Symptom Clusters in Patients With Gynecologic Cancer Receiving Chemotherapy

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OBJECTIVES: To describe ratings of symptom occurrence, severity, and distress for 38 symptoms and to identify and compare the number and types of symptom clusters identified using these ratings. Although patients with gynecologic cancer experience multiple co-occurring symptoms, little is known about how these symptoms cluster together.

SAMPLE & SETTING: Eligible patients (N = 232) had gynecologic cancer and were receiving chemotherapy.

METHODS & VARIABLES: Symptoms were assessed using the Memorial Symptom Assessment Scale. Symptom clusters were identified through exploratory factor analysis. Geomin-rotated factor loadings with absolute values of 0.3 or greater were considered meaningful. Factor solutions (i.e., symptom clusters) were assessed for simple structure and clinical relevance.

RESULTS: Lack of energy, hair loss, and "I don't look like myself" were the most common, severe, and distressing symptoms. Hormonal, respiratory, and weight change clusters were identified across all three dimensions.

IMPLICATIONS FOR NURSING: Research that explores how symptom clusters change over time and their underlying mechanisms is warranted.

KEYWORDS symptoms; symptom clusters; ovarian neoplasms; uterine neoplasms; chemotherapy
***ONF, 48*(4), 441–452**
DOI 10.1188/21.ONF.441-452

More than 113,000 individuals in the United States are diagnosed with gynecologic cancer each year (Siegel et al., 2020). These patients experience a high burden from physical and psychological symptoms that is most acute during active treatment (Lefkowits et al., 2014). Chemotherapy is a mainstay of treatment for most patients with ovarian, fallopian tube, or primary peritoneal carcinoma; locally advanced cervical carcinoma; and recurrent, metastatic, or high-risk uterine carcinoma (Armstrong et al., 2019; Koh et al., 2018, 2019). Patients who receive chemotherapy experience an average of 10 co-occurring symptoms, and these co-occurring symptoms are associated with decreases in quality of life (Esther Kim et al., 2009). Nevertheless, most symptom management research in patients with gynecologic cancer has focused on the assessment and management of individual symptoms (del Carmen & Rice, 2017; Kim et al., 2015; Landrum et al., 2015; Wang & Woodruff, 2015).

Symptom clusters are comprised of multiple co-occurring symptoms that are related to each other (Miaskowski et al., 2017). Symptoms that are part of a symptom cluster may share common underlying mechanisms and may respond to a single treatment (Miaskowski et al., 2017). Identification of symptom clusters in patients with gynecologic cancer receiving chemotherapy may inform the development of novel interventions to improve multiple co-occurring symptoms. Although it is known that a patient's symptom experience is shaped not only by a symptom's occurrence but also by its severity and associated distress, it is unclear which dimension of the symptom experience should be used to identify symptom clusters de novo (Miaskowski et al., 2017).

Of the following five studies of symptom clusters in patients with gynecologic cancer, all identified symptom clusters using a single dimension of the

symptom experience (Fox & Lyon, 2007; Huang et al., 2016; Hwang et al., 2016; Kim et al., 2018; Nho et al., 2017). In the study by Hwang et al. (2016), symptom clusters were identified using occurrence rates. In the remaining four studies, symptom clusters were identified using ratings of severity (Fox & Lyon, 2007; Huang et al., 2016; Kim et al., 2018; Nho et al., 2017). To date, no study has compared the number and types of symptom clusters across the dimensions of occurrence, severity, and distress in patients with gynecologic cancer receiving chemotherapy. Knowledge of whether symptom clusters vary across dimensions of the symptom experience will inform efforts to improve symptom management in these patients. Therefore, the purposes of this study, in a sample of patients with gynecologic cancer receiving chemotherapy (N = 232), were to (a) describe ratings of symptom occurrence, severity, and distress for 38 symptoms and (b) identify and compare the number and types of symptom clusters identified using these ratings.

