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# Stability of Symptom Clusters in Patients with Gynecologic Cancer Receiving Chemotherapy

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## Abstract

**Background:** Patients with gynecologic cancer undergoing chemotherapy experience multiple co-occurring symptoms. Understanding how symptom clusters change over time is essential to the development of interventions that target multiple co-occurring symptoms.

**Objective:** Assess the relative stability of symptom clusters across a chemotherapy cycle in patients with gynecologic cancer.

**Methods:** Longitudinal, descriptive study. Eligible patients (n=232) were English-speaking adults (≥18 years) with gynecologic cancer. Data were collected in the week before patients' second or third cycle of chemotherapy (T1) and at one (T2) and two (T3) weeks after chemotherapy. Three dimensions of the symptom experience (occurrence, severity, distress) were assessed using a modified version of the Memorial Symptom Assessment Scale. Symptom clusters for each dimension and time point were identified through exploratory factor analysis (EFA).

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**Results:** A five-factor solution was selected for each EFA. Hormonal, respiratory, and weight change clusters were identified across all dimensions and time points. A psychological symptom cluster was identified at T1 for occurrence and severity and at T2 and T3 for all three dimensions. A gastrointestinal symptom cluster was identified at T1 for occurrence and at T2 and T3 for all three dimensions. The hormonal, respiratory, psychological, and weight change symptom clusters exhibited common symptoms across dimensions and time points.

**Conclusions:** Hormonal, respiratory, weight change, and psychological symptom clusters are relatively stable across a cycle of chemotherapy in patients with gynecologic cancer.

**Implications for Practice:** Clinicians need to assess patients for multiple co-occurring symptoms and initiate multimodal interventions.

### Keywords

symptoms; symptom clusters; ovarian neoplasms; uterine neoplasms; chemotherapy; exploratory factor analysis

## INTRODUCTION

In the United States, gynecologic cancer, including ovarian, uterine, and cervical cancer, accounts for more than 113,000 new cancer diagnoses and 33,620 deaths each year.[1] The symptom experience of patients with gynecologic cancer is unique. Patients with gynecologic cancer experience an average of 10 to 13 co-occurring symptoms, many of which are attributable to tumor burden and treatment-related toxicities.[2] Gastrointestinal symptoms, such as abdominal bloating and constipation, are common given the proximity of gynecologic tumors to the gastrointestinal system. In addition, hot flashes may occur as a result of surgical or chemotherapy induced menopause and dyspnea may occur with pleural effusions.[3] In addition to these distinctive symptoms, patients with gynecologic cancer experience symptoms that are common to most patients with cancer, including fatigue, sleep disturbance, pain, and distress.[4] Several of these symptoms may be precipitated or exacerbated by chemotherapy, which is indicated for most patients with ovarian, fallopian tube, or primary peritoneal carcinoma; locally advanced cervical carcinoma; or recurrent, metastatic, or high-risk uterine carcinoma.[5–7] As such, symptom burden among patients with gynecologic cancer tends to be highest during active treatment.[8] The symptom experiences of patients receiving chemotherapy are multidimensional and may vary throughout treatment.[9] Nevertheless, limited research has assessed variations in symptoms according to the dimensions of occurrence, severity, and distress in patients with gynecologic cancer over a cycle of chemotherapy.

Assessment of symptom clusters is appropriate when patients experience multiple co-occurring symptoms that are related to each other.[10] An increased understanding of symptom clusters may facilitate the development of interventions that target the underlying mechanisms for these co-occurring symptoms.[10] For example, a cognitive-behavioral intervention demonstrated preliminary efficacy in reducing the severity of a pain, fatigue, and sleep disturbance symptom cluster among patients with advanced cancer.[11] Prior studies have identified psychological,[12–14] abdominal,[13] and menopausal[12] symptom clusters in

patients with ovarian cancer receiving chemotherapy. These three studies identified symptom clusters using ratings of either occurrence or severity. No study has identified symptom clusters in patients with gynecologic cancer using ratings of distress. Of the three studies cited above, only one was longitudinal.[12] In the longitudinal study, symptom clusters were identified using severity ratings that were obtained prior to and one week after the first, third, and sixth cycles of chemotherapy.[12] While the types of symptom clusters varied over time, it is unknown if the same variation occurs when occurrence rates or distress ratings are used to identify the clusters.

Comparisons of symptom clusters that are identified using two different dimensions of the symptom experience may inform best practices in research and patient care. At this time, it is unclear whether the identification of symptom clusters using different dimensions of the symptom experience will provide new insights on patients' symptom burden and/or mechanism(s) that underlie these symptom clusters.[10] Additionally, symptom clusters that differ across dimensions of the symptom experience may reveal previously unidentified patterns. For example, a symptom cluster that is identified using distress ratings may suggest associations between symptoms that do not typically co-occur. Likewise, it is unknown whether symptom clusters vary when they are evaluated at different time points across a chemotherapy cycle. Given that patients are most often seen in clinic prior to chemotherapy administration, comparisons of symptom clusters identified across a chemotherapy cycle may enrich our understanding of the patient's symptom experience between clinic visits.[15] Therefore, the purposes of this study, in a sample of patients with gynecologic cancer, were to evaluate the occurrence, severity, and distress of 38 symptoms across a cycle of chemotherapy; evaluate for differences in the number and types of symptoms within various symptom clusters across a cycle of chemotherapy; and assess the stability of symptom clusters identified over a cycle of chemotherapy using three dimensions of the symptom experience.

## METHODS

### Patients and Settings

This specific analysis was planned as one of the specific aims of a longitudinal descriptive study that evaluated the symptom experience of oncology outpatients receiving chemotherapy.[16–18] The Theory of Symptom Management developed by faculty members at the University of California, San Francisco (UCSF) provided the theoretical framework for this study.[19] All of the eligible patients were ≥18 years of age; had a diagnosis of breast, lung, gastrointestinal, or gynecologic cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; and were able to read, write, and understand English. A convenience sample was recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. For this specific analysis, from a total sample of 1343 patients, 232 patients with gynecologic cancer were evaluated.

## Procedures

Eligible patients were approached by a research staff member in the infusion unit, during their first or second cycle of chemotherapy, to discuss participation in the study. Written informed consent was obtained from all patients. Patients completed questionnaires in their home and returned them in a postage paid envelope a total of six times over two cycles of chemotherapy. Data from the first three assessments were used in these analyses. Assessments took place in the week prior to patients' second or third cycle of chemotherapy (T1), approximately one week after chemotherapy (T2), and approximately two weeks after chemotherapy (T3). We conceptualized T1 as representing the patient's recovery from the previous cycle, T2 as the patients' acute symptoms,[15] and T3 as the potential nadir. Medical records were reviewed for disease and treatment information. The study procedures were approved by the Committee on Human Research at UCSF, the Dana-Farber/Harvard Cancer Center Institutional Review Board, and the Institutional Review Board at each study site.

## Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. The Karnofsky Performance Status (KPS) scale was used to evaluate patients' functional status.[20] The Self-Administered Comorbidity Questionnaire (SCQ) was used to evaluate 13 common medical conditions.[21]

A modified version of the Memorial Symptom Assessment Scale (MSAS) was used to evaluate the occurrence, severity, and distress of 38 symptoms commonly associated with cancer and its treatment.[22] Six additional symptoms that are common in oncology patients were assessed: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain. Using the MSAS, patients reported 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 severity and distress. Symptom severity was measured using a four-point Likert scale (1 = slight, 2 = moderate, 3 = severe, 4 = very severe). Symptom distress was measured using a five-point Likert scale (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.[22]

## Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences Version 27 (IBM Corporation, Armonk, NY) and Mplus Version 8.4.[23] Descriptive statistics and frequency distributions were calculated for the demographic and clinical characteristics, symptom occurrence rates, and severity and distress ratings. To identify the symptom clusters, exploratory factor analyses (EFAs) were done for the dichotomous (i.e., occurrence) and ordinal (i.e., severity, distress) items.[24] All the EFAs were done using MPlus.[23]

For the EFAs, factor loadings were considered meaningful if the loading was ≥0.30.[23] 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 ≥0.30.[24] 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 preset criteria of ≥0.30 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 used.[24, 25]

To have sufficient variation and covariation to perform the EFAs, only symptoms that were present in >20% and <80% of the patients at T1 were included in these analyses. Based on these criteria, for each of the EFAs, 31 of the 38 MSAS symptoms were used. Seven symptoms on the MSAS were excluded from the EFAs owing to insufficient variation in the occurrence of these symptoms. Lack of energy was reported by >80% of the patients and problems with urination, chest tightness, mouth sores, swelling of arms or legs, vomiting, and difficulty swallowing were reported by <20% of the patients.

