



Published in final edited form as:

*J Pain Symptom Manage.* 2018 January ; 55(1): 39–55. doi:10.1016/j.jpainsymman.2017.08.008.

## STABILITY OF SYMPTOM CLUSTERS IN PATIENTS WITH BREAST CANCER RECEIVING CHEMOTHERAPY

Carmen Ward Sullivan, RN, PhD(c)<sup>1</sup>, Heather Leutwyler, RN, PhD<sup>1</sup>, Laura B. Dunn, MD<sup>2</sup>, Bruce A. Cooper, PhD<sup>1</sup>, Steven M. Paul, PhD<sup>1</sup>, Jon D. Levine, MD, PhD<sup>3</sup>, Marilyn Hammer, RN, PhD<sup>4</sup>, Yvette P. Conley, PhD<sup>5</sup>, and Christine A. Miaskowski, RN, PhD<sup>1</sup>

<sup>1</sup>School of Nursing, University of California, San Francisco, CA

<sup>2</sup>School of Medicine, Stanford University, Palo Alto, CA

<sup>3</sup>School of Medicine, University of California, San Francisco, CA

<sup>4</sup>Department of Nursing, Mount Sinai Medical Center, New York, NY

<sup>5</sup>School of Nursing, University of Pittsburgh, Pittsburgh, PA

### Abstract

**Context**—Patients with breast cancer who undergo chemotherapy (CTX) experience between 10 and 32 concurrent symptoms. An evaluation of how these symptoms cluster together and how these symptom clusters change over time may provide insights into how to treat these multiple co-occurring symptoms.

**Objectives**—The purposes of this study were to: determine the occurrence rates and severity ratings for 38 common symptoms, evaluate for differences in the number and types of symptom clusters, and evaluate for changes over time in these symptom clusters (i.e., prior to CTX, the week following CTX, and two weeks following CTX).

**Methods**—At each of the assessments, a modified version of the Memorial Symptom Assessment Scale was used to assess the occurrence and severity of the 38 symptoms. Exploratory factor analyses were used to extract the symptom clusters.

**Results**—While across the two symptom dimensions (i.e., occurrence, severity) and the three assessments, eight distinct symptom clusters were identified, only five were relatively stable across both dimensions and across time (i.e., psychological, hormonal, nutritional, gastrointestinal, epithelial). Two of the additional clusters varied by time but not by symptom dimension (i.e., sickness behavior, weight change). The CTX neuropathy cluster was identified only at the assessment done in the week following CTX.

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Address correspondence to: Christine Miaskowski, RN, PhD, FAAN, Professor, Department of Physiological Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143-0610, 415-476-9407 (phone), 415-476-8899 (fax), [chris.miaskowski@ucsf.edu](mailto:chris.miaskowski@ucsf.edu).

Conflict of interest: The authors have no conflicts of interest to declare.

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**Conclusion**—These findings provide insights into the most common symptom clusters in patients undergoing CTX for breast cancer. In addition, the most common symptoms within each cluster appear to be relatively stable across the two dimensions, as well as across time.

### Keywords

symptoms; symptom clusters; breast cancer; chemotherapy; symptom occurrence; symptom severity

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## INTRODUCTION

An evaluation of symptom clusters is an important area in symptom management research and the science of symptom clusters is steadily advancing.<sup>1</sup> In a recent review,<sup>1</sup> an expert panel provided a number of recommendations for future research on symptom clusters. They noted that two important areas for symptom clusters research included: a determination of the congruence in the number and types of symptom clusters using different dimensions of the symptom experience (e.g., occurrence versus severity) and an evaluation of the stability of symptom clusters over time. Since the majority of symptom clusters research was done in oncology patients who were heterogeneous in terms of their cancer diagnoses and treatments,<sup>3</sup> in two recent reviews, Miaskowski<sup>1</sup> and Barsevick<sup>4</sup> suggested that the research questions cited above need to be evaluated in oncology patients with homogenous diagnoses. Because they experience multiple co-occurring symptoms,<sup>5</sup> patients with breast cancer undergoing chemotherapy (CTX) represent an ideal sample to investigate these research priorities.

To date, only five studies have evaluated for differences in the number and types of symptom clusters in patients with breast cancer who underwent CTX.<sup>5-9</sup> Two of these studies were cross-sectional<sup>5,7</sup> and three were longitudinal.<sup>6,8,9</sup> In the first cross-sectional study that evaluated for differences in symptom clusters using occurrence and distress ratings,<sup>7</sup> patients were assessed at different points in their CTX treatments. While the specific symptoms within each cluster were different, across the two dimensions, three relatively similar clusters were identified (i.e., emotions-related, gastrointestinal (GI)-related, and image/cutaneous-related). Recent work from our group,<sup>5</sup> evaluated for differences in symptom clusters using symptom occurrence and severity ratings. Patients completed the Memorial Symptom Assessment Scale (MSAS) approximately one week after the receipt of CTX. Both the number and types of symptom clusters were similar. Consistent with the previous cross-sectional study,<sup>7</sup> psychological and GI-related symptom clusters were identified. In addition, we identified hormonal, nutritional, and epithelial symptom clusters. Differences in the number of symptom clusters identified may relate to differences in the number of symptoms assessed, sample sizes, and the dimensions of the symptom experience that were evaluated.

In the first longitudinal study that combined data from patients with breast cancer who received CTX or radiation therapy (RT),<sup>8</sup> occurrence rates were used to create the symptom clusters. The two symptom clusters identified (i.e., psychoneurological and upper GI) remained relatively stable over time. In the second study that evaluated patients receiving

adjuvant CTX for breast cancer,<sup>6</sup> distress ratings from the MSAS were used to create the symptom clusters. Patients were assessed prior to CTX, before receiving their second cycle, and 1 month after the completion of CTX. Of the five symptom clusters identified, three (i.e., menopausal, psychological-related self-image, and GI-related fatigue) remained relatively stable over time. In the most recent study of women undergoing adjuvant CTX for breast cancer,<sup>9</sup> patients were assessed prior to CTX, during their third and fourth cycles of CTX, and one month after the completion of CTX. While a treatment-related symptom cluster was identified at each time point, a GI cluster was found only at the first and last assessments. In addition, the specific symptoms within each cluster were not consistent over time. These authors concluded that symptom clusters during CTX appear to be dynamic. Across these five studies,<sup>5-9</sup> evidence for a GI symptom cluster is beginning to emerge. However, findings are inconclusive as to whether or not the number and types of symptom clusters vary based on the dimension used to create the symptom clusters and whether symptom clusters remain stable over time.

Therefore, given the paucity of symptom clusters research in patients with breast cancer, this paper extends our previous research with this sample.<sup>5</sup> The purposes of this study, in a sample of patients with breast cancer (n=540) who received CTX, were: to determine the occurrence and severity of symptoms prior to receipt of the next dose of CTX (Time 1 (T1)); approximately one week after receiving CTX, (Time 2, (T2)); and approximately two weeks after receiving CTX (Time 3 (T3)); to evaluate for differences in the number and types of symptom clusters at each of these three time points using ratings of occurrence and severity; and to evaluate for changes in these symptom clusters over time.

## METHODS

### Patients and Settings

This study is part of a descriptive, longitudinal study that evaluated the symptom experience of oncology outpatients receiving CTX. The methods for this study are described in detail elsewhere.<sup>5,10-12</sup> In brief, 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 in the larger study. The major reason for refusal was reported as being too overwhelmed with their cancer treatment. For this study, only patients with breast cancer (n=540) were included in the analyses.

### Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. Patients rated their functional status using the Karnofsky Performance Status (KPS) scale.<sup>13,14</sup> Patients

completed the Self-Administered Comorbidity Questionnaire (SCQ) that assesses the occurrence of, treatment for, and impact of 13 common medical conditions. The total SCQ score ranges from 0 to 39. The SCQ has well established validity and reliability.<sup>15</sup>

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. The AUDIT has well established validity and reliability.<sup>16,17</sup> 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 or not 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 validity and reliability of the MSAS are well established in studies of oncology inpatients and outpatients.<sup>18,19</sup>

## Study Procedures

This 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 cycles (most patients were on 21 or 28 day cycles), patients completed questionnaires in their homes, a total of six times over two cycles of CTX. For this analysis, the symptom assessment data from the enrollment cycle (i.e., approximately one week prior to receiving CTX, T1), 1 week after receiving CTX (i.e., acute symptoms following the administration of CTX, T2), and approximately 2 weeks after receiving CTX (i.e., potential nadir, T3)) were analyzed. Medical records were reviewed for disease and treatment information.