Methods

Patients and Settings

This analysis is part of a longitudinal descriptive study that evaluated the symptom experience of outpatients with cancer receiving chemotherapy (Han et al., 2019; Ward Sullivan et al., 2017; Wong et al., 2017). The theory of symptom management provided the theoretical framework for the parent study (Bender et al., 2018). Eligibility criteria for the parent study were as follows:

- Aged 18 years or older
- Diagnosed with breast, lung, gastrointestinal, or gynecologic cancer
- Had received chemotherapy within the previous four weeks
- Had the ability to read, write, and understand English
- Provided written informed consent

For the parent study, patients were recruited from four community-based oncology programs, two comprehensive cancer centers, and one Veterans Affairs hospital. For the current analysis, 232 patients with gynecologic cancer were evaluated, of the total sample of 1,343 patients.

Procedures

Research staff members approached patients meeting the eligibility criteria in the infusion unit for their first or second cycle of chemotherapy to discuss study participation. All patients provided written informed consent. Patients completed questionnaires at home and returned them in a postage-paid envelope six times during two cycles of chemotherapy. Data from the enrollment assessment, which evaluated symptoms during the week before patients' second or third cycle of chemotherapy and primarily during recovery from the previous cycle of chemotherapy, were used for these analyses. Patients' medical records were reviewed for information about disease and treatment. The study procedures were approved by the Committee on Human Research at the University of California, San Francisco, the Dana-Farber/Harvard Cancer Center Institutional Review Board, and the institutional review board at each of the study sites.

Instruments

A demographic questionnaire was used to obtain information about patients' age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. Patients' functional status was evaluated with the Karnofsky Performance Status (KPS) scale (Karnofsky, 1977). Thirteen common medical conditions were evaluated with the Self-Administered Comorbidity Questionnaire (Sangha et al., 2003), which has a total score ranging from 0 to 39, with higher scores indicating a worse comorbidity profile. A modified version of the 32-item Memorial Symptom Assessment Scale (MSAS) was used to evaluate the occurrence, severity, and distress of 38 symptoms commonly associated with cancer and its treatment (Portenoy et al., 1994). The added six symptoms common in patients with cancer were hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain. For each symptom on the MSAS, patients were asked to indicate whether they had experienced that symptom during the past week; if they had, patients were asked to rate its severity (measured using a four-point Likert-type scale ranging from 1 [slight] to 4 [very severe]) and distress (measured using a five-point Likert-type scale ranging from 0 [not at all] to 4 [very much]). The validity and reliability of the MSAS are well-established (Portenoy et al., 1994).

Data Analysis

Data were analyzed using IBM SPSS Statistics, version 27.0, and Mplus, version 8.4. For demographic and clinical characteristics, symptom occurrence rates, and severity and distress ratings, descriptive statistics and frequency distributions were calculated. For symptom cluster identification, exploratory factor

analyses (EFAs) were done for the dichotomous (i.e., occurrence) and ordinal (i.e., severity and distress) items (Brown, 2015). As noted by Skerman et al. (2009), EFA is the preferred method to identify symptom clusters. Mplus was used for all EFAs because the program provides appropriate estimation for dichotomous and ordinal items.

Factor loadings for EFA were considered to be meaningful if the loading was 0.3 or greater. Relatedly, factors were determined to be adequately defined if at least two items, or symptoms, had loadings (i.e., structure coefficients following rotation) of 0.3 or greater (Brown, 2015). Although it is common to require that each item load strongly on only one factor, in the current study, items that loaded on two factors (i.e., were cross-loaded) and were within the preset criteria of 0.3 or greater were retained and used to define both factors (i.e., the symptom clusters). Cross-loading of symptoms on more than one factor may be beneficial in terms of interpreting potential causal mechanisms, particularly when oblique rotation is used (Brown, 2015; Miaskowski et al., 2007).

To permit sufficient variation and covariation for EFA performance, only those symptoms present in greater than 20% and less than 80% of patients were included in these analyses. As a result of these criteria, 31 of the 38 MSAS symptoms were used for each of the EFAs; the remaining seven MSAS symptoms were excluded because of insufficient variation in the occurrence of these symptoms. Lack of energy was reported by more than 80% of patients, and problems with urination, chest tightness, mouth sores, swelling of arms or legs, vomiting, and difficulty swallowing were reported by less than 20% of patients.