For the EFA using the dichotomous occurrence items, tetrachoric correlations were used to create the matrix of associations.[23] For the EFAs using the ordinal severity and distress ratings, polychoric correlations were used to create the matrix of associations. The simple structure for the occurrence, severity, and distress EFAs were estimated using the method of unweighted least squares with geomin (i.e., oblique) rotation. The geomin 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.[23] 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[23]) was selected to achieve more reliable results because the scales for the MSAS items are dichotomous (i.e., occurrence) and ordinal (i.e., severity and distress).

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. The EFA for distress was done using distress ratings that included a zero (did not have the symptom) and the original ratings shifted from 1 (not at all) to 5 (very much). The initial EFA analyses were done using severity and distress ratings that did not include zero (i.e., 1, 2, 3, 4, 5). However, the pairwise missingness (i.e., 1-covariance coverage for each of the item pairs) was over 90% and the estimation failed to converge.

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

To evaluate the stability of the symptom clusters, we assessed symptom agreement within each cluster identified according to occurrence, severity, and distress ratings across all three time points. We defined agreement according to the criteria proposed by Kirkova and Walsh.[26] These authors 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 most important symptom, namely the symptom with the greatest weight from the factor analyses. By way of example, symptom agreement over time for the hormonal symptom cluster at T1 was calculated as follows for the occurrence dimension: (number of symptoms identified according to occurrence at T1 ÷ number of symptoms identified according to occurrence at all time points) × 100 = (9 ÷ 11) × 100 = 81.8% agreement. Sweats and hot flashes had the highest rotated factor loadings according to occurrence and were present at each time point. As such, the hormonal cluster identified according to occurrence met criteria for stability over time.

## RESULTS

### Demographic and clinical characteristics

Demographic and clinical characteristics of the 232 patients with gynecologic cancer are provided in Table 1. In brief, across the total sample, 55.1% of the patients were married or partnered, 77.1% were White, 54.6% reported an annual household income of ≥$70,000. These patients had an average of 16.0 (±2.9) years of education. The majority of the sample was non-smokers (65.8%) and exercised on a regular basis (70.9%). Patients had 2.4 (±1.4) comorbid conditions and a KPS score of 78.4 (±12.4). The most common gynecologic cancer diagnoses were ovarian cancer/fallopian tube/primary peritoneal (65.4%) and uterine cancer (32.9%). Patients were 2.1 (±3.5) years from their cancer diagnosis (median = 0.52 years) and 95.0% had undergone surgery.

### Symptom prevalence and characteristics over time

The mean number of symptoms was 14.2 (±7.1) at T1, 15.3 (±7.1) at T2, and 12.8 (±7.1) at T3. Symptom occurrence rates and severity and distress ratings across time points are provided in Table 2. Across the three time points, lack of energy had the highest occurrence rate. Among the patients who reported them, the most severe symptoms were hair loss at T1 and problems with sexual interest or activity at T2 and T3. The symptoms with the highest distress ratings were “I don’t look like myself” at T1, problems with sexual interest or activity at T2, and vomiting at T3.

### Symptom clusters according to occurrence

A five-factor solution was selected for the occurrence EFAs (Table 3). The hormonal cluster was comprised of four (T2, T3) to nine (T1) symptoms. While sweats had the highest factor loading at T1 and T2, hot flashes had the highest factor loading at T3. The respiratory cluster was comprised of three (T3) to nine (T1) symptoms. While difficulty breathing had the highest factor loading at T1 and T3, shortness of breath had the highest factor loading at T2. The psychological cluster was comprised of eight (T3) to twelve (T1) symptoms. While worrying had the highest factor loading at T1 and T3, feeling sad had the highest factor loading at T2. The gastrointestinal cluster was comprised of six (T1) to thirteen (T2, T3) symptoms. While diarrhea had the highest factor loading at T1 at T3, lack of appetite had the highest factor loading at T2. The weight change cluster was comprised of three (T2) to five (T3) symptoms. Weight gain had the highest factor loading across all three time points.

Symptoms that did not load on any factor included: nausea at T1; pain and diarrhea at T2; and pain, difficulty sleeping, hair loss, and numbness/tingling in hands/feet at T3.

### Symptom clusters according to severity

A five-factor solution was selected for the severity EFAs (Table 3). The hormonal cluster was comprised of four (T2) to five (T1, T3) symptoms. While sweats had the highest factor loading at T1, hot flashes had the highest factor loading at T2 and T3. The respiratory cluster was comprised of three (T2, T3) to four (T1) symptoms. While difficulty breathing had the highest factor loading at T1 and T3, shortness of breath had the highest factor loading at T2. The psychological cluster was comprised of five (T1) to eleven (T3) symptoms. While worrying had the highest factor loading at T1 and T3, feeling sad had the highest factor loading at T2. The gastrointestinal cluster identified at T2 and T3 was comprised of 13 symptoms at T2 and 11 symptoms at T3. While lack of appetite had the highest factor loading at T2, weight loss had the highest factor loading at T3. The weight change cluster was comprised of three (T1, T2) to four (T3) symptoms. Weight gain had the highest factor loading across all three time points. Symptoms that did not load on any factor included: feeling bloated, numbness/tingling in hands/feet, difficulty sleeping, diarrhea, feeling drowsy, and dry mouth at T1; changes in skin, numbness/tingling in hands/feet, and constipation at T2; and feeling drowsy, feeling bloated, and numbness/tingling in hands/feet at T3.

### Symptom clusters according to distress

A five-factor solution was selected for the distress EFAs (Table 3). The hormonal cluster was comprised of four (T1, T3) to five (T2) symptoms. Hot flashes had the highest factor loading at all three time points. The respiratory cluster was comprised of three symptoms at all three time points. While difficulty breathing had the highest factor loading at T1 and T3, shortness of breath had the highest factor loading at T2. The psychological cluster that was identified at T2 and T3 was comprised of nine symptoms at T2 and 10 symptoms at T3. While feeling sad had the highest factor loading at T2, worrying had the highest factor loading at T3. The gastrointestinal cluster identified at T2 and T3 was comprised of 15 symptoms at T2 and 12 symptoms at T3. While weight loss had the highest factor loading at T2, lack of appetite had the highest factor loading at T3. The weight change cluster was comprised of five (T1, T2) to six (T3) symptoms. Weight gain had the highest factor loading across all three time points. Symptoms that did not load on any factor included: numbness/tingling in hands/feet and difficulty sleeping at T1; numbness/tingling in hands/feet, itching, and feeling bloated at T2; and feeling drowsy and numbness/tingling in hands/feet at T3.

### Similarities and differences in the number and types of symptom clusters

Across all three symptom dimensions and time points, the number of symptom clusters identified was five. As summarized in Table 3, the hormonal, respiratory, and weight change symptom clusters were identified across all three symptom dimensions and time points. A gastrointestinal cluster was identified at T1 for occurrence and at T2 and T3 for all three symptom dimensions. A psychological/gastrointestinal cluster was identified at T1 for distress, while a gastrointestinal/epithelial cluster was identified at T1 for severity and distress.

Subsets of symptoms appeared consistently within each cluster. For the hormonal cluster, three symptoms were included in all nine EFAs: sweats, hot flashes, and problems with sexual interest or activity. For the respiratory cluster, three symptoms were included in all nine EFAs: difficulty breathing, shortness of breath, and cough. For the psychological cluster, four symptoms were included in all eight EFAs in which the psychological cluster was identified: worrying, feeling sad, feeling irritable, and feeling nervous. For the gastrointestinal cluster, abdominal cramps were included in all seven EFAs for which the gastrointestinal cluster was identified. For the weight change cluster, weight gain and increased appetite were included in all nine EFAs. Consistent subsets of symptoms were not assessed for the psychological/gastrointestinal or gastrointestinal/epithelial clusters, which were only identified at one time point.