## Data Analysis

Data were analyzed using International Business Machines Statistical Package for the Social Sciences (IBM SPSS) 23<sup>20</sup> and MPlus Version 7.3.<sup>21</sup> Descriptive statistics and frequency distributions were calculated for the demographic and clinical characteristics.

## Creation of Symptom Clusters Using Exploratory Factor Analysis

As described by Miaskowski,<sup>1</sup> the “de novo” identification of symptom clusters was the approach used in this study. Exploratory factor analyses (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).<sup>22</sup> 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.<sup>23,24</sup> All of the EFAs were done using MPlus.<sup>21,25</sup>

For each EFA, factor loadings were considered meaningful if the loading had an absolute value of  $\geq 0.40$ .<sup>21,25,26</sup> 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 met our pre-set criterion of  $\geq 0.40$ , 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.<sup>22,26,27</sup>

EFA was used to identify symptom clusters from the occurrence rates and the severity ratings of 30 out of the 38 MSAS symptoms assessed. 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. Eight symptoms on the MSAS (i.e., lack of energy, difficulty breathing, problems with urination, vomiting, increased appetite, difficulty swallowing, swelling of arms or legs, chest tightness) were excluded from the analyses due to insufficient variation in the occurrence of these symptoms.

The occurrence items were evaluated as dichotomous variables (i.e., had versus did not have the symptom).<sup>21,25</sup> For these EFAs, tetrachoric correlations were used to create the matrix of associations. The severity items were examined as ordinal items. For these EFAs, polychoric correlations were used to create the matrix of associations. 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.<sup>21,25</sup> 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<sup>21,25</sup>) 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 EFAs for severity were 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. This approach was used because in the initial analyses that were done with severity ratings that did not include zero (i.e., 1, 2, 3, 4), the pairwise

missingness (i.e., 1-covariance coverage for each of the item pairs) was over 90% and the estimation failed.

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). Separate EFAs were done for the symptom occurrence and symptom severity ratings at the each of the three assessments (i.e., T1, T2, and T3). By conducting EFAs at three specific time points, we were able to compare the stability of the symptom clusters over time.

### Differences in the 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.<sup>28</sup> 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 of the Patients

The demographic and clinical characteristics of the patients are summarized in Table 1. The sample was 99.1% female and 66.3% were married or partnered with a mean age of  $53.26 \pm 11.62$  years. The majority of the patients was White (67.0%) and well educated ( $16.40 \pm 2.93$  years). Patients had an average of  $2.20 \pm 1.34$  comorbid conditions and their mean KPS score was  $80.46 \pm 12.14$ .

### Symptom Characteristics

The mean number of symptoms at each of the time points was  $14.69 \pm 7.08$  at T1;  $14.67 \pm 6.86$  at T2; and  $12.74 \pm 6.72$  at T3 (Table 1). As shown in Table 2, across the three assessments, lack of energy, difficulty sleeping, and pain were among the top five symptoms with the highest occurrence rates. While the exact rank order of the five symptoms with the highest severity ratings differed, the specific symptoms were the same across the three assessments.

### Symptom Clusters Based on Occurrence Ratings

As shown in Table 3, for the T1 assessment, a six factor solution was found. Factor 1 consisted of seven symptoms (i.e., pain, dry mouth, nausea, feeling drowsy, numbness/tingling in hands/feet, lack of appetite, dizziness) and was named the *sickness behavior* cluster. Factor 2 consisted of six symptoms (i.e., difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, “I don’t look like myself”) and was named the *psychological* cluster. Factor 3 consisted of two symptoms (i.e., hot flashes, sweats) and was named the hormonal cluster. Factor 4 consisted of four symptoms (i.e., difficulty sleeping, abdominal cramps, shortness of breath, weight loss) and was named the *GI* cluster. Factor 5 consisted of two symptoms (i.e., weight gain, weight loss) and was named the *weight change*



cluster. Of note, weight loss loaded negatively on the weight change symptom cluster, which indicates that lower scores on this symptom (i.e., weight gain) was more likely to be present among patients with this symptom cluster. Factor 6 consisted of five symptoms (i.e., weight gain, mouth sores, hair loss, change in the way food tastes, changes in skin) and was named the *epithelial* cluster.

As shown in Table 4, for the T2 assessment, a five factor solution was found. Factor 1 consisted of five symptoms (i.e., feeling nervous, feeling sad, worrying, feeling irritable, “I don’t look like myself”) and was named the *psychological* cluster. Factor 2 consisted of four symptoms (i.e., hot flashes, difficulty sleeping, sweats, problems with sexual interest or activity) and was named the *hormonal* cluster. Factor 3 consisted of seven symptoms (i.e., dry mouth, nausea, lack of appetite, change in the way food tastes, weight loss, abdominal cramps, diarrhea) and was named the *nutritional* cluster. Factor 4 consisted of three symptoms (i.e., weight loss, feeling bloated, weight gain) and was named the *GI* cluster. Of note, weight loss loaded negatively on the GI symptom cluster, which indicates that lower scores on this symptom (i.e., weight gain) was more likely to be present among patients with this symptom cluster. Factor 5 consisted of four symptoms (i.e., “I don’t look like myself”, change in the way food tastes, hair loss, mouth sores) and was named the *epithelial* cluster.

As shown in Table 5, for the T3 assessment, a five factor solution was found. Factor 1 consisted of two symptoms (i.e., hot flashes, sweats) and was named the *hormonal* cluster. Factor 2 consisted of six symptoms (i.e., worrying, feeling irritable, difficulty concentrating, feeling nervous, feeling drowsy, feeling sad) and was named the *psychological* cluster. Factor 3 consisted of five symptoms (i.e., abdominal cramps, difficulty sleeping, feeling bloated, weight gain, nausea) and was named the *GI* cluster. Factor 4 consisted of five symptoms (i.e., weight gain, nausea, lack of appetite, weight loss, change in the way food tastes) and was named the *nutritional* cluster. Of note, weight gain loaded negatively on the nutritional symptom cluster, which indicates that lower scores on this symptom (i.e., weight loss) were more likely to be present among patients with this symptom cluster. Factor 5 consisted of five symptoms (i.e., change in the way food tastes, changes in skin, itching, mouth sores, “I don’t look like myself”) and was named the *epithelial* cluster.

### Symptom Clusters Based on Severity Ratings

As shown in Table 6, for the T1 assessment, a six factor solution was found. Factor 1 consisted of six symptoms (i.e., difficulty concentrating, feeling nervous, feeling sad, worrying, feeling irritable, “I don’t look like myself”) and was named the *psychological* cluster. Factor 2 consisted of five symptoms (i.e., pain, dry mouth, nausea, feeling drowsy, dizziness) and was named the *sickness behavior* cluster. Factor 3 consisted of two symptoms (i.e., sweats, hot flashes) and was named the *hormonal* cluster. Factor 4 consisted of three symptoms (i.e., feeling bloated, diarrhea, abdominal cramps) and was named the *GI* cluster. Factor 5 consisted of three symptoms (i.e., lack of appetite, weight gain, weight loss) and was named the *weight change* cluster. Of note, weight gain loaded negatively on the weight change symptom cluster, which indicates that lower scores on this symptom (i.e., weight loss) were more likely to be present among patients with this symptom cluster. Factor 6

consisted of five symptoms (i.e., “I don’t look like myself”, weight gain, hair loss, change in the way food tastes, changes in skin) and was named the *epithelial* cluster.

As shown in Table 7, for the T2 assessment, a six factor solution was found. Factor 1 consisted of two symptoms (i.e., hot flashes, sweats) and was named the *hormonal* cluster. Factor 2 consisted of four symptoms (i.e., feeling sad, feeling nervous, worrying, feeling irritable) and was named the *psychological* cluster. Factor 3 consisted of three symptoms (i.e., feeling drowsy, numbness in hands/feet, pain) and was named the *CTX-neuropathy* cluster. Factor 4 consisted of three symptoms (i.e., feeling bloated, abdominal cramps, weight gain) and was named the *GI* cluster. Factor 5 consisted of four symptoms (i.e., weight gain, weight loss, nausea, lack of appetite) and was named the *nutritional* cluster. Of note, weight gain loaded negatively on the nutritional symptom cluster, which indicates that lower scores on this symptom (i.e., weight loss) were more likely to be present among patients with this symptom cluster. Factor 6 consisted of five symptoms (i.e., hair loss, change in the way food tastes, “I don’t look like myself”, changes in skin, mouth sores) and was named the *epithelial* cluster.