Tetrachoric correlations were used to create the matrix of associations for the EFA using the dichotomous occurrence items. Polychoric correlations were used to create the matrix of associations for the EFAs using the ordinal severity and distress ratings. Simple structures for the occurrence, severity, and distress EFAs were estimated using the method of unweighted least squares with geomin, or oblique, rotation. This method was used to create the best fit for the model, and it allowed for an improved representation of how the factors were correlated and improved the interpretability of each factor solution. Because the scales for the MSAS items are dichotomous (i.e., occurrence) and ordinal (i.e., severity and distress), the unweighted least squares estimator was selected to achieve more reliable results.

The EFA for severity employed a severity rating of 0, which was assigned if a patient indicated that they did not have the symptom (i.e., occurrence). Similarly, the EFA for distress employed a distress rating of 0 (did not have the symptom), and the original ratings shifted from 1 (not at all) to 5 (very much). Although the initial EFAs were done using severity and distress ratings that did not include zero, the pairwise missingness was greater than 90% and the estimation failed to converge.

Factor solutions were estimated for two to six factors. All factor solutions were examined, and the factor solution with the greatest interpretability and clinical meaningfulness was selected if it met the criteria set for evaluating a simple structure (i.e., size of item loadings and number of items on a factor). Each factor solution was then examined to determine a clinically appropriate name for the symptom cluster, based on the highest factor loadings and the majority of the symptoms in the cluster.

Differences Among Symptom Clusters

To evaluate the percentage of agreement among the symptoms within the same cluster using occurrence, severity, and distress ratings, the criteria proposed by Kirkova and Walsh (2007) were employed. According to Kirkova and Walsh (2007), to be in agreement with each other, at least 75% of the symptoms in the clusters should be present, including the most prominent and most important symptom (i.e., the symptom with the greatest weight from the EFAs). To illustrate, percentage of agreement for the weight change symptom cluster, which consisted of a total of five symptoms across all three dimensions, was calculated as follows for the occurrence dimension: 4 symptoms divided by 5 symptoms multiplied by 100 equals 80% agreement.

Results

Sample Characteristics

Demographic and clinical characteristics of the 232 patients with gynecologic cancer are provided in Table 1. In brief, 55% of the patients were married or partnered, 77% were White, 54% reported an annual household income of $70,000 or greater, and had an average of 16 years (SD = 2.88) of education. The majority were non-smokers (66%) and exercised regularly (71%). Patients had an average of 2.4 (SD = 1.43) comorbid conditions and an average KPS score of 78.41 (SD = 12.39). The most common gynecologic cancer diagnoses were ovarian and uterine. Patients were an average of 2.05 years (SD = 3.52) from their cancer diagnosis (median = 0.52 years) and had received an average of 1.8 (SD = 1.12) previous cancer

treatments. Patients reported an average of 14.22 (SD = 7.14) concurrent symptoms on the MSAS before their next cycle of chemotherapy.

Symptom Prevalence and Characteristics

Occurrence, severity, and distress ratings for each symptom are provided in Table 2. Lack of energy was the most common symptom, followed by difficulty sleeping, pain, feeling drowsy, and worrying. Mean severity ratings were calculated in two ways: with and without zeros. In the with zeros analysis, all 232 patients were included; patients who did not report the symptom were assigned a severity score of 0. When zeros were included in the calculation of mean severity scores, lack of energy was rated as the most severe symptom, followed by difficulty sleeping, hair loss, pain, and feeling drowsy. In the without zeros analysis, only patients who reported each symptom were included; severity scores could range from 1 to 4. When zeros were not included in mean severity scores, hair loss was rated as the most severe symptom, followed by problems with sexual interest or activity, "I don't look like myself," difficulty sleeping, and vomiting. The most distressing symptom was "I don't look like myself," followed by vomiting, problems with sexual interest or activity, lack of energy, and hair loss.