### Stability of symptom clusters over time

The respiratory cluster had the highest level of symptom agreement over time, with ≥75% agreement at all time points for the severity and distress EFAs and at T1 for the occurrence EFA (Table 4). The psychological cluster had the next highest level of symptom agreement, with ≥75% agreement at T2 and T3 for the severity and distress EFAs. The gastrointestinal cluster had ≥75% agreement at T2 for the severity and distress EFAs. The weight change cluster had ≥75% agreement at T1 and T3 for the occurrence EFA, while the hormonal cluster had ≥75% agreement at T1 for the occurrence EFA and at T2 for the distress EFA. For the hormonal, respiratory, psychological, and weight change clusters, the symptom with the highest rotated factor loading on each EFA was present across all time points for each dimension (Table 3). Stability over time was not calculated for the psychological/gastrointestinal and gastrointestinal/epithelial clusters, that were identified only at T1.

### Stability of symptom clusters across dimensions of the symptom experience

The gastrointestinal cluster had the highest level of symptom agreement across dimensions of the symptom experience, with ≥75% agreement for all three symptom dimensions at T2 and T3 (Table 4). The psychological symptom cluster had ≥75% agreement at T1 for the occurrence EFA, at T2 for all three dimensions, and at T3 for the severity and distress EFAs. The hormonal cluster had ≥75% symptom agreement at T1 for the occurrence EFA, at T2 for the distress EFA, and at T3 for all three dimensions. The respiratory cluster had ≥75% agreement at T1 and T2 for the occurrence EFAs and at T3 for all three dimensions. The gastrointestinal/epithelial cluster, that was identified only at T1, had ≥75% symptom agreement for the severity and distress EFAs. The weight change cluster had ≥75% symptom agreement at T1 for the occurrence and distress EFAs and at T2 for the distress EFA. For the hormonal, respiratory, psychological, gastrointestinal, gastrointestinal/epithelial, and weight change clusters, the symptom with the highest rotated factor loading for each EFA was present across all three dimensions at each time point (Table 3). Stability across dimensions of the symptom experience was not assessed for the psychological/gastrointestinal symptom cluster, that was identified only for the distress EFA.

### Stability of symptom clusters over time and across dimensions of the symptom experience

The hormonal and respiratory clusters had ≥75% symptom agreement at T1 for the occurrence EFA (Table 4). The gastrointestinal cluster had ≥75% symptom agreement at

T2 for the distress EFA. No other symptom clusters had ≥75% symptom agreement over time and across dimensions of the symptom experience. For the hormonal, respiratory, psychological, and weight change clusters, the symptom with the highest rotated factor loading on each EFA was present across all time points and for each dimension (Table 3). Stability over time and across dimensions were not assessed for the psychological/gastrointestinal or the gastrointestinal/epithelial clusters, that were identified only at T1.

## DISCUSSION

This study is the first to evaluate the occurrence, severity, and distress of 38 symptoms over one cycle of chemotherapy in patients with gynecologic cancer. In this study, the mean number of symptoms reported by patients was highest in the week following the administration of chemotherapy. Occurrence rates, as well as mean severity and mean distress ratings for 11 symptoms (i.e., abdominal cramps, change in the way food tastes, difficulty concentrating, difficulty swallowing, dizziness, feeling drowsy, feeling sad, lack of appetite, lack of energy, nausea, and pain) tended to increase from T1 to T2 and decreased from T2 to T3. These findings suggest that the most acute symptoms may occur within the first week after chemotherapy administration and warrant pre-emptive management.

Consistent with our analyses of symptom clusters in patients with breast and gastrointestinal cancer receiving chemotherapy,[27, 28] lack of energy was the most common symptom across all three time points. The most severe symptoms were hair loss (T1) and problems with sexual interest or activity (T2 and T3). In a previous longitudinal study of symptom clusters in patients with ovarian cancer,[12] hair loss was the most severe symptom one week after the third and sixth cycles of chemotherapy. This finding is not surprising given that diffuse alopecia is a known side effect of taxanes, which are one of the mainstays of treatment for gynecologic cancers.[29] In our prior longitudinal study of patients with gastrointestinal cancer,[27] problems with sexual interest or activity was the most severe symptom across all three time points. This symptom may be experienced as severe because of its impact on patients' intimate relationships and perceived social roles.[30] Moreover, patients may experience challenges communicating with clinicians about sexual concerns and may receive limited guidance on how to manage sexual problems.[31, 32] Clinicians need to initiate these types of discussions and provide appropriate information and referrals for sexual and mental health resources.[31]

In this study, the symptoms with the highest distress ratings were "I don't look like myself" (T1), problems with sexual interest or activity (T2), and vomiting (T3). Concerns about body image and sexual health in patients with gynecologic cancer were identified in several studies.[33, 34] Notably, the mean distress rating for vomiting was lower at T2 than at T3, which highlights the need to remind patients to continue their anti-emetic regimens in the week following the administration of chemotherapy. Consistent with previous reports,[27, 28] the most severe symptoms were not necessarily the most distressing and vice-versa. These findings underscore the importance of ongoing multidimensional symptom assessments.

Consistent with our longitudinal studies of patients with breast,[28] lung,[35] and gastrointestinal[27] cancers, the number and types of symptom clusters in patients with

gynecologic cancer were relatively consistent across a cycle of chemotherapy. Our finding that the gastrointestinal symptom cluster was not identified at T1, using ratings of severity or distress, is consistent with prior research. In a previous study of patients with ovarian cancer, a gastrointestinal cluster included nausea, vomiting, and weight loss.[12] While not present prior to the first cycle of chemotherapy, this cluster occurred during the week following the administration of chemotherapy and during the third and sixth cycles.[12] Conversely, in our previous study of patients with gastrointestinal cancer,[27] a gastrointestinal cluster was identified across all three symptom dimensions, but only at T1. Given that gastrointestinal symptoms are common in patients with both gastrointestinal and gynecologic cancers, it is surprising that this cluster was not stable over time. Additional research is warranted to understand the trajectory of individual symptoms in the gastrointestinal cluster and to identify common underlying mechanisms for this heterogeneous symptom cluster.

In the current study, the hormonal, respiratory, psychological, and weight change clusters met criteria for stability over time. Likewise, the hormonal, respiratory, psychological, gastrointestinal, gastrointestinal/epithelial, and weight change clusters met criteria for stability across dimensions of the symptom experience. These findings suggest symptom clusters may be accurately identified using any dimension of the symptom experience, as well as across a cycle of chemotherapy. However, it is important to note that only the hormonal and respiratory clusters met criteria for stability over time and across dimensions of the symptom experience. This finding may reflect substantial inter-individual variability in the symptom trajectories of patients with gynecologic cancers. Additional research is warranted to identify subgroups of patients with gynecologic cancer who experience distinct symptom trajectories.

Several limitations warrant consideration. The heterogeneity in the patients' gynecologic cancer diagnoses (e.g., ovarian, uterine), chemotherapy agents, and previous cancer treatments may influence the numbers and types of symptom clusters. Research that aims to evaluate the stability of symptom clusters over multiple cycles of chemotherapy is warranted. In addition, the use of a convenience sample, that was primarily White and well educated, may limit the generalizability of these findings. A strength of this study includes its use of well-established methods to identify symptom clusters.[16–18, 28, 35] The results of this study offer novel insights into symptom clusters and symptom occurrence, severity, and distress experienced by patients with gynecologic cancer over a cycle of chemotherapy.

## CONCLUSION

Patients with gynecologic cancer may experience multiple co-occurring symptoms that remain stable throughout a cycle of chemotherapy. Clinicians who care for patients with gynecologic cancer receiving chemotherapy should perform multidimensional symptom assessments, provide anticipatory guidance, and support symptom self-management in the weeks that follow chemotherapy administration. In addition, findings from this study suggest that these patients warrant referrals sexual and mental health counseling and ongoing education about the use of symptom management strategies, particularly for nausea.