As shown in Table 8, for the T3 assessment, a five factor solution was found. Factor 1 consisted of two symptoms (i.e., hot flashes, sweats) and was named the *hormonal* cluster. Factor 2 consisted of six symptoms (i.e., difficulty concentrating, feeling nervous, feeling sad, feeling drowsy, worrying, feeling irritable) and was named the *psychological* cluster. Factor 3 consisted of three symptoms (i.e., feeling bloated, abdominal cramps, weight gain) and was named the *GI* cluster. Factor 4 consisted of five symptoms (i.e., weight gain, nausea, lack of appetite, weight loss, change in the way food tastes) and was named the *nutritional* cluster. Of note, weight gain loaded negatively on the nutritional symptom cluster, which indicates that lower scores on this symptom (i.e., weight loss) were more likely to be present among patients with this symptom cluster. Factor 5 consisted of five symptoms (i.e., change in the way food tastes, mouth sores, hair loss, “I don’t look like myself”, changes in skin) and was named the *epithelial* cluster.

### **Similarities and Differences in the Number and Types of Symptom Clusters**

As shown in Table 9, for the occurrence dimension, the number of symptom clusters ranged from five to six. Across the three occurrence assessments, the four common symptom clusters were: psychological, hormonal, GI, and epithelial. While at T1, sickness behavior and weight change clusters were identified neither were found at T2 or T3. While a nutritional symptom cluster was identified at T2 and T3, it was not found at T1.

For the severity dimension, the number of symptom clusters ranged from five to six. Across the three severity assessments, the four common symptom clusters were: psychological, hormonal, GI, and epithelial. While at T1, sickness behavior and weight change clusters were identified, neither symptom cluster was found at T2 or T3. While a nutritional cluster was identified at T2 and T3, it was not found at T1. In addition, a CTX neuropathy cluster was identified only at T2.



### Agreement in the Types of Symptoms Within Each Symptom Cluster

Table 9 presents a summary of the percentage agreement among the symptoms within each cluster across the occurrence and severity dimensions and across time. For the psychological cluster, the total number of symptoms ranged from 4 to 6 and the percent agreement ranged from 57.1% to 85.7%. The four symptoms that were included in all of these EFAs, regardless of the dimension were: feeling nervous, feeling sad, worrying, and feeling irritable. For the hormonal 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 across all of these EFAs were: hot flashes and sweats. For the nutritional cluster, the total number of symptoms ranged from 0 to 7 and the percent agreement ranged from 0.0% to 85.7%. The three symptoms that were included across all of these EFAs were: nausea, lack of appetite, and weight loss. For the GI symptom, the total number of symptoms ranged from 3 to 5 and the percent agreement ranged from 37.5% to 62.5%. None of the symptoms were found in all six symptom cluster solutions. However, feeling bloated was included in two of the occurrence EFAs (i.e., T2 and T3) and in all of the severity EFAs. In addition, abdominal cramps was included in two of the occurrence EFAs (i.e., T1 and T3) and in all of the severity EFAs.

For the epithelial cluster, the total number of symptoms ranged from 4 to 5 and the percent agreement ranged from 57.1% to 71.4%. The only symptom that was included across all of these EFAs was: change in the way food tastes. For the sickness behavior cluster, the total number of symptoms ranged from 0 to 7 and the percent agreement ranged from 0.0% to 100%. At the T1 assessment, the five symptoms that were identified for both the occurrence and severity dimensions were: pain, dry mouth, nausea, feeling drowsy, and dizziness. For the weight change cluster, the total number of symptoms ranged from 0 to 3 and the percent agreement ranged from 0.0% to 100%. At the T1 assessment, the two symptoms that were identified for both the occurrence and severity dimensions were: weight loss and weight gain. For the CTX neuropathy cluster, the total number of symptoms ranged from 0 to 3 and the percent agreement ranged from 0.0% to 100%. This symptom cluster was identified only at T2 using the severity dimension.

## DISCUSSION

To our knowledge, this study is the first to evaluate for changes over time in the number and types of symptom clusters in patients with breast cancer who underwent CTX using occurrence rates and severity ratings. As summarized in Table 9, while across the two symptom dimensions and the three assessments, eight distinct symptom clusters were identified, only five were relatively stable across both dimensions and across time (i.e., psychological, hormonal, nutritional, GI, epithelial). Two of the additional symptom clusters varied by time but not by symptom dimension. Prior to the receipt of the next dose of CTX (T1), for both occurrence and severity, a sickness behavior cluster and a weight change cluster were identified. The final cluster (i.e., CTX neuropathy) was identified only using the severity dimension at T2. Overall, our findings suggest that regardless of the dimension used, symptom clusters remain relatively stable over time. The remainder of the discussion will describe each of the symptom clusters in terms of variability in the specific symptoms

within each cluster; how each of the clusters compares with previous findings; and the clinical implications of each of the symptom clusters.

### Psychological Symptom Cluster

A psychological cluster was identified in all six EFAs. While the number of symptoms in this cluster ranged from four to seven, feeling nervous, feeling sad, worrying, and feeling irritable were included across both dimensions and at all three time points. Of note, across the three studies of patients with breast cancer<sup>6-8</sup> and the eight studies of patients with a variety of cancer diagnoses,<sup>29-36</sup> some type of psychological or mood related cluster was found. Taken together, this consistent finding highlights the importance of psychological symptoms in oncology patients.

Depending on the symptom assessment instrument used, the specific symptoms within the psychological cluster varied across the ten studies.<sup>6-8,29-34,36</sup> In the three studies of patients with heterogeneous diagnoses<sup>29,30,34</sup> and in the study of patients with liver cancer<sup>35</sup> that used the MD Anderson Symptom Inventory (MDASI), distress and sadness were the two symptoms found in the psychological cluster. Across the five studies of patients with breast,<sup>6,7</sup> ovarian,<sup>31,36</sup> or heterogeneous<sup>33</sup> cancers that used the MSAS, feeling nervous, worrying, and feeling sad were present in the psychological cluster. In addition, in four of these studies,<sup>6,7,33,36</sup> feeling irritable was included in this symptom cluster.

This growing body of evidence suggests that a psychological cluster in oncology patients includes the symptoms of feeling nervous, feeling sad, worrying, and feeling irritable. Given the high occurrence rates for anxiety<sup>37-39</sup> and depression<sup>37,38,40</sup> as single symptoms, as well as the fact that between 10% and 28% of patients with breast cancer report the co-occurrence of anxiety and depression,<sup>38</sup> this symptom cluster warrants careful and ongoing assessments and management in oncology patients regardless of their cancer diagnosis.

### Hormonal Symptom Cluster

In the current study, a hormonal symptom was identified in all six EFAs. The total number of symptoms ranged from two to four. Hot flashes and sweats were included across both dimensions and across all three time points. While in the three studies of patients with breast cancer,<sup>6-8</sup> only one<sup>6</sup> found a hormonal cluster, in the studies of patients with ovarian cancer<sup>36</sup> or patients with heterogeneous cancers,<sup>33</sup> this symptom cluster was identified. Across these three studies,<sup>6,33,36</sup> sweats was the only symptom that was common to our study. In two of the previous studies,<sup>33,36</sup> difficulty sleeping, which was identified only once in our study (i.e., occurrence T2), was part of the hormonal cluster. It is interesting to note that in the study by Yates and colleagues,<sup>33</sup> the hormonal cluster was found only in patients who were <60 years of age. In their sample, 48.3% of the patients in the younger age group, compared to 21.8% of the patients ≥ 60 years of age, had a diagnosis of breast cancer.

In terms of hot flashes, only one study<sup>6</sup> had this symptom in their hormonal cluster. The reason for this inconsistent finding is because the original MSAS did not include hot flashes. An equally important finding from the Phligbua et al., study,<sup>6</sup> was the identification of night sweats and mood swings as part of their hormonal cluster. These symptoms were identified as part of this cluster because the investigators added a number of menopausal symptoms to

the MSAS. Given that CTX<sup>41-43</sup> and aromatase inhibitors<sup>44</sup> can produce menopausal-associated symptoms in women with breast cancer and that these symptoms are common in healthy women as well,<sup>45</sup> future studies of symptom clusters in patients with breast cancer should include these common menopausal-associated symptoms as part of the assessment instrument.