Symptom Clusters by Occurrence

A five-factor solution was selected for the occurrence EFA (see Table 3). The hormonal symptom cluster was comprised of nine symptoms, with sweats having the highest factor loading. The respiratory symptom cluster was comprised of nine symptoms, with difficulty breathing having the highest factor loading. The psychological symptom cluster was comprised of 12 symptoms, with worrying having the highest factor loading. The gastrointestinal symptom cluster was comprised of six symptoms. Hot flashes cross-loaded with the hormonal symptom cluster and had the highest factor loading (loaded negatively). Diarrhea had the highest factor loading of the non–cross-loaded symptoms. The weight change symptom cluster was comprised of four symptoms, with weight gain having the highest factor loading. One symptom, nausea, did not load on any factor.

Symptom Clusters by Severity

A five-factor solution was selected for the severity EFA. The hormonal symptom cluster was comprised of five symptoms, with sweats having the highest factor loading. The respiratory symptom cluster

TABLE 1. Sample Characteristics (N = 232)

Characteristic	$\bar{X}$	SD
Age (years)	59.62	12.73
Body mass index (kg/m^2)	27.43	6.54
Comorbidities (of 13)	2.4	1.43
Education (years)	16	2.88
KPS score	78.41	12.39
MAX2 index score	0.15	0.06
Metastatic sites excluding lymph node involvement (of 8)	1.05	1.11
Metastatic sites including lymph node involvement (of 9)	1.46	1.31
MSAS symptoms (of 38)	14.22	7.14
Prior cancer treatments (of 9)	1.8	1.12
Self-Administered Comorbidity Questionnaire score	5.43	3.29
Time since diagnosis (years)	2.05	3.52
Characteristic	**n**	**%**
Adult care responsibilities (N = 211)		
No	193	91
Yes	18	9
Antiemetic regimen (N = 224)		
Serotonin receptor antagonist and steroid	105	47
Steroid alone or serotonin receptor antagonist alone	60	27
Neurokinin-1 receptor antagonist and two other antiemetics	35	16
None	24	11
Childcare responsibilities		
No	209	90
Yes	23	10
Current employment (N = 227)		
No	156	69
Yes	71	31
Current smoker or history of smoking (N = 228)		
No	150	66
Yes	78	34
Cycle length of chemotherapy (days)		
14	13	6
21	187	81
28	32	14
Ethnicity (N = 227)		
White	175	77
Hispanic, mixed, or other	24	11
Asian or Pacific Islander	20	9
Black	8	4

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TABLE 1. Sample Characteristics (N = 232) *(Continued)*

Characteristic	n	%
Emetogenicity of chemotherapy regimen		
Minimal/low	43	19
Moderate	173	75
High	16	7
Exercise regularly (N = 227)		
Yes	161	71
No	66	29
Gynecologic cancer diagnoses[a]		
Ovarian	130	54
Uterine	75	31
Fallopian tube	15	6
Other	13	5
Primary peritoneal	8	3
Income ($) (N = 209)		
Less than 30,000	38	18
30,000–69,999	57	27
70,000–99,999	34	16
100,000 or greater	80	38
Living alone (N = 227)		
No	151	67
Yes	76	33
Married or partnered (N = 225)		
Yes	124	55
No	101	45
Prior cancer treatment (N = 228)		
Only chemotherapy or surgery, or RT	123	54
Chemotherapy and surgery, or chemotherapy and RT, or surgery and RT	78	34
Chemotherapy, surgery, RT	19	8
No prior treatment	8	4

[a] Patients could select more than one option; 241 responses were received.
KPS—Karnofsky Performance Status; MSAS—Memorial Symptom Assessment Scale; RT—radiation therapy
Note. Because of rounding, percentages may not total 100.
Note. KPS scores reflect patients' functional status; possible scores range from 0 (dead) to 100 (typical activity, with no evidence of disease). The Self-Administered Comorbidity Questionnaire evaluated 13 common medical conditions; total scores ranged from 0 to 39, with higher scores indicating a worse comorbidity profile. MAX2 scores range from 0 to 1, with higher scores indicating greater toxicity.

was comprised of four symptoms, with difficulty breathing having the highest factor loading. The psychological symptom cluster was comprised of five symptoms, with worrying having the highest factor loading. The gastrointestinal/epithelial symptom cluster was comprised of 10 symptoms, with lack of appetite having the highest factor loading. The weight change symptom cluster was comprised of three symptoms, with weight gain having the highest factor loading. Six symptoms did not load on any factor (i.e., feeling bloated, numbness/tingling in hands/feet, difficulty sleeping, diarrhea, feeling drowsy, and dry mouth).