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## REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2020. Atlanta, GA: American Cancer Society; 2020.
2. Donovan HS, Hartenbach EM, Method MW. Patient-provider communication and perceived control for women experiencing multiple symptoms associated with ovarian cancer. Gynecol Oncol. 2005;99(2):404–411. [PubMed: 16112174]
3. Wang XS, Shi Q, Williams LA, et al. Validation and application of a module of the MD Anderson Symptom Inventory for measuring perioperative symptom burden in patients with gynecologic cancer (the MDASI-PeriOp-GYN). Gynecol Oncol. 2019;152(3):492–500. [PubMed: 30876494]
4. Cleeland CS, Zhao F, Chang VT, et al. The symptom burden of cancer: Evidence for a core set of cancer-related and treatment-related symptoms from the Eastern Cooperative Oncology Group Symptom Outcomes and Practice Patterns study. Cancer. 2013;119(24):4333–4340. [PubMed: 24114037]
5. Koh WJ, Abu-Rustum NR, Bean S, et al. Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(2):170–199. [PubMed: 29439178]
6. Koh WJ, Abu-Rustum NR, Bean S, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(1):64–84. [PubMed: 30659131]
7. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. NCCN Guidelines Insights: Ovarian Cancer, Version 1.2019. J Natl Compr Canc Netw. 2019;17(8):896–909. [PubMed: 31390583]
8. Lefkowits C, WR M, ES A, et al. Predictors of high symptom burden in gynecologic oncology outpatients: who should be referred to outpatient palliative care? Gynecol Oncol. 2014;132(3):698–702. [PubMed: 24472408]
9. Kristensen A, Solheim TS, Amundsen T, et al. Measurement of health-related quality of life during chemotherapy - the importance of timing. Acta Oncol. 2017;56(5):737–745. [PubMed: 28117614]
10. Miaskowski C, Barsevick A, Berger A, et al. Advancing symptom science through symptom cluster research: Expert panel proceedings and recommendations. J Natl Cancer Inst. 2017;109(4).
11. Kwekkeboom KL, Abbott-Anderson K, Cherwin C, Roiland R, Serlin RC, Ward SE. Pilot randomized controlled trial of a patient-controlled cognitive-behavioral intervention for the pain, fatigue, and sleep disturbance symptom cluster in cancer. J Pain Symptom Manage. 2012;44(6):810–822. [PubMed: 22771125]
12. Huang J, Gu L, Zhang L, Lu X, Zhuang W, Yang Y. Symptom clusters in ovarian cancer patients with chemotherapy after surgery: A longitudinal survey. Cancer Nurs. 2016;39(2):106–116. [PubMed: 25837811]
13. Hwang KH, Cho OH, Yoo YS. Symptom clusters of ovarian cancer patients undergoing chemotherapy, and their emotional status and quality of life. Eur J Oncol Nurs. 2016;21:215–222. [PubMed: 26645947]
14. Nho JH, Reul Kim S, Nam JH. Symptom clustering and quality of life in patients with ovarian cancer undergoing chemotherapy. Eur J Oncol Nurs. 2017;30:8–14. [PubMed: 29031318]
15. Giesinger JM, Wintner LM, Zabernigg A, et al. Assessing quality of life on the day of chemotherapy administration underestimates patients' true symptom burden. BMC Cancer. 2014;14(1):758–758. [PubMed: 25305067]
16. Ward Sullivan C, Leutwyler H, Dunn LB, et al. Differences in symptom clusters identified using symptom occurrence rates versus severity ratings in patients with breast cancer undergoing chemotherapy. Eur J Oncol Nurs. 2017;28:122–132. [PubMed: 28478849]

17. Han CJ, Reding K, Cooper BA, et al. Symptom clusters in patients with gastrointestinal cancers using different dimensions of the symptom experience. J Pain Symptom Manage. 2019;58(2):224–234. [PubMed: 31077784]
18. Wong ML, Cooper BA, Paul SM, et al. Differences in symptom clusters identified using ratings of symptom occurrence vs. severity in lung cancer patients receiving chemotherapy. J Pain Symptom Manage. 2017;54(2):194–203. [PubMed: 28533161]
19. Humphreys J, Janson S, Donesky D, et al. A middle range theory of symptom management. In: Smith MJ, Liehr PR, eds. Middle Range Theory in Nursing. 3rd ed. New York: Springer Publishing Company; 2014:141–164.
20. Karnofsky D Performance scale. In: Kennealey G, Mitchell M, eds. Factors that influence the therapeutic response in cancer: a comprehensive treatise. New York, NY: Plenum Press; 1977.
21. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum. 2003;49(2):156–163. [PubMed: 12687505]
22. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer. 1994;30a(9):1326–1336. [PubMed: 7999421]
23. Mplus [computer program]. Version 8.4 Los Angeles, CA: Muthen & Muthen; 2019.
24. Brown T The common factor model and exploratory factor analysis. 2 ed. London: The Guilford Press; 2015.
25. Miaskowski C, Aouizerat BE, Dodd M, Cooper B. Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. JNCI Monographs. 2007; (37):39–46.
26. Kirkova J, Walsh D. Cancer symptom clusters—a dynamic construct. Support Care Cancer. 2007;15(9):1011–1013. [PubMed: 17479300]
27. Han CJ, Reding K, Cooper BA, et al. Stability of symptom clusters in patients with gastrointestinal cancers receiving chemotherapy. J Pain Symptom Manage. 2019;58(6):989–1001. [PubMed: 31404646]
28. Sullivan CW, Leutwyler H, Dunn LB, et al. Stability of symptom clusters in patients with breast cancer receiving chemotherapy. J Pain Symptom Manage. 2018;55(1):39–55. [PubMed: 28838866]
29. Rubio-Gonzalez B, Juhasz M, Fortman J, Mesinkovska NA. Pathogenesis and treatment options for chemotherapy-induced alopecia: a systematic review. Int J Dermatol. 2018;57(12):1417–1424. [PubMed: 29377091]
30. Abbott-Anderson K, Kwekkeboom KL. A systematic review of sexual concerns reported by gynecological cancer survivors. Gynecol Oncol. 2012;124(3):477–489. [PubMed: 22134375]
31. Dai Y, Cook OY, Yeganeh L, Huang C, Ding J, Johnson CE. Patient-reported barriers and facilitators to seeking and accessing support in gynecologic and breast cancer survivors with sexual problems: A systematic review of qualitative and quantitative studies. J Sex Med. 2020;17(7):1326–1358. [PubMed: 32331967]
32. Reese JB, Sorice K, Beach MC, et al. Patient-provider communication about sexual concerns in cancer: a systematic review. J Cancer Surviv. 2017;11(2):175–188. [PubMed: 27858322]
33. Teo I, Cheung YB, Lim TYK, Namuduri RP, Long V, Tewani K. The relationship between symptom prevalence, body image, and quality of life in Asian gynecologic cancer patients. Psychooncology. 2018;27(1):69–74. [PubMed: 28508411]
34. Wilson CM, McGuire DB, Rodgers BL, Elswick RK Jr., Temkin SM. Body image, sexuality, and sexual functioning in women with gynecologic cancer: An integrative review of the literature and implications for research. Cancer Nurs. 2020.
35. Russell J, Wong ML, Mackin L, et al. Stability of symptom clusters in patients with lung cancer receiving chemotherapy. J Pain Symptom Manage. May 2019;57(5):909–922. [PubMed: 30768960]