### GI Symptom Cluster

The third symptom cluster that we identified across all six EFAs was labeled the GI cluster. While the number of symptoms ranged from three to five, none of the symptoms were present for both dimensions at all three time points. However, feeling bloated and abdominal cramps were found in all of the severity EFAs and in two of the occurrence EFAs. While this symptom cluster was identified in studies of patients with breast,<sup>7-9</sup> lung,<sup>34,46</sup> ovarian,<sup>31,36</sup> liver,<sup>35</sup> and hepatocellular<sup>47</sup> cancers, as well as in studies that included patients with heterogeneous cancer diagnoses,<sup>29,30,33,48,49</sup> the specific symptoms within this cluster were extremely variable depending on the symptom assessment instrument that was used.

In the six studies that used the MSAS,<sup>6,7,31,33,36,48</sup> only one did not identify a GI cluster.<sup>6</sup> In the other five studies, feeling bloated was the only symptom in this cluster that was the same as in our GI cluster. Across the fourteen studies that identified a GI cluster, with the exception of the study by Yates and colleagues,<sup>33</sup> nausea and vomiting were the two symptoms that loaded on this cluster. In our study, nausea, but not vomiting loaded on the GI cluster. Given the number of studies that identified a GI cluster, additional research is warranted with a consistent set of GI related symptoms to determine the common symptoms in this cluster, as well as the unique symptoms that may be specific to certain cancer diagnoses (e.g., difficulty swallowing with esophageal cancer<sup>50</sup>) or cancer treatments (e.g., diarrhea with pelvic radiation<sup>51</sup>). This information can be used to develop and test more effective symptom management interventions.

### Epithelial Symptom Cluster

The epithelial cluster was the fourth cluster that we identified across all six EFAs. While the number of symptoms ranged from four to five, change in the way food tastes was the only symptom included in this cluster across the two symptom dimensions and across all three time points. However, “I don’t look like myself”, hair loss, and changes in skin were found in all of the severity EFAs and in two of the occurrence EFAs. While mouth sores was found in all of the occurrence EFAs, this symptom was found in only two of the severity EFAs.

Across the five studies that used the MSAS,<sup>6,7,33,36,48</sup> while the names of the clusters varied (i.e., CTX toxicity cluster,<sup>33</sup> body image cluster,<sup>36</sup> image-related cutaneous symptoms<sup>7</sup>) all five identified a symptom cluster that included, “I don’t look like myself” and hair loss. In addition, in four of the five studies,<sup>6,7,33,48</sup> skin changes loaded on this cluster. Of note, while change in the way food tastes was found in all six of our EFAs, this symptom was found as a part of this cluster in only two studies.<sup>7,33</sup> Taken together, these findings suggest that the symptoms of hair loss, skin changes, and “I don’t look like myself”, should be part of a comprehensive symptom inventory for oncology patients. The frequency with which

these symptoms were associated with each other makes sense, given that hair loss and changes in skin can have a significant impact on oncology patients' body image.<sup>52,53</sup>

### **Nutritional Symptom Cluster**

In our study, the nutritional cluster was not identified at the assessment immediately prior to the patients' next dose of CTX (i.e., T1). At the other two assessments, this cluster, which consisted of four to seven symptoms, was found across both symptom dimensions. Nausea, lack of appetite, and weight loss were the three symptoms present in all four EFAs. In the studies that used the MSAS,<sup>6,7,33,36,48</sup> neither study of breast cancer patients<sup>6,7</sup> nor the study by Molassiotis and colleagues,<sup>48</sup> identified this type of symptom cluster. However, in a study of ovarian cancer patients,<sup>36</sup> nausea, weight loss, lack of appetite, and change in the way food tastes were part of a GI cluster. In the study by Yates and colleagues,<sup>33</sup> that included a heterogeneous sample in terms of both cancer diagnoses and treatments, in the patients <60 years of age, the following symptoms were part of a treatment-related cluster: dry mouth, lack of appetite, nausea, weight loss, and change in the way food tastes. In contrast, in the patients who were ≥ 60 years of age, a nutrition cluster was identified that included: weight loss, lack of appetite, and change in the way food tastes.

The nutritional status of patients undergoing cancer treatment is extremely important.<sup>54</sup> The fact that nausea, lack of appetite, change in the way food tastes, and weight loss were found as a cluster in several studies suggests that this symptom cluster warrants additional investigation. Research is needed to determine if the GI and the nutritional clusters are distinct or related clusters. The identification of two distinct clusters may be related to patients' cancer diagnoses and/or the timing of the symptom assessments in relationship to the patients' treatment regimens.

### **Sickness Behavior Symptom Cluster**

It is not entirely clear why the sickness behavior cluster was identified only in the occurrence and severity EFAs at the assessment prior to the next dose of CTX. "Sickness behavior" is a term that was first described in studies of animals following the injection of endotoxin.<sup>55,56</sup> As part of the inflammatory response, these animals exhibited fatigue, somnolence, decreased appetite, decreased activity, and depressive symptoms. Cleeland and colleagues<sup>56</sup> suggested that this biological response may be the underlying mechanism for common symptoms associated with cancer and its treatments. Consistent with our findings, in previous studies that used the MDASI to evaluate symptom clusters, a sickness symptom cluster<sup>29,30</sup> or a "general" symptom cluster<sup>46</sup> were identified that included the symptoms of pain, lack of appetite, and drowsiness. In addition, in the study by Wang and colleagues,<sup>46</sup> dry mouth and numbness were included in their cluster.

It is interesting to note that in the studies that used the MSAS to identify symptom clusters,<sup>6,7,31,33,36,48</sup> only the study by Yates and colleagues,<sup>33</sup> identified a "treatment-related" cluster in the patients who were <60 years of age. The symptoms that their study had in common with our findings were: dry mouth, nausea, pain, lack of appetite, dizziness, and feeling drowsy. Across these nine studies,<sup>6,7,29-31,33,36,46,48</sup> the variability in both the identification of a sickness behavior cluster, as well as the specific symptoms within the

cluster, may be related to the differences in the number of symptoms evaluated using the MDASI (i.e., 13 symptoms) versus the MSAS (i.e., 32 to 38 symptoms); the patients' cancer diagnoses; the treatments the patients received; and/or the timing of the assessments. Additional research is warranted to confirm or refute the clinical significance of this symptom cluster.

### **Weight Change Symptom Cluster**

Similar to the sickness behavior symptom cluster, it is not entirely clear why a weight change cluster was identified for both symptom dimensions only at the assessment done prior to the next dose of CTX (T1). In the occurrence EFA, weight loss loaded negatively on this cluster. However, in the severity EFA, weight gain loaded negatively on this cluster. In addition, both weight loss and weight gain were included in our GI and nutritional clusters. Given that in previous studies, weight loss was the only symptom included on the MSAS,<sup>6,7,31,33,36,48</sup> additional research is warranted to confirm this distinct symptom cluster.

### **Chemotherapy Neuropathy Symptom Cluster**

Given that CTX-induced neuropathy is the most common neurologic complication of platinum and taxane compounds,<sup>57,58</sup> it is somewhat surprising that this symptom cluster was identified only using severity ratings based on symptoms reported in the week following the administration of CTX (T2). One potential explanation for this finding is that the patients in our study were recruited during the initial cycles of their CTX treatment. In previous studies of patients with breast,<sup>6-9</sup> ovarian,<sup>31,36</sup> lung,<sup>34,46,59-61</sup> or heterogeneous<sup>29,30,32,33,48,49,62,63</sup> cancers, a symptom cluster that included numbness/tingling of the hands/feet was identified. Again, this symptom cluster warrants confirmation in future studies, particularly at the completion of CTX.

### **Limitations**

Several limitations warrant consideration. Because our study included patients who received neoadjuvant and adjuvant CTX, our findings may not generalize to all patients with breast cancer. In addition, since only a small sample of men with breast cancer were included (n=5) and they were not analyzed separately, these findings may not be representative of the symptom clusters of men with breast cancer. Given that the primary reason for refusal was being too overwhelmed with their cancer diagnosis, our findings may underestimate the symptom burden in these patients. Lastly, because the majority of our sample was White, our findings may not generalize to patients from other ethnic or minority groups.