Symptom Clusters by Distress

A five-factor solution was selected for the distress EFA. The hormonal symptom cluster was comprised of four symptoms, with hot flashes having the highest factor loading. The respiratory symptom cluster was comprised of three symptoms, with difficulty breathing having the highest factor loading. The psychological/gastrointestinal symptom cluster was comprised of 12 symptoms, with abdominal cramps having the highest factor loading. The gastrointestinal/epithelial symptom cluster was comprised of 10 symptoms, with "I don't look like myself" having the highest factor loading. The weight change symptom cluster was comprised of five symptoms, with weight gain having the highest factor loading. Two symptoms, numbness/tingling in hands/feet and difficulty sleeping, did not load on any factor.

Agreement Within Each Symptom Cluster

For the hormonal symptom cluster, the percentage of agreement across dimensions of the symptom experience ranged from 44% (distress) to 100% (occurrence). For the respiratory symptom cluster, the percentage of agreement ranged from 33% (distress) to 100% (occurrence). For the psychological symptom cluster, the percentage of agreement ranged from 38% (severity) to 92% (occurrence). For the gastrointestinal/epithelial symptom cluster, the percentage of agreement was 83% across the dimensions of severity and distress. For the weight change symptom cluster, the percentage of agreement ranged from 60% (occurrence) to 100% (distress). Percentage of agreement was not calculated for the psychological/gastrointestinal and gastrointestinal symptom clusters, which were identified for only one dimension.

Symptoms present across all three dimensions included sweats, hot flashes, problems with sexual interest or activity, and pain for the hormonal symptom cluster; difficulty breathing, shortness of breath, and cough for the respiratory symptom cluster; and weight gain, increased appetite, and weight loss

(loaded negatively) for the weight change symptom cluster. For the psychological symptom cluster identified for occurrence and severity, worrying, feeling sad, feeling irritable, and feeling nervous were present across both dimensions. For the gastrointestinal/epithelial symptom cluster that was identified for

TABLE 2. Occurrence Rates and Severity and Distress Ratings for Symptoms Prior to Chemotherapy (N = 232)