**Table 1.**

Demographic and Clinical Characteristics of Patients with Gynecologic Cancers ($n$=232)

| Characteristic | Mean | SD |
|---|---|---|
| Age (years) | 59.6 | 12.7 |
| Education (years) | 16.0 | 2.9 |
| Karnofsky Performance Status score | 78.4 | 12.4 |
| Number of comorbidities out of 13 | 2.4 | 1.4 |
| Self-administered Comorbidity Questionnaire score | 5.4 | 3.3 |
| Time since cancer diagnosis (years) | 2.1 | 3.5 |
| Time since diagnosis (median) | 0.52 | |
| Mean number of MSAS symptoms (out of 38) | 14.2 | 7.1 |
| | | |
| | n | (%) |
| Ethnicity | | |
| White | 175 | 77.1 |
| Black | 8 | 3.5 |
| Asian or Pacific Islander | 20 | 8.8 |
| Hispanic, Mixed, or Other | 24 | 10.6 |
| Married or partnered (% yes) | 124 | 55.1 |
| Currently employed (% yes) | 71 | 31.0 |
| Income | | |
| < $30,000 | 38 | 18.2 |
| $30,000 to < $70,000 | 57 | 27.3 |
| $70,000 to < $100,000 | 34 | 16.3 |
| ≥ $100,000 | 80 | 38.3 |
| Type of prior cancer treatment | | |
| No prior treatment | 8 | 3.4 |
| Surgery | 211 | 95.0 |
| Chemotherapy | 93 | 41.9 |
| Radiation therapy | 32 | 14.4 |
| Monoclonal antibodies | 26 | 11.7 |
| Growth factors | 28 | 12.6 |
| Hormonal therapy | 7 | 3.2 |
| Bisphosphonates | 1 | 0.5 |
| Gynecologic cancer diagnoses | | |
| Ovarian | 130 | 57.0 |
| Fallopian tube | 15 | 6.6 |
| Uterine (including endometrial) | 75 | 32.9 |
| Primary peritoneal carcinoma | 8 | 3.5 |
| Other | 13 | 5.6 |

Abbreviations: MSAS = Memorial Symptom Assessment Scale, SD = standard deviation

**Table 2.**

Occurrence Rates and Severity and Distress Ratings for Symptoms Over One Cycle of Chemotherapy in Patients with Gynecologic Cancer

| Symptoms[a] | Occurrence Rates % (n) | | | Severity Ratings with Zeros[b] Mean (SD) | | | Severity Ratings without Zeros[c] Mean (SD) | | | Distress Ratings[d] Mean (SD) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Time 1* | Time 2 | Time 3 | Time 1 | Time 2 | Time 3 | Time 1 | Time 2 | Time 3 | Time 1 | Time 2 | Time 3 |
| Lack of energy | 83.2 (193) | 90.4 (197) | 85.0 (182) | 1.74 (1.0) | 2.09 (1.0) | 1.77 (1.1) | 2.11 (0.7) | 2.32 (0.8) | 2.10 (0.8) | 1.9 (1.1) | 2.14 (1.1) | 1.85 (1.1) |
| Difficulty sleeping | 70.3 (163) | 76.6 (167) | 69.6 (149) | 1.50 (1.2) | 1.58 (1.1) | 1.34 (1.1) | 2.14 (0.8) | 2.07 (0.8) | 1.94 (0.8) | 1.89 (1.1) | 1.94 (1.0) | 1.71 (1.1) |
| Pain | 64.2 (149) | 77.5 (169) | 64.5 (138) | 1.23 (1.1) | 1.56 (1.1) | 1.22 (1.1) | 1.93 (0.7) | 2.03 (0.7) | 1.91 (0.7) | 1.79 (1.0) | 2.08 (1.0) | 1.77 (1.0) |
| Feeling drowsy | 61.6 (143) | 72.0 (157) | 59.8 (128) | 1.08 (1.0) | 1.31 (1.0) | 1.03 (1.0) | 1.79 (0.7) | 1.84 (0.7) | 1.74 (0.6) | 1.09 (1.1) | 1.29 (1.1) | 1.07 (1.0) |
| Worrying | 58.6 (136) | 61.0 (133) | 49.5 (106) | 1.06 (1.1) | 1.08 (1.0) | 0.84 (1.0) | 1.84 (0.8) | 1.77 (0.7) | 1.73 (0.6) | 1.70 (1.0) | 1.54 (1.0) | 1.60 (0.9) |
| Difficulty concentrating | 56.9 (132) | 66.1 (144) | 57.5 (123) | 0.90 (0.9) | 1.11 (1.0) | 0.88 (0.9) | 1.62 (0.6) | 1.72 (0.7) | 1.55 (0.7) | 1.49 (1.0) | 1.59 (1.1) | 1.29 (0.9) |
| Numbness/tingling in hands/feet | 56.9 (132) | 59.6 (130) | 56.1 (120) | 1.00 (1.1) | 1.06 (1.1) | 1.03 (1.1) | 1.78 (0.8) | 1.81 (0.8) | 1.88 (0.8) | 1.54 (1.2) | 1.62 (1.2) | 1.68 (1.2) |
| Hair loss | 56.5 (131) | 54.1 (118) | 49.5 (106) | 1.46 (1.5) | 1.35 (1.5) | 1.18 (1.5) | 2.60 (1.1) | 2.54 (1.2) | 2.43 (1.1) | 1.90 (1.4) | 1.94 (1.5) | 1.94 (1.4) |
| Feeling sad | 52.6 (122) | 53.2 (116) | 44.4 (95) | 0.86 (1.0) | 0.91 (1.0) | 0.73 (1.0) | 1.65 (0.7) | 1.73 (0.7) | 1.70 (0.7) | 1.56 (1.1) | 1.62 (1.0) | 1.52 (0.8) |
| Feeling nervous | 47.4 (110) | 40.4 (88) | 28.0 (60) | 0.77 (0.9) | 0.65 (0.9) | 0.43 (0.8) | 1.69 (0.6) | 1.65 (0.7) | 1.60 (0.7) | 1.44 (0.9) | 1.55 (0.9) | 1.46 (1.0) |
| Constipation | 45.7 (106) | 56.4 (123) | 39.7 (85) | 0.85 (1.1) | 1.06 (1.1) | 0.74 (1.0) | 1.92 (0.8) | 1.89 (0.8) | 1.93 (0.7) | 1.76 (1.2) | 1.66 (1.1) | 1.77 (1.1) |
| Feeling irritable | 44.4 (103) | 50.0 (109) | 43.0 (92) | 0.75 (1.0) | 0.84 (1.0) | 0.70 (1.0) | 1.74 (0.7) | 1.71 (0.7) | 1.69 (0.7) | 1.51 (0.9) | 1.44 (0.9) | 1.44 (0.9) |
| Nausea | 41.4 (96) | 63.8 (139) | 35.0 (75) | 0.71 (1.0) | 1.13 (1.1) | 0.55 (0.9) | 1.78 (0.9) | 1.82 (0.8) | 1.65 (0.7) | 1.79 (1.1) | 1.79 (1.1) | 1.66 (1.0) |
| Hot flashes | 40.5 (94) | 34.4 (75) | 36.0 (77) | 0.80 (1.1) | 0.71 (1.1) | 0.66 (1.1) | 2.03 (0.8) | 2.09 (0.9) | 1.93 (0.9) | 1.52 (1.3) | 1.81 (1.3) | 1.54 (1.2) |
| Change in the way food tastes | 40.1 (93) | 53.2 (116) | 43.0 (92) | 0.76 (1.1) | 1.01 (1.2) | 0.73 (1.0) | 1.91 (0.9) | 1.93 (0.9) | 1.74 (0.8) | 1.45 (1.1) | 1.63 (1.1) | 1.33 (1.1) |
| Sweats | 37.9 (88) | 38.1 (83) | 31.3 (67) | 0.68 (1.0) | 0.68 (1.0) | 0.58 (1.0) | 1.85 (0.8) | 1.84 (0.8) | 1.89 (0.9) | 1.34 (1.1) | 1.33 (1.1) | 1.49 (1.1) |
| Cough | 37.1 (86) | 28.9 (63) | 22.0 (47) | 0.44 (0.7) | 0.38 (0.7) | 0.30 (0.6) | 1.25 (0.5) | 1.37 (0.6) | 1.44 (0.6) | 0.81 (1.0) | 0.86 (1.0) | 1.04 (0.9) |
| “I don’t look like myself” | 37.1 (86) | 45.9 (100) | 43.9 (94) | 0.82 (1.3) | 0.99 (1.3) | 0.93 (1.2) | 2.27 (1.0) | 2.22 (0.9) | 2.16 (1.0) | 2.02 (1.4) | 2.09 (1.3) | 1.93 (1.2) |
| Dry mouth | 36.6 (85) | 36.2 (79) | 24.8 (53) | 0.59 (0.9) | 0.59 (0.9) | 0.44 (0.9) | 1.68 (0.7) | 1.69 (0.8) | 1.88 (0.9) | 1.23 (1.1) | 1.21 (1.1) | 1.53 (1.3) |
| Feeling bloated | 36.6 (85) | 37.6 (82) | 29.9 (64) | 0.63 (0.9) | 0.65 (1.0) | 0.51 (0.9) | 1.76 (0.7) | 1.75 (0.8) | 1.76 (0.7) | 1.56 (1.0) | 1.58 (1.1) | 1.75 (1.1) |
| Lack of appetite | 34.9 (81) | 52.3 (114) | 33.2 (71) | 0.64 (1.0) | 1.03 (1.1) | 0.52 (0.9) | 1.91 (0.8) | 1.99 (0.7) | 1.64 (0.8) | 1.23 (1.1) | 1.34 (1.1) | 1.11 (1.1) |
| Dizziness | 34.1 (79) | 35.8 (78) | 28.0 (60) | 0.50 (0.8) | 0.57 (0.9) | 0.42 (0.8) | 1.48 (0.7) | 1.62 (0.7) | 1.52 (0.6) | 1.36 (1.0) | 1.56 (1.1) | 1.40 (0.9) |
| Changes in skin | 32.3 (75) | 27.5 (60) | 29.4 (63) | 0.56 (0.9) | 0.49 (0.9) | 0.52 (0.9) | 1.73 (0.7) | 1.81 (0.8) | 1.83 (0.8) | 1.55 (1.2) | 1.62 (1.2) | 1.55 (1.1) |