### **Conclusions**

Despite these limitations, our findings suggest that five symptom clusters (i.e., psychological, hormonal, nutritional, GI, epithelial) were relatively stable across both symptom dimensions and across time. These five clusters warrant additional investigation to establish the specific symptoms that are an integral part of each of these symptom clusters. In addition, the three clusters that lacked consistency across dimensions and time (i.e., sickness behavior, weight change, CTX neuropathy) warrant confirmation in future studies.

## Implications for Clinical Practice and Research

Findings from this study confirm that patients with breast cancer undergoing CTX experience a high symptom burden and that five symptom clusters persist over the entire cycle of CTX. Clinicians need to focus their ongoing assessments on these persistent symptom clusters and prescribe appropriate interventions. Given that the psychological symptom cluster is so common, clinicians need to consider referrals to mental health professionals to assist patients to cope with the psychological sequelae of cancer and its treatment. In addition, referrals to dietitians may be warranted to assist patients to manage the symptoms associated with the nutritional and GI symptom clusters.

Future studies are needed to confirm the three symptom clusters that were not found consistently across our assessments. In addition, research is needed on the most appropriate interventions to treat single or multiple symptom clusters. Future studies are warranted that evaluate the common and distinct mechanisms that underlie these symptom clusters.

## Acknowledgments

This study was funded by a grant from the National Cancer Institute (NCI, CA134900). Dr. Christine Miaskowski is an American Cancer Society Clinical Research Professor and is funded by a K05 award from the NCI (CA168960). Ms. Ward Sullivan was funded by a National Institute of Health (NIH) T32 grant (NR007088).

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**Table 1**

Demographic and Clinical Characteristics of Patients With Breast Cancer Undergoing Chemotherapy (n=540)

Characteristic	Mean (SD)
Age (years)	53.26 (11.62)
Education (years)	16.40 (2.93)
Body mass index (kg/m <sup>2</sup> )	26.23 (5.81)
Karnofsky Performance Status score	80.46 (12.14)
Number of comorbidities	2.20 (1.34)
Self-administered Comorbidity Questionnaire score	4.99 (2.90)
Alcohol Use Disorders Identification Test score	2.82 (2.34)
Time since cancer diagnosis (years)	2.54 (4.77)
Time since cancer diagnosis (median)	0.42
Number of prior cancer treatments	1.73 (1.77)
Number of metastatic sites including lymph node involvement	0.95 (1.26)
Number of metastatic sites excluding lymph node involvement	0.51 (1.04)
Mean number of MSAS symptoms at each time point (out of 38 symptoms)	
Time 1 (recovery from previous cycle)	14.69 (7.08)
Time 2 (acute symptoms)	14.67 (6.86)
Time 3 (potential nadir)	12.74 (6.72)
	% (n)
Gender	
Female	99.1 (535)
Male	0.9 (5)
Ethnicity	
White	67.0 (359)
Black	6.7 (36)
Asian or Pacific Islander	14.9 (80)
Hispanic Mixed or Other	11.4 (61)
Married or partnered (% yes)	66.3 (352)
Lives alone (% yes)	17.1 (91)
Child care responsibilities (% yes)	30.9 (162)
Care of adult responsibilities (% yes)	8.2 (40)

Characteristic	Mean (SD)
Currently employed (% yes)	41.0 (220)
<b>Income</b>	
< \$30,000	14.6 (70)
\$30,000 to <\$70,000	18.2 (87)
\$70,000 to < \$100,000	17.6 (84)
\$100,000	49.5 (237)
<b>Specific comorbidities (% yes)</b>	
Heart disease	3.7 (20)
High blood pressure	23.0 (124)
Lung disease	4.1 (22)
Diabetes	6.3 (34)
Ulcer or stomach disease	3.1 (17)
Kidney disease	0.9 (5)
Liver disease	4.3 (23)
Anemia or blood disease	14.3(77)
Depression	22.0 (119)
Osteoarthritis	11.1 (60)
Back pain	25.6 (138)
Rheumatoid arthritis	2.8 (15)
Exercise on a regular basis (% yes)	75.0 (392)
Smoking, current or history of (% yes)	28.5 (153)
Receiving neoadjuvant CTX (% yes)	25.6 (137)
<b>Type of prior cancer treatment</b>	
No prior treatment	27.2 (144)
Only surgery, CTX, or RT	42.3 (224)
Surgery and CTX, or surgery and RT, or CTX and RT	13.4 (71)
Surgery and CTX and RT	17.0 (90)
Sentinel lymph node biopsy (% yes)	53.5 (281)
Axillary lymph node dissection (% yes)	42.6 (223)
Reconstruction to the affected breast (% yes)	23.3 (124)
<b>Type of surgery</b>	
Breast conservation	20.6 (73)
Mastectomy	18.6 (66)
Bilateral mastectomy	15.5 (55)
Unknown	0.6 (2)
Not applicable	44.6 (158)
Estrogen receptor (ER) status	

Characteristic	Mean (SD)
ER positive	68.2 (364)
ER negative	30.3 (162)
Progesterone receptor (PR) status	
PR negative	55.1 (294)
PR positive	43.3 (231)
Breast cancer gene 1 (BRCA1) (% positive)	3.9 (21)
Breast cancer gene 2 (BRCA2) (% positive)	2.6 (14)
Human epidermal growth factor receptor (HER)-2 (% negative)	63.5 (339)
On hormone replacement therapy prior to cancer diagnosis	
Yes	8.4 (45)
No	56.9 (304)
Unknown	34.6 (185)

Abbreviations: CTX = chemotherapy; kg = kilograms, m<sup>2</sup> = meter squared, MSAS = Memorial Symptom Assessment Scale, RT = radiation therapy, SD = standard deviation



**Table 2**  
Symptom Occurrence Rates and Severity Ratings for Symptoms at the Three Time Points

Symptom	Occurrence Rates % (n)			Severity Ratings Mean (SD)		
	Time 1* n=534	Time 2 n=515	Time 3 n=500	Time 1 n=534	Time 2 n=515	Time 3 n=500
Lack of energy	86.3 (461)	90.3 (465)	86.2 (431)	1.70 (0.96)	1.98 (1.00)	1.71 (0.98)
Difficulty sleeping	74.5 (398)	72.2 (372)	66.6 (333)	1.49 (1.11)	1.47 (1.14)	1.32 (1.18)
Hair loss	69.5 (371)	57.3 (295)	54.4 (272)	1.86 (1.55)	1.44 (1.54)	1.30 (1.49)
Pain	60.7 (324)	69.7 (359)	62.4 (312)	1.14 (1.10)	1.36 (1.11)	1.16 (1.09)
Feeling drowsy	60.3 (322)	65.6 (338)	51.8 (259)	1.01 (0.98)	1.16 (1.06)	0.85 (0.99)
Difficulty concentrating	57.5 (307)	61.4 (316)	58.4 (292)	0.87 (0.89)	1.00 (0.97)	0.91 (0.95)
Change in the way food tastes	54.7 (292)	60.8 (313)	49.8 (249)	1.19 (1.29)	1.39 (1.35)	1.02 (1.24)
Worrying	54.5 (291)	47.6 (245)	44.2 (221)	0.99 (1.07)	0.87 (1.07)	0.77 (1.04)
Feeling sad	49.4 (264)	50.5 (260)	44.0 (220)	0.85 (1.01)	0.86 (1.02)	0.75 (0.98)
"I don't look like myself"	48.7 (260)	50.5 (260)	46.6 (233)	1.06 (1.27)	1.09 (1.30)	0.95 (1.21)
Dry mouth	47.6 (254)	48.7 (251)	35.6 (178)	0.82 (1.02)	0.85 (1.05)	0.63 (0.98)
Nausea	47.4 (253)	58.3 (300)	39.0 (195)	0.80 (1.02)	1.06 (1.12)	0.68 (1.01)
Feeling irritable	44.2 (236)	47.2 (243)	44.6 (223)	0.76 (0.99)	0.79 (0.99)	0.69 (0.90)
Numbness or tingling in hands/feet	44.0 (235)	44.1 (227)	43.2 (216)	0.78 (1.05)	0.78 (1.06)	0.77 (1.07)
Changes in skin	43.1 (230)	45.4 (234)	40.2 (201)	0.83 (1.12)	0.82 (1.06)	0.71 (1.01)
Hot flashes	42.3 (226)	42.1 (217)	37.2 (186)	0.77 (1.04)	0.74 (1.02)	0.69 (1.02)
Feeling nervous	42.1 (225)	32.6 (168)	29.0 (145)	0.65 (0.90)	0.50 (0.83)	0.45 (0.83)
Lack of appetite	41.8 (223)	49.7 (256)	36.2 (181)	0.75 (1.05)	0.94 (1.14)	0.64 (0.99)
Constipation	41.0 (219)	44.7 (230)	31.4 (157)	0.78 (1.08)	0.84 (1.09)	0.56 (0.96)
Sweats	36.1 (193)	33.2 (171)	27.2 (136)	0.62 (0.96)	0.58 (0.94)	0.48 (0.88)
Feeling bloated	35.2 (188)	33.0 (170)	28.8 (144)	0.61 (0.93)	0.58 (0.94)	0.48 (0.86)
Problems with sexual interest or activity	33.5 (179)	30.5 (157)	30.4 (152)	0.81 (1.29)	0.75 (1.26)	0.73 (1.24)
Dizziness	31.6 (169)	33.2 (171)	24.4 (122)	0.46 (0.78)	0.50 (0.82)	0.34 (0.71)
Cough	31.6 (169)	28.0 (144)	31.4 (157)	0.45 (0.76)	0.43 (0.80)	0.49 (0.84)
Shortness of breath	29.4 (157)	27.2 (140)	23.0 (115)	0.45 (0.80)	0.44 (0.82)	0.37 (0.76)