	Occurrence		Severity (Zeros)[b]		Severity (No Zeros)[c]		Distress[d]	
Characteristic[a]	n	%	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Lack of energy	193	83	1.74	1.03	2.11	0.72	1.9	1.14
Difficulty sleeping	163	70	1.5	1.18	2.14	0.77	1.89	1.06
Pain	149	64	1.23	1.08	1.93	0.68	1.79	1.05
Feeling drowsy	143	62	1.08	1.02	1.79	0.67	1.09	1.06
Worrying	136	59	1.06	1.08	1.84	0.76	1.7	1.03
Difficulty concentrating	132	57	0.9	0.94	1.62	0.64	1.49	0.98
Numbness/tingling in hands/feet	132	57	1	1.07	1.78	0.8	1.54	1.24
Hair loss	131	57	1.46	1.55	2.6	1.14	1.9	1.37
Feeling sad	122	53	0.86	0.97	1.65	0.71	1.56	1.09
Feeling nervous	110	47	0.77	0.95	1.69	0.65	1.44	0.95
Constipation	106	46	0.85	1.11	1.92	0.83	1.76	1.24
Feeling irritable	103	44	0.75	0.99	1.74	0.72	1.51	0.95
Nausea	96	41	0.71	1.03	1.78	0.85	1.79	1.12
Hot flashes	94	41	0.8	1.13	2.03	0.84	1.52	1.29
Change in the way food tastes	93	40	0.76	1.09	1.91	0.87	1.45	1.14
Sweats	88	38	0.68	1.01	1.85	0.8	1.34	1.06
Cough	86	37	0.44	0.67	1.25	0.51	0.81	0.99
“I don’t look like myself.”	86	37	0.82	1.26	2.27	1.05	2.02	1.37
Dry mouth	85	37	0.59	0.9	1.68	0.67	1.23	1.06
Feeling bloated	85	37	0.63	0.95	1.76	0.71	1.56	1.01
Lack of appetite	81	35	0.64	1.02	1.91	0.8	1.23	1.09
Dizziness	79	34	0.5	0.8	1.48	0.66	1.36	1.02
Changes in skin	75	32	0.56	0.91	1.73	0.72	1.55	1.21
Problems with sexual interest/activity	66	28	0.67	1.19	2.43	0.91	1.94	1.2
Abdominal cramps	65	28	0.5	0.91	1.89	0.69	1.73	1.14
Diarrhea	63	27	0.48	0.89	1.8	0.75	1.38	1.19
Increased appetite	63	27	0.45	0.84	1.78	0.65	0.92	1.15
Itching	60	26	0.43	0.85	1.77	0.76	1.31	1.15
Weight gain	60	26	0.37	0.71	1.47	0.63	1.49	1.3
Shortness of breath	56	24	0.43	0.84	1.81	0.7	1.59	0.98
Weight loss	52	22	0.32	0.68	1.47	0.64	0.81	1.01
Difficulty breathing	47	20	0.32	0.72	1.62	0.72	1.64	1.03
Problems with urination	43	19	0.33	0.79	1.81	0.86	1.64	1.34
Chest tightness	40	17	0.25	0.62	1.49	0.64	1.45	0.82
Mouth sores	39	17	0.26	0.68	1.61	0.82	1.3	0.88
Swelling of arms or legs	38	16	0.34	0.86	2.05	1.01	1.71	1.35
Vomiting	25	11	0.23	0.74	2.12	1.01	2	1.28
Difficulty swallowing	14	6	0.09	0.43	1.57	0.85	1.29	1.14

[a] Symptoms are from the Memorial Symptom Assessment Scale, with the addition of the following: chest tightness, difficulty breathing, increased appetite, hot flashes, abdominal cramps, and weight gain.
[b] Severity ratings with zeros ranged from 0 (did not have the symptoms) to 4 (very severe).
[c] Severity ratings without zeros ranged from 1 (slight) to 4 (very severe).
[d] Distress ratings ranged from 0 (not at all) to 4 (very much).

severity and distress, lack of appetite, change in the way food tastes, changes in skin, nausea, dizziness, itching, "I don't look like myself," and hair loss were present across both dimensions.

In three symptom clusters, the symptom with the highest rotated factor loading was consistent across each dimension of the symptom experience. These symptoms included difficulty breathing in the respiratory symptom cluster, weight gain in the weight change symptom cluster, and worrying in the psychological symptom cluster. In every symptom cluster that was identified using more than one dimension, the symptom with the highest rotated factor loading was present across the dimensions.

Discussion

The results of this study highlight the most common, severe, and distressing symptoms among patients with gynecologic cancer receiving chemotherapy. Lack of energy was the most common symptom and the most severe symptom when zeros were included in the calculation of mean severity scores. In prior studies of symptom clusters in patients with ovarian cancer receiving chemotherapy, lack of energy ranged from the third most common to the most common symptom (Huang et al., 2016; Hwang et al., 2016). Fatigue, which may occur as a result of cancer or its treatment (Wang & Woodruff, 2015), is widely acknowledged to be one of the most prevalent symptoms among patients with cancer (Ma et al., 2020). Cancer-related fatigue has a negative impact on patients' quality of life (Jung et al., 2018) and may persist for months to years after treatment completion (Poort et al., 2020; Wang et al., 2014). Taken together, these results underscore the importance of assessing and treating fatigue during chemotherapy.

When zeros were not included in the mean severity scores, hair loss was rated as the most severe symptom. In a longitudinal study of symptom clusters in patients with ovarian cancer undergoing chemotherapy, hair loss was reported by 100% of patients and had the highest severity rating starting one week after the third cycle of chemotherapy (Huang et