| Symptoms[a] | Occurrence Rates % (n) | | | Severity Ratings with Zeros[b] Mean (SD) | | | Severity Ratings without Zeros[c] Mean (SD) | | | Distress Ratings[d] Mean (SD) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Time 1* | Time 2 | Time 3 | Time 1 | Time 2 | Time 3 | Time 1 | Time 2 | Time 3 | Time 1 | Time 2 | Time 3 |
| Problems with sexual interest/activity | 28.4 (66) | 25.2 (55) | 22.9 (49) | 0.67 (1.2) | 0.62 (1.2) | 0.55 (1.1) | 2.43 (0.9) | 2.61 (0.9) | 2.52 (1.0) | 1.94 (1.2) | 2.21 (1.1) | 2.09 (1.1) |
| Abdominal cramps | 28.0 (65) | 32.6 (71) | 23.8 (51) | 0.50 (0.9) | 0.64 (1.0) | 0.45 (0.9) | 1.89 (0.7) | 2.06 (0.8) | 1.98 (0.8) | 1.73 (1.1) | 1.87 (1.1) | 1.85 (1.2) |
| Diarrhea | 27.2 (63) | 30.3 (66) | 22.0 (47) | 0.48 (0.9) | 0.55 (0.9) | 0.42 (0.9) | 1.80 (0.7) | 1.85 (0.8) | 1.89 (0.9) | 1.38 (1.2) | 1.64 (1.1) | 1.74 (1.1) |
| Increased appetite | 27.2 (63) | 22.5 (49) | 30.4 (65) | 0.45 (0.8) | 0.40 (0.9) | 0.53 (0.9) | 1.78 (0.7) | 1.89 (0.8) | 1.79 (0.7) | 0.92 (1.1) | 1.28 (1.2) | 1.21 (1.2) |
| Itching | 25.9 (60) | 24.8 (54) | 24.3 (52) | 0.43 (0.9) | 0.43 (0.9) | 0.37 (0.7) | 1.77 (0.8) | 1.77 (0.8) | 1.59 (0.6) | 1.31 (1.2) | 1.44 (1.1) | 1.21 (0.9) |
| Weight gain | 25.9 (60) | 18.8 (41) | 24.3 (52) | 0.37 (0.7) | 0.26 (0.6) | 0.37 (0.7) | 1.47 (0.6) | 1.56 (0.6) | 1.65 (0.6) | 1.49 (1.3) | 1.45 (143) | 1.57 (1.2) |
| Shortness of breath | 24.1 (56) | 24.3 (53) | 22.9 (49) | 0.43 (0.8) | 0.39 (0.8) | 0.36 (0.7) | 1.81 (0.7) | 1.65 (0.6) | 1.58 (0.7) | 1.59 (1.0) | 1.52 (1.0) | 1.58 (0.9) |
| Weight loss | 22.4 (52) | 28.4 (62) | 16.8 (36) | 0.32 (0.7) | 0.41 (0.7) | 0.27 (0.7) | 1.47 (0.6) | 1.48 (0.6) | 1.66 (0.9) | 0.81 (1.0) | 0.72 (1.0) | 1.29 (1.3) |
| Difficulty breathing | 20.3 (47) | 16.5 (36) | 11.7 (25) | 0.32 (0.7) | 0.26 (0.7) | 0.18 (0.6) | 1.62 (0.7) | 1.68 (0.8) | 1.58 (0.8) | 1.64 (1.0) | 1.66 (1.0) | 1.42 (1.0) |
| Problems with urination | 18.5 (43) | 18.3 (40) | 15.9 (34) | 0.33 (0.8) | 0.33 (0.8) | 0.31 (0.8) | 1.81 (0.9) | 1.82 (0.8) | 1.94 (0.9) | 1.64 (1.3) | 1.59 (1.3) | 1.79 (1.1) |
| Chest tightness | 17.2 (40) | 16.1 (35) | 10.7 (23) | 0.25 (0.6) | 0.27 (0.7) | 0.18 (0.6) | 1.49 (0.6) | 1.71 (0.8) | 1.73 (0.8) | 1.45 (0.8) | 1.74 (1.0) | 1.73 (0.9) |
| Mouth sore | 16.8 (39) | 16.1 (35) | 16.8 (36) | 0.26 (0.7) | 0.27 (0.7) | 0.30 (0.8) | 1.61 (0.8) | 1.69 (0.8) | 1.83 (0.9) | 1.30 (0.9) | 1.45 (1.1) | 1.71 (1.4) |
| Swelling of arms or legs | 16.4 (38) | 16.1 (35) | 18.7 (40) | 0.34 (0.9) | 0.28 (0.7) | 0.35 (0.8) | 2.05 (1.0) | 1.85 (0.8) | 1.97 (0.9) | 1.71 (1.4) | 1.82 (1.2) | 1.63 (1.3) |
| Vomiting | 10.8 (25) | 16.5 (36) | 8.9 (19) | 0.23 (0.7) | 0.33 (0.8) | 0.15 (0.6) | 2.12 (1.0) | 2.09 (0.8) | 1.83 (0.8) | 2.00 (1.3) | 1.73 (1.3) | 2.17 (1.1) |
| Difficulty swallowing | 6.0 (14) | 7.8 (17) | 6.5 (14) | 0.09 (0.4) | 0.12 (0.5) | 0.10 (0.4) | 1.57 (0.9) | 1.59 (0.9) | 1.50 (0.9) | 1.29 (1.1) | 1.94 (1.1) | 1.36 (1.0) |

Abbreviation: SD = standard deviation;

*Orientation column in rank order

Timing of symptom assessments: Time 1 = prior to the initiation of next cycle of chemotherapy (i.e, recovery from the second or third cycle of chemotherapy), Time 2 = approximately one week after chemotherapy (i.e., acute symptoms), Time 3 = approximately two weeks after chemotherapy (i.e., potential nadir).

[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 with zeros: 0 = did not have the symptoms, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe.

[c]Severity ratings without zeros: 1 = slight, 2 = moderate, 3 = severe, 4 = very severe.

[d]Distress ratings: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much.

**Table 3.**

Number and Types of Symptoms within Each Symptom Cluster Over a Cycle of Chemotherapy[a]

| Symptom Cluster | Symptoms | Time 1 | | | Time 2 | | | Time 3 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Occurrence | Severity | Distress | Occurrence | Severity | Distress | Occurrence | Severity | Distress |
| Hormonal | Sweats | 0.855 | 0.932 | 0.750 | 0.938 | 0.841 | 0.788 | 0.612 | 0.666 | 0.603 |
| | Hot flashes | 0.801 | 0.904 | 0.992 | 0.826 | 0.890 | 0.958 | 0.727 | 0.863 | 0.788 |
| | Problems with sexual interest or activity | 0.800 | 0.539 | 0.425 | 0.627 | 0.574 | 0.576 | 0.710 | 0.433 | 0.378 |
| | Abdominal cramps | 0.652 | – | – | – | – | – | – | – | – |
| | Difficulty concentrating | 0.555 | 0.314 | – | – | – | 0.331 | – | – | – |
| | Feeling irritable | 0.469 | – | – | – | – | – | – | – | – |
| | Feeling drowsy | 0.468 | – | – | – | – | – | – | – | – |
| | Pain | 0.433 | 0.305 | 0.330 | – | 0.355 | 0.366 | – | – | – |
| | Feeling bloated | 0.343 | – | – | – | – | – | – | – | – |
| | Numbness/tingling in hands/feet | – | – | – | 0.305 | – | – | – | – | – |
| | Dizziness | – | – | – | – | – | – | 0.543 | 0.418 | 0.501 |
| | “I don’t look like myself” | – | – | – | – | – | – | – | −0.373 | |
| | Total number of symptoms | 9/12 | 5/12 | 4/12 | 4/12 | 4/12 | 5/12 | 4/12 | 5/12 | 4/12 |
| Respiratory | Difficulty breathing | 0.962 | 0.909 | 0.869 | 0.833 | 0.876 | 0.799 | 1.088 | 1.090 | 1.029 |
| | Shortness of breath | 0.900 | 0.873 | 0.864 | 1.092 | 1.037 | 0.920 | 0.774 | 0.783 | 0.789 |
| | Pain | 0.512 | 0.362 | – | – | – | – | – | – | – |
| | Cough | 0.473 | 0.422 | 0.332 | 0.524 | 0.437 | 0.527 | 0.555 | 0.513 | 0.552 |
| | Dry mouth | 0.455 | – | – | – | – | – | – | – | – |
| | Numbness/tingling in hands/feet | 0.410 | – | – | – | – | – | – | – | – |
| | Feeling bloated | 0.383 | – | – | 0.325 | – | – | – | – | – |
| | Dizziness | 0.362 | – | – | – | – | – | – | – | – |
| | Difficulty sleeping | 0.356 | – | – | – | – | – | – | – | – |
| | Difficulty concentrating | – | – | – | 0.472 | – | – | – | – | – |
| | Total number of symptoms | 9/10 | 4/10 | 3/10 | 5/10 | 3/10 | 3/10 | 3/10 | 3/10 | 3/10 |
| Psychological | Worrying | 0.702 | 0.764 | Not identified | 0.872 | 0.853 | 0.786 | 0.939 | 0.918 | 0.929 |

| Symptom Cluster | Symptoms | Time 1 | | | Time 2 | | | Time 3 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Occurrence | Severity | Distress | Occurrence | Severity | Distress | Occurrence | Severity | Distress |
| | Hair loss | 0.579 | – | | – | 0.360 | 0.363 | – | 0.311 | 0.322 |
| | Feeling sad | 0.571 | 0.738 | | 0.947 | 0.960 | 0.859 | 0.772 | 0.733 | 0.661 |
| | “I don’t look like myself” | 0.492 | – | | 0.371 | 0.455 | 0.504 | 0.436 | 0.607 | 0.576 |
| | Changes in skin | 0.492 | – | | 0.351 | – | – | – | | – |
| | Weight loss | 0.462 | – | | – | – | – | – | | – |
| | Change in the way food tastes | 0.441 | – | | – | – | – | – | | – |
| | Itching | 0.411 | – | | – | – | – | – | | – |
| | Lack of appetite | 0.405 | – | | – | – | – | – | | – |
| | Dizziness | 0.354 | – | | – | – | – | – | | – |
| | Feeling irritable | 0.350 | 0.397 | | 0.469 | 0.632 | 0.562 | 0.643 | 0.662 | 0.596 |
| | Feeling nervous | 0.323 | 0.724 | | 0.617 | 0.611 | 0.557 | 0.711 | 0.694 | 0.675 |
| | Abdominal cramps | – | 0.427 | | 0.331 | – | 0.355 | – | 0.318 | – |
| | Difficulty concentrating | – | – | | 0.412 | 0.356 | 0.301 | 0.377 | 0.399 | 0.453 |
| | Feeling bloated | – | – | | 0.335 | 0.334 | – | – | | – |
| | Problems with sexual interest or activity | – | – | | 0.325 | 0.366 | 0.467 | 0.458 | 0.639 | 0.608 |
| | Pain | – | – | | – | – | – | – | 0.345 | 0.403 |
| | Difficulty sleeping | – | – | | – | – | – | – | 0.380 | 0.357 |
| | Diarrhea | – | – | | – | – | – | −0.315 | | |
| | Total number of symptoms | 12/19 | 5/19 | | 10/19 | 9/19 | 9/19 | 8/19 | 11/19 | 10/19 |
| Psychological / gastrointestinal | Abdominal cramps | Not identified | | 0.746 | Not identified | | | | | |
| | Feeling sad | | | 0.618 | | | | | | |
| | Feeling bloated | | | 0.585 | | | | | | |
| | Worrying | | | 0.579 | | | | | | |
| | Feeling nervous | | | 0.539 | | | | | | |
| | Diarrhea | | | 0.493 | | | | | | |
| | Problems with sexual interest or activity | | | 0.457 | | | | | | |
| | Difficulty concentrating | | | 0.426 | | | | | | |

| Symptom Cluster | Symptoms | Time 1 | | | Time 2 | | | Time 3 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Occurrence | Severity | Distress | Occurrence | Severity | Distress | Occurrence | Severity | Distress |
| | Feeling drowsy | | | 0.405 | | | | | | |
| | Constipation | | | 0.389 | | | | | | |
| | Feeling irritable | | | 0.376 | | | | | | |
| | Itching | | | −0.314 | | | | | | |
| | Total number of symptoms | | | 12/12 | | | | | | |
| Gastrointestinal | Diarrhea | 0.482 | | | – | 0.335 | 0.363 | 0.788 | 0.678 | 0.628 |
| | Abdominal cramps | 0.435 | | | 0.392 | 0.416 | 0.354 | 0.497 | 0.463 | 0.521 |
| | Constipation | 0.360 | | | 0.388 | – | 0.442 | 0.483 | 0.509 | 0.538 |
| | Sweats | −0.318 | | | – | – | – | – | – | – |
| | Itching | −0.401 | | | 0.323 | 0.367 | – | 0.610 | 0.571 | 0.580 |
| | Hot flashes | −0.505 | | | – | – | – | – | – | – |
| | Dry mouth | – | | | 0.500 | 0.538 | 0.534 | 0.467 | 0.442 | 0.385 |
| | Nausea | – | | | 0.685 | 0.614 | 0.527 | 0.610 | 0.607 | 0.548 |
| | Feeling drowsy | – | | | 0.447 | 0.359 | 0.396 | 0.427 | – | – |
| | Difficulty sleeping | – | | | 0.407 | 0.364 | 0.428 | – | – | – |
| | Lack of appetite | – | Not identified | Not identified | 0.808 | 0.787 | 0.685 | 0.746 | 0.773 | 0.823 |
| | Dizziness | – | | | 0.431 | 0.465 | 0.608 | – | – | – |
| | Weight loss | – | | | 0.702 | 0.698 | 0.795 | 0.745 | 0.790 | 0.739 |
| | Hair loss | – | | | 0.453 | 0.303 | 0.381 | – | – | – |
| | Change in the way food tastes | – | | | 0.494 | 0.488 | 0.465 | 0.504 | 0.494 | 0.582 |
| | “I don’t look like myself” | – | | | 0.414 | 0.306 | 0.349 | 0.418 | 0.349 | 0.375 |
| | Problems with sexual interest or activity | – | | | – | – | −0.358 | – | – | – |
| | Changes in skin | – | | | – | – | 0.396 | 0.519 | 0.591 | 0.594 |
| | Feeling bloated | – | | | – | – | – | 0.424 | – | 0.347 |
| | Total number of symptoms | 6/19 | | | 13/19 | 13/19 | 15/19 | 13/19 | 11/19 | 12/19 |
| Gastrointestinal / epithelial | Lack of appetite | Not identified | 0.856 | 0.479 | Not identified | | | | | |
| | Change in the way food tastes | | 0.669 | 0.526 | | | | | | |
| | Weight loss | | 0.580 | – | | | | | | |

| Symptom Cluster | Symptoms | Time 1 | | | Time 2 | | | Time 3 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Occurrence | Severity | Distress | Occurrence | Severity | Distress | Occurrence | Severity | Distress |
| | Changes in skin | | 0.543 | 0.654 | | | | | | |
| | Constipation | | 0.537 | – | | | | | | |
| | Nausea | | 0.452 | 0.309 | | | | | | |
| | Dizziness | | 0.440 | 0.593 | | | | | | |
| | Itching | | 0.387 | 0.626 | | | | | | |
| | “I don’t look like myself” | | 0.382 | 0.688 | | | | | | |
| | Hair loss | | 0.317 | 0.616 | | | | | | |
| | Dry mouth | | – | 0.324 | | | | | | |
| | Feeling irritable | | – | 0.302 | | | | | | |
| | Total number of symptoms | | 10/12 | 10/12 | | | | | | |
| Weight change | Weight gain | 0.902 | 0.907 | 0.897 | 0.899 | 1.019 | 0.902 | 0.930 | 1.067 | 0.981 |
| | Increased appetite | 0.728 | 0.785 | 0.813 | 0.831 | 0.682 | 0.784 | 0.742 | 0.696 | 0.720 |
| | Lack of appetite | −0.416 | – | −0.313 | −0.543 | −0.468 | −0.483 | −0.344 | – | – |
| | Weight loss | −0.474 | −0.401 | −0.356 | – | – | – | −0.380 | – | – |
| | Feeling bloated | – | – | 0.304 | – | – | – | – | – | 0.312 |
| | Nausea | – | – | – | – | – | −0.320 | – | – | – |
| | Changes in skin | – | – | – | – | – | 0.341 | – | – | – |
| | Hot flashes | – | – | – | – | – | – | – | – | 0.348 |
| | Sweats | – | – | – | – | – | – | – | 0.313 | 0.442 |
| | Itching | – | – | – | – | – | – | – | 0.303 | 0.431 |
| | Feeling drowsy | – | – | – | – | – | – | 0.346 | – | – |
| | Total number of symptoms | 4/11 | 3/11 | 5/11 | 3/11 | 3/11 | 5/11 | 5/11 | 4/11 | 6/11 |

[a]Extraction method: unweighted least squares. Rotation method: Geomin (oblique) rotation.

Timing of symptom assessments: Time 1 = prior to the initiation of next cycle of chemotherapy (i.e., recovery from the second or third cycle of chemotherapy), Time 2 = approximately one week after chemotherapy (i.e., acute symptoms), Time 3 = approximately two weeks after chemotherapy (i.e., potential nadir).

For total number of symptoms, the numerator represents the number of symptoms identified at the corresponding time point according to the corresponding dimension of the symptom experience. The denominator represents the total number of symptoms identified across all time points and according to all dimensions of the symptom experience.

Not identified = This symptom cluster was not identified at the corresponding time point according to the corresponding dimension of the symptom experience.

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– = Factor loadings for these symptoms were <0.30.

**Table 4.**

Stability of Symptom Clusters Over Time and Across Dimensions of the Symptom Experience[a]

| | Time 1 | | | Time 2 | | | Time 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Occurrence** | **Severity** | **Distress** | **Occurrence** | **Severity** | **Distress** | **Occurrence** | **Severity** | **Distress** |
| Symptom agreement over time (%) | | | | | | | | | |
| Hormonal | **81.8** | 71.4 | 66.7 | 36.4 | 57.1 | **83.3** | 36.4 | 71.4 | 66.7 |
| Respiratory | **90.0** | **100.0** | **100.0** | 50.0 | **75.0** | **100.0** | 30.0 | **75.0** | **100.0** |
| Psychological | 70.6 | 41.7 | – | 58.8 | **75.0** | **81.8** | 47.1 | **91.7** | **90.9** |
| Psychological / gastrointestinal | – | – | N/A | – | – | – | – | – | – |
| Gastrointestinal | 33.3 | – | – | 72.2 | **86.7** | **88.2** | 72.2 | 73.3 | 70.6 |
| Gastrointestinal / epithelial | – | N/A | N/A | – | – | – | – | – | – |
| Weight change | **80.0** | 50.0 | 50.0 | 60.0 | 50.0 | 50.0 | **100.0** | 66.7 | 60.0 |
| Symptom agreement across dimensions (%) | | | | | | | | | |
| Hormonal | **100.0** | 55.6 | 44.4 | 66.7 | 66.7 | **83.3** | **80.0** | **100.0** | **80.0** |
| Respiratory | **100.0** | 44.4 | 33.3 | **100.0** | 60.0 | 60.0 | **100.0** | **100.0** | **100.0** |
| Psychological | **92.3** | 38.5 | – | **90.9** | **81.8** | **81.8** | 66.7 | **91.7** | **83.3** |
| Psychological / gastrointestinal | – | – | N/A | – | – | – | – | – | – |
| Gastrointestinal | **100.0** | – | – | **81.3** | **81.3** | **93.8** | **100.0** | **84.6** | **92.3** |
| Gastrointestinal / epithelial | – | **83.3** | **83.3** | – | – | – | – | – | – |
| Weight change | **80.0** | 60.0 | **100.0** | 60.0 | 60.0 | **100.0** | 55.6 | 44.4 | 66.7 |
| Symptom agreement over time and across dimensions (%) | | | | | | | | | |
| Hormonal | **75.0** | 41.7 | 33.3 | 33.3 | 33.3 | 41.7 | 33.3 | 41.7 | 33.3 |
| Respiratory | **90.0** | 40.0 | 30.0 | 50.0 | 30.0 | 30.0 | 30.0 | 30.0 | 30.0 |
| Psychological | 63.2 | 26.3 | | 52.6 | 47.4 | 47.4 | 42.1 | 57.9 | 52.6 |
| Psychological / gastrointestinal | – | – | N/A | – | – | – | – | – | – |
| Gastrointestinal | 31.6 | – | – | 68.4 | 68.4 | **78.9** | 68.4 | 57.9 | 63.2 |
| Gastrointestinal / epithelial | – | N/A | N/A | – | – | – | – | – | – |
| Weight change | 36.4 | 27.3 | 45.5 | 27.3 | 27.3 | 45.5 | 45.5 | 36.4 | 54.5 |

[a]Symptom agreement calculations for the hormonal symptom cluster identified according to occurrence at Time 1 are provided as exemplars. Symptom agreement over time was calculated as follows: (number of symptoms identified according to occurrence at Time 1 ÷ number of symptoms identified according to occurrence at all time points) × 100 = (9 ÷ 11) × 100 = 81.8%. Symptom agreement across

dimensions was calculated as follows: (number of symptoms identified according to occurrence at Time 1 ÷ number of symptoms identified according to all three dimensions at Time 1) × 100 = (9 ÷ 9) × 100 = 100.0%. Symptom agreement over time and across dimensions for the occurrence dimension at Time 1 was calculated as follows: (number of symptoms identified according to occurrence at Time 1 ÷ number of symptoms identified according to all three dimensions at all time points) × 100 = (9 ÷ 12) × 100 = 75.0%.

Timing of symptom assessments: Time 1 = prior to the initiation of next cycle of chemotherapy (i.e., recovery from the second or third cycle of chemotherapy), Time 2 = approximately one week after chemotherapy (i.e., acute symptoms), Time 3 = approximately two weeks after chemotherapy (i.e., potential nadir).

– = Symptom cluster was not identified according to this dimension at this time point.

N/A = Unable to calculate; symptom cluster was not identified at more than one time point and/or according to more than one dimension.