Symptom	Occurrence Rates % (n)			Severity Ratings Mean (SD)		
	Time 1* n=534	Time 2 n=515	Time 3 n=500	Time 1 n=534	Time 2 n=515	Time 3 n=500
Itching	27.3 (146)	22.5 (116)	22.2 (111)	0.43 (0.80)	0.37 (0.80)	0.38 (0.81)
Diarrhea	27.2 (145)	25.0 (129)	20.2 (101)	0.48 (0.90)	0.42 (0.83)	0.34 (0.78)
Weight gain	27.2 (145)	24.1 (124)	23.2 (116)	0.44 (0.84)	0.38 (0.80)	0.38 (0.80)
Increased appetite	26.8 (143)	20.0 (103)	22.0 (110)	0.45 (0.84)	0.35 (0.78)	0.38 (0.79)
Mouth sores	22.8 (122)	21.9 (113)	20.4 (102)	0.39 (0.79)	0.38 (0.82)	0.32 (0.73)
Weight loss	21.9 (117)	21.0 (108)	16.6 (83)	0.29 (0.62)	0.27 (0.60)	0.21 (0.55)
Chest tightness	20.0 (107)	16.7 (86)	13.4 (67)	0.30 (0.69)	0.23 (0.60)	0.21 (0.59)
Difficulty breathing	19.5 (104)	17.3 (89)	15.8 (79)	0.28 (0.65)	0.27 (0.67)	0.24 (0.63)
Abdominal cramps	18.2 (97)	22.9 (118)	13.6 (68)	0.32 (0.77)	0.41 (0.87)	0.24 (0.68)
Swelling of arms or legs	15.7 (84)	15.0 (77)	15.6 (78)	0.28 (0.73)	0.25 (0.71)	0.25 (0.67)
Difficulty swallowing	14.2 (76)	15.3 (79)	13.8 (69)	0.22 (0.64)	0.25 (0.70)	0.23 (0.66)
Problems with urination	11.0 (59)	12.4 (64)	8.6 (43)	0.18 (0.58)	0.20 (0.59)	0.14 (0.51)
Vomiting	9.9 (53)	10.9 (56)	5.8 (29)	0.15 (0.56)	0.19 (0.63)	0.09 (0.43)

Abbreviation: SD = standard deviation

<sup>a</sup>Severity ratings: 0 =did not have the symptom, 1=slight, 2=moderate, 3=severe, 4=very severe

Timing of symptom assessment: Time 1=prior to CTX, Time 2=acute symptoms (approximately 1 week post CTX), Time 3=potential nadir (approximately 2 weeks post CTX)

\* Orientation column in rank order

Table 3

Exploratory Factor Analysis Using Ratings of Symptom Occurrence Approximately One Week Prior to Chemotherapy Administration <sup>a</sup>

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
	Sickness Behavior Symptom Cluster	Psychological Symptom Cluster	Hormonal Symptom Cluster	Gastrointestinal Symptom Cluster	Weight Change Symptom Cluster	Epithelial Symptom Cluster
Pain	<b>0.609</b>	0.078	-0.097	0.113	0.152	-0.108
Dry mouth	<b>0.471</b>	-0.063	0.002	0.000	-0.080	0.304
Nausea	<b>0.698</b>	0.004	0.149	-0.069	-0.106	0.125
Feeling drowsy	<b>0.530</b>	0.307	0.018	-0.103	0.098	0.048
Numbness/tingling in hands/feet	<b>0.471</b>	0.027	-0.230	0.196	0.249	0.009
Lack of appetite	<b>0.541</b>	-0.026	0.139	0.207	-0.393	0.006
Dizziness	<b>0.466</b>	0.081	0.076	0.151	-0.166	0.002
Difficulty concentrating	0.238	<b>0.501</b>	0.092	-0.030	0.167	-0.021
Feeling nervous	0.060	<b>0.806</b>	-0.070	-0.114	0.024	0.077
Feeling sad	-0.018	<b>0.848</b>	-0.033	0.070	-0.097	-0.059
Worrying	-0.099	<b>0.853</b>	0.083	0.065	-0.094	0.011
Feeling irritable	0.141	<b>0.682</b>	-0.014	0.066	-0.006	-0.007
"I don't look like myself"	0.017	<b>0.470</b>	-0.007	0.044	0.091	0.293
Hot flashes	0.135	-0.028	<b>0.873</b>	0.016	0.112	-0.009
Sweats	-0.026	0.141	<b>0.725</b>	0.031	-0.050	0.094
Difficulty sleeping	-0.009	0.080	0.309	<b>0.575</b>	-0.018	-0.031
Abdominal cramps	0.086	-0.015	0.001	<b>0.561</b>	0.011	0.225
Shortness of breath	0.200	0.003	-0.065	<b>0.519</b>	0.002	-0.054
Weight loss	0.006	0.031	-0.007	<b>0.419</b>	<b>-0.774</b>	0.083
Weight gain	-0.018	0.004	0.042	0.068	<b>0.726</b>	<b>0.439</b>
Mouth sores	0.032	0.119	-0.061	-0.018	-0.123	<b>0.458</b>
Hair loss	-0.037	0.092	0.036	-0.038	-0.036	<b>0.577</b>
Change in the way food tastes	0.257	-0.150	-0.056	-0.003	-0.063	<b>0.549</b>
Changes in skin	0.077	0.190	0.040	0.049	0.157	<b>0.411</b>

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
	Sickness Behavior Symptom Cluster	Psychological Symptom Cluster	Hormonal Symptom Cluster	Gastrointestinal Symptom Cluster	Weight Change Symptom Cluster	Epithelial Symptom Cluster
Feeling bloated	-0.005	0.121	0.061	0.390	0.226	0.278
Cough	0.189	0.046	-0.093	0.145	0.105	0.090
Diarrhea	0.182	-0.001	-0.047	0.310	-0.034	0.220
Problems with sexual interest or activity	0.146	0.272	0.357	-0.038	0.094	-0.024
Itching	-0.006	-0.039	0.044	0.359	0.094	0.210
Constipation	0.276	0.178	0.100	0.104	-0.155	0.092
Total number of symptoms in the cluster	7	6	2	4	2	5

<sup>a</sup>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 Occurrence Approximately One Week After Chemotherapy Administration <sup>a</sup>

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	<b>0.818</b>	0.007	0.046	0.039	-0.051
Feeling sad	<b>0.805</b>	0.079	0.000	-0.018	0.018
Worrying	<b>0.811</b>	0.154	-0.094	-0.048	0.105
Feeling irritable	<b>0.501</b>	0.127	0.047	0.057	0.246
"I don't look like myself"	<b>0.417</b>	-0.008	-0.019	-0.024	<b>0.523</b>
Hot flashes	-0.031	<b>0.880</b>	-0.023	0.002	-0.249
Difficulty sleeping	0.166	<b>0.475</b>	0.113	0.159	0.106
Sweats	0.076	<b>0.787</b>	0.028	0.125	-0.175
Problems with sexual interest or activity	0.226	<b>0.403</b>	-0.073	0.028	0.159
Dry mouth	-0.008	0.153	<b>0.448</b>	0.037	0.031
Nausea	-0.091	0.261	<b>0.663</b>	-0.076	-0.152
Lack of appetite	0.018	0.117	<b>0.728</b>	-0.372	0.053
Change in the way food tastes	-0.277	0.022	<b>0.427</b>	-0.009	<b>0.410</b>
Weight loss	0.113	-0.058	<b>0.479</b>	<b>-0.444</b>	0.140
Abdominal cramps	-0.046	-0.040	<b>0.583</b>	0.358	0.048
Diarrhea	0.069	-0.132	<b>0.474</b>	0.148	-0.103
Feeling bloated	0.060	0.173	0.274	<b>0.447</b>	0.033
Weight gain	0.014	0.035	-0.066	<b>0.826</b>	0.146
Hair loss	0.018	-0.018	0.046	0.041	<b>0.618</b>
Mouth sores	-0.005	0.084	0.066	0.001	<b>0.464</b>
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

<sup>4</sup>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.

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Table 5

Exploratory Factor Analysis Using Ratings of Symptom Occurrence Approximately Two Weeks After Chemotherapy Administration <sup>a</sup>

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Hormonal Symptom Cluster	Psychological Symptom Cluster	Gastrointestinal Symptom Cluster	Nutritional Symptom Cluster	Epithelial Symptom Cluster
Hot flashes	<b>1.125</b>	-0.018	-0.026	-0.002	-0.026
Sweats	<b>0.648</b>	0.122	0.142	0.022	0.018
Worrying	-0.0008	<b>0.954</b>	-0.032	-0.033	-0.075
Feeling irritable	0.050	<b>0.567</b>	0.059	0.079	0.220
Difficulty concentrating	0.061	<b>0.530</b>	0.196	-0.003	0.112
Feeling nervous	-0.010	<b>0.774</b>	0.008	-0.001	0.093
Feeling drowsy	-0.044	<b>0.435</b>	0.218	0.087	0.079
Feeling sad	-0.006	<b>0.828</b>	0.004	-0.020	0.022
Abdominal cramps	-0.149	-0.023	<b>0.914</b>	0.015	-0.178
Difficulty sleeping	0.111	0.335	<b>0.488</b>	-0.049	-0.054
Feeling bloated	0.040	-0.010	<b>0.768</b>	-0.374	-0.016
Weight gain	0.004	0.062	<b>0.438</b>	<b>-0.538</b>	0.193
Nausea	0.216	-0.016	<b>0.420</b>	<b>0.501</b>	0.013
Lack of appetite	0.024	0.191	0.246	<b>0.642</b>	0.038
Weight loss	-0.142	0.353	-0.019	<b>0.698</b>	-0.075
Change in the way food tastes	0.037	-0.125	-0.004	<b>0.429</b>	<b>0.558</b>
Changes in skin	-0.002	0.095	-0.090	-0.086	<b>0.709</b>
Itching	0.033	0.025	0.155	-0.090	<b>0.450</b>
Mouth sores	-0.054	0.033	0.076	0.123	<b>0.419</b>
"I don't look like myself"	0.108	0.358	-0.048	0.005	<b>0.400</b>
Hair loss	0.011	0.100	0.080	-0.027	0.242
Constipation	0.078	0.076	0.307	0.264	0.051
Pain	0.076	0.135	0.388	0.017	0.125
Cough	-0.152	0.022	0.152	0.030	0.388
Dry mouth	-0.003	0.049	0.231	0.305	0.210

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Hormonal Symptom Cluster	Psychological Symptom Cluster	Gastrointestinal Symptom Cluster	Nutritional Symptom Cluster	Epithelial Symptom Cluster
Numbness/tingling in hands/feet	-0.074	0.033	0.191	-0.138	0.347
Shortness of breath	-0.065	-0.033	0.251	0.061	0.295
Diarrhea	-0.039	-0.063	0.375	0.182	0.124
Problems with sexual interest or activity	0.256	0.186	0.178	-0.176	0.048
Dizziness	-0.026	0.169	0.346	0.191	0.089
Total number of symptoms in the cluster	2	6	5	5	5

<sup>4</sup>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 6

Exploratory Factor Analysis Using Ratings of Symptom Severity Approximately One Week Prior to Chemotherapy Administration <sup>a</sup>

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
	Psychological Symptom Cluster	Sickness Behavior Symptom Cluster	Hormonal Symptom Cluster	Gastrointestinal Symptom Cluster	Weight Change Symptom Cluster	Epithelial Symptom Cluster
Difficulty concentrating	<b>0.418</b>	0.362	0.023	0.080	-0.138	-0.050
Feeling nervous	<b>0.686</b>	0.076	-0.045	0.119	-0.036	-0.020
Feeling sad	<b>0.842</b>	0.054	0.006	0.001	0.041	0.011
Worrying	<b>0.837</b>	-0.035	0.117	0.007	0.017	0.021
Feeling irritable	<b>0.589</b>	0.270	-0.004	-0.025	0.045	0.023
"I don't look like myself"	<b>0.497</b>	-0.193	0.000	0.006	0.004	<b>0.581</b>
Pain	0.054	<b>0.459</b>	-0.041	0.225	-0.046	-0.046
Dry mouth	-0.094	<b>0.444</b>	0.018	0.089	0.295	0.117
Nausea	-0.019	<b>0.540</b>	0.136	-0.011	0.309	0.099
Feeling drowsy	0.238	<b>0.588</b>	-0.066	-0.077	-0.011	0.005
Dizziness	0.076	<b>0.572</b>	0.105	0.005	0.215	-0.105
Sweats	0.146	-0.065	<b>0.792</b>	0.007	0.047	0.023
Hot flashes	-0.052	0.083	<b>0.875</b>	0.025	-0.094	-0.025
Feeling bloated	0.159	0.036	0.105	<b>0.400</b>	-0.110	0.180
Diarrhea	-0.033	0.043	-0.057	<b>0.577</b>	0.121	0.086
Abdominal cramps	0.009	-0.046	0.073	<b>0.809</b>	0.046	-0.017
Lack of appetite	-0.015	0.347	0.106	0.168	<b>0.477</b>	0.038
Weight gain	0.007	0.159	0.063	0.065	<b>-0.548</b>	<b>0.417</b>
Weight loss	0.084	-0.002	-0.041	0.188	<b>0.762</b>	-0.065
Hair loss	0.056	-0.061	0.019	-0.022	0.193	<b>0.496</b>
Change in the way food tastes	-0.094	0.092	-0.029	-0.010	0.345	<b>0.577</b>
Changes in skin	0.183	0.051	0.071	0.037	-0.030	<b>0.416</b>
Constipation	0.084	0.354	0.119	-0.028	0.184	0.010
Cough	-0.015	0.255	-0.118	0.037	-0.042	0.099

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
	Psychological Symptom Cluster	Sickness Behavior Symptom Cluster	Hormonal Symptom Cluster	Gastrointestinal Symptom Cluster	Weight Change Symptom Cluster	Epithelial Symptom Cluster
Numbness/tingling in hands/feet	0.032	0.324	-0.114	0.036	-0.079	0.224
Difficulty sleeping	0.223	0.217	0.246	0.111	0.074	0.029
Shortness of breath	0.047	0.321	-0.063	0.264	-0.018	-0.035
Problems with sexual interest or activity	0.188	0.162	0.343	-0.077	-0.090	0.072
Itching	0.060	0.077	-0.031	0.208	0.022	0.108
Mouth sores	0.052	0.070	0.008	0.062	0.335	0.249
Total number of symptoms in the cluster	6	5	2	3	3	5

<sup>a</sup>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 7

Exploratory Factor Analysis Using Ratings of Symptom Severity Approximately One Week After Chemotherapy Administration <sup>a</sup>

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	<b>0.988</b>	-0.012	-0.022	-0.081	0.040	0.025
Sweats	<b>0.739</b>	0.087	0.077	0.077	-0.039	-0.025
Feeling sad	-0.012	<b>0.826</b>	-0.001	0.087	0.019	-0.039
Feeling nervous	0.054	<b>0.759</b>	0.068	0.025	-0.014	-0.028
Worrying	0.043	<b>0.903</b>	-0.071	0.023	-0.004	0.004
Feeling irritable	0.030	<b>0.590</b>	0.106	0.044	0.009	0.124
Feeling drowsy	0.079	0.191	<b>0.456</b>	-0.022	0.083	-0.005
Numbness/tingling in hands/feet	-0.047	0.025	<b>0.718</b>	-0.007	-0.252	-0.019
Pain	-0.006	-0.078	<b>0.463</b>	0.380	-0.047	-0.012
Feeling bloated	-0.010	0.146	-0.100	<b>0.663</b>	-0.085	0.095
Abdominal cramps	-0.172	-0.008	0.017	<b>0.796</b>	0.171	-0.035
Weight gain	0.074	0.045	0.013	<b>0.502</b>	-0.607	0.297
Weight loss	-0.168	0.197	-0.028	-0.112	<b>0.627</b>	0.091
Nausea	0.123	0.033	0.131	0.277	<b>0.488</b>	-0.122
Lack of appetite	0.048	0.072	0.169	0.010	<b>0.719</b>	0.033
Hair loss	-0.068	0.061	-0.002	-0.003	-0.014	<b>0.631</b>
Change in the way food tastes	0.042	-0.205	-0.035	0.137	0.349	<b>0.569</b>
"I don't look like myself"	-0.090	0.398	0.055	-0.055	0.015	<b>0.532</b>
Changes in skin	0.012	0.151	0.156	-0.038	-0.056	<b>0.484</b>
Mouth sores	-0.015	0.011	0.063	0.046	0.061	<b>0.442</b>
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
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

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
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

<sup>a</sup>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.

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Table 8

Exploratory Factor Analysis Using Ratings of Symptom Severity Approximately Two Weeks After Chemotherapy Administration <sup>a</sup>

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Hormonal Symptom Cluster	Psychological Symptom Cluster	Gastrointestinal Symptom Cluster	Nutritional Symptom Cluster	Epithelial Symptom Cluster
Hot flashes	<b>1.277</b>	-0.023	-0.033	-0.005	-0.022
Sweats	<b>0.538</b>	0.141	0.171	-0.007	0.008
Difficulty concentrating	0.069	<b>0.533</b>	0.195	-0.001	0.133
Feeling nervous	-0.041	<b>0.861</b>	0.005	0.007	-0.029
Feeling sad	-0.019	<b>0.843</b>	0.010	-0.019	0.004
Feeling drowsy	-0.003	<b>0.442</b>	0.244	0.109	0.023
Worrying	0.018	<b>0.848</b>	-0.034	-0.051	0.014
Feeling irritable	0.041	<b>0.578</b>	0.112	0.105	0.131
Feeling bloated	0.013	0.005	<b>0.753</b>	-0.362	0.008
Abdominal cramps	-0.100	-0.064	<b>0.953</b>	-0.019	-0.213
Weight gain	0.006	0.117	<b>0.458</b>	<b>-0.534</b>	0.193
Nausea	0.111	0.028	0.383	<b>0.465</b>	0.017
Lack of appetite	0.022	0.069	0.199	<b>0.650</b>	0.083
Weight loss	-0.098	0.214	-0.063	<b>0.712</b>	-0.022
Change in the way food tastes	0.016	-0.142	0.025	<b>0.457</b>	<b>0.574</b>
Mouth sores	-0.035	0.069	0.013	0.166	<b>0.445</b>
Hair loss	-0.083	0.064	0.027	-0.057	<b>0.436</b>
"I don't look like myself"	-0.007	0.343	-0.055	-0.043	<b>0.547</b>
Changes in skin	0.004	0.165	-0.065	-0.023	<b>0.613</b>
Pain	0.112	0.252	0.265	0.088	0.048
Cough	-0.050	-0.062	0.101	0.184	0.368
Dry mouth	-0.013	0.095	0.161	0.316	0.177
Numbness/tingling in hands/feet	-0.021	0.176	0.176	0.019	0.213
Difficulty sleeping	0.138	0.325	0.289	0.042	0.024
Shortness of breath	0.021	-0.137	0.341	0.086	0.282

Symptom	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Factor 1 Hormonal Symptom Cluster	Factor 2 Psychological Symptom Cluster	Factor 3 Gastrointestinal Symptom Cluster	Factor 4 Nutritional Symptom Cluster	Factor 5 Epithelial Symptom Cluster
Diarrhea	-0.069	0.095	0.354	0.177	-0.009
Problems with sexual interest or activity	0.153	0.124	0.219	-0.172	0.178
Itching	0.105	0.210	0.088	-0.012	0.273
Dizziness	0.005	0.303	0.347	0.167	-0.087
Constipation	0.066	0.053	0.322	0.255	0.072
Total number of symptoms in the cluster	2	6	3	5	5

<sup>4</sup>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 9**

Summary of Symptom Clusters Over Time Using Occurrence Rates and Severity Ratings

Symptom Cluster	Symptoms Within the Cluster	Occurrence			Severity		
		Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
<i>Psychological Symptom Cluster</i>	Feeling nervous	●	●	●	●	●	●
	Feeling sad	●	●	●	●	●	●
	Worrying	●	●	●	●	●	●
	Feeling irritable	●	●	●	●	●	●
	Difficulty concentrating	●	●	●	●	●	●
	"I don't look like myself"	●	●	●	●	●	●
	Feeling drowsy			●			●
	Percent agreement	85.7	71.4	85.7	85.7	57.1	85.7
	Hot flashes	●	●	●	●	●	●
	Sweats	●	●	●	●	●	●
<i>Hormonal Symptom Cluster</i>	Difficulty sleeping		●				
	Problems with sexual interest or activity		●				
	Percent agreement	50.0	100.0	50.0	50.0	50.0	50.0
	Nausea		●	●		●	●
	Lack of appetite		●	●		●	●
	Weight loss		●	●		●	●
	Weight gain			●		●	●
	Change in the way food tastes		●	●		●	●
	Diarrhea		●				
	Dry mouth		●				
<i>Nutritional Symptom Cluster</i>	Abdominal cramps		●				
	Percent agreement	0.0	87.5	62.5	0.0	50.0	62.5
	Feeling bloated		●	●	●	●	●
	Abdominal cramps	●		●	●	●	●
	Weight gain		●	●		●	●
	Weight loss	●	●	●		●	●
	Diarrhea						
	Dry mouth						
	Abdominal cramps						
	Percent agreement	0.0	87.5	62.5	0.0	50.0	62.5
<i>Gastrointestinal Symptom Cluster</i>	Feeling bloated		●	●	●	●	●
	Abdominal cramps	●		●	●	●	●
	Weight gain		●	●		●	●
	Weight loss	●	●	●		●	●
	Diarrhea						
	Dry mouth						
	Abdominal cramps						
	Percent agreement	0.0	87.5	62.5	0.0	50.0	62.5
	Feeling bloated		●	●	●	●	●
	Abdominal cramps	●		●	●	●	●

Symptom Cluster	Symptoms Within the Cluster	Occurrence			Severity		
		Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
<i>Epithelial Symptom Cluster</i>	Difficulty sleeping	●		●			
	Shortness of breath	●					
	Nausea			●			
	Diarrhea				●		
	Percent agreement	50.0	37.5	62.5	37.5	37.5	37.5
	Change in the way food tastes	●	●	●	●	●	●
	"I don't look like myself"		●	●	●	●	●
	Hair loss	●	●		●	●	●
	Mouth sores	●	●	●	●	●	●
	Changes in skin	●	●	●	●	●	●
<i>Sickness Behavior Symptom Cluster</i>	Weight gain	●			●		
	Itching			●			
	Percent agreement	71.4	57.1	71.4	71.4	71.4	71.4
	Pain	●			●		
	Dry mouth	●			●		
	Nausea	●			●		
	Feeling drowsy	●			●		
	Dizziness	●			●		
	Lack of appetite	●			●		
	Numbness/tingling in hands/feet	●			●		
<i>Weight Change Symptom Cluster</i>	Percent agreement	100.0	0.0	0.0	71.4	0.0	0.0
	Weight loss	●			●		
	Weight gain	●			●		
	Lack of appetite				●		
	Percent agreement	66.7	0.0	0.0	100.0	0.0	0.0
<i>Chemotherapy Neuropathy Symptom Cluster</i>	Feeling drowsy					●	
	Numbness/tingling in hands/feet	Not Identified	Not Identified	Not Identified	Not Identified	●	Not Identified
	Pain	Not Identified	Not Identified	Not Identified	Not Identified	●	Not Identified

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Symptom Cluster	Symptoms Within the Cluster			Occurrence			Severity		
	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
	0.0	0.0	0.0	0.0	100.0	0.0	6	6	0.0
Number of symptom clusters	6	5	5	6	6	5	6	6	5
	Percent agreement								