.289	−0.039	0.213	0.183	−0.086
Shortness of breath	0.322	−0.106	0.288	0.057	0.001
Itching	0.195	0.002	0.220	0.098	0.010
Dizziness	0.049	0.256	0.317	−0.002	0.173

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Psychological Symptom Cluster	**Hormonal Symptom Cluster**	**Nutritional Symptom Cluster**	**Gastrointestinal Symptom Cluster**	**Epithelial Symptom Cluster**
Constipation	0.041	0.207	0.371	0.006	0.145
Changes in skin	0.203	−0.043	0.119	0.110	0.376
Difficulty concentrating	0.302	0.303	0.167	−0.041	0.163
Pain	0.042	0.218	0.295	0.249	0.007
Cough	0.385	−0.226	0.304	0.039	−0.124
Total number of symptoms in the cluster	5	4	7	3	4

[a]Extraction method: unweighted least squares.

Rotation method: Geomin (oblique) rotation.

The eight symptoms that did not meet our specific criterion for inclusion in the exploratory factor analyses were: lack of energy, chest discomfort, difficulty breathing, problems with urination, vomiting, increased appetite, difficulty swallowing, and swelling of arms or legs.

Table 4

Exploratory Factor Analysis Using Ratings of Symptom Severity Approximately One Week After Chemotherapy Administration [a]

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
	Hormonal Symptom Cluster	Psychological Symptom Cluster	Chemotherapy Neuropathy Symptom Cluster	Gastrointestinal Symptom Cluster	Nutritional Symptom Cluster	Epithelial Symptom Cluster
Hot flashes	**0.988**	−0.012	−0.022	−0.081	0.040	0.025
Sweats	**0.739**	0.087	0.077	0.077	−0.039	−0.025
Feeling sad	−0.012	**0.826**	−0.001	0.087	0.019	−0.039
Feeling nervous	0.054	**0.759**	0.068	0.025	−0.014	−0.028
Worrying	0.043	**0.903**	−0.071	0.023	−0.004	0.004
Feeling irritable	0.030	**0.590**	0.106	0.044	0.009	0.124
Feeling drowsy	0.079	0.191	**0.456**	−0.022	0.083	−0.005
Numbness/tingling in hands/feet	−0.047	0.025	**0.718**	−0.007	−0.252	−0.019
Pain	−0.006	−0.078	**0.463**	0.380	−0.047	−0.012
Feeling bloated	−0.010	0.146	−0.100	**0.663**	−0.085	0.095
Abdominal cramps	−0.172	−0.008	0.017	**0.796**	0.171	−0.035
Weight gain	0.074	0.045	0.013	**0.502**	**−0.607**	0.297
Weight loss	−0.168	0.197	−0.028	−0.112	**0.627**	0.091
Nausea	0.123	0.033	0.131	0.277	**0.488**	−0.122
Lack of appetite	0.048	0.072	0.169	0.010	**0.719**	0.033
Hair loss	−0.068	0.061	−0.002	−0.003	−0.014	**0.631**
Change in the way food tastes	0.042	−0.205	−0.035	0.137	0.349	**0.569**
“I don’t look like myself”	−0.090	0.398	0.055	−0.055	0.015	**0.532**
Changes in skin	0.012	0.151	0.156	−0.038	−0.056	**0.484**
Mouth sores	−0.015	0.011	0.063	0.046	0.061	**0.442**
Difficulty concentrating	0.056	0.294	0.312	0.119	0.073	0.066
Cough	−0.089	0.146	0.218	−0.006	0.092	0.014
Dry mouth	0.093	−0.061	0.238	0.076	0.177	0.246
Difficulty sleeping	0.222	0.180	0.086	0.255	0.052	0.140

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
	Hormonal Symptom Cluster	**Psychological Symptom Cluster**	**Chemotherapy Neuropathy Symptom Cluster**	**Gastrointestinal Symptom Cluster**	**Nutritional Symptom Cluster**	**Epithelial Symptom Cluster**
Shortness of breath	−0.065	0.175	0.207	0.059	0.094	0.103
Diarrhea	−0.155	−0.002	0.215	0.264	0.124	0.039
Problems with sexual interest or activity	0.227	0.288	−0.036	0.044	−0.019	0.117
Itching	0.023	0.137	0.374	−0.098	−0.045	0.100
Dizziness	0.117	0.000	0.343	0.105	0.148	0.119
Constipation	0.040	0.105	0.185	0.185	0.249	0.057
Total number of symptoms in the cluster	2	4	3	3	4	5

[a]Extraction method: unweighted least squares.

Rotation method: Geomin (oblique) rotation.

The eight symptoms that did not meet our specific criterion for inclusion in the exploratory factor analyses were: lack of energy, chest discomfort, difficulty breathing, problems with urination, vomiting, increased appetite, difficulty swallowing, and swelling of arms or legs.

Table 5

Comparison of Symptoms Within and Across the Occurrence and Severity Symptom Clusters

Symptom Cluster	Symptoms	Occurrence	Severity
Psychological	Feeling nervous	●	●
	Feeling sad	●	●
	Worrying	●	●
	Feeling irritable	●	●
	"I don't look like myself"	●	
	Percent agreement	100.0	80.0
Hormonal	Hot flashes	●	●
	Sweats	●	●
	Difficulty sleeping	●	
	Problems with sexual interest or activity	●	
	Percent agreement	100.0	50.0
Nutritional	Nausea	●	●
	Lack of appetite	●	●
	Weight loss	●	
	Dry mouth	●	
	Change in the way food tastes	●	
	Weight gain		●
	Diarrhea	●	
	Abdominal cramps	●	
	Percent agreement	87.5	50.0
Gastrointestinal	Weight gain	●	●
	Feeling bloated	●	●
	Weight loss	●	
	Abdominal cramps		●
	Percent agreement	75.0	75.0
Epithelial	"I don't look like myself"	●	●
	Change in the way food tastes	●	●
	Hair loss	●	●
	Mouth sores	●	●
	Changes in skin		●
	Percent agreement	80.0	100.0
Chemotherapy Neuropathy	Feeling drowsy	Not identified	●
	Numbness/tingling in hands/feet		●
	Pain		●
	Percent agreement	0.0	100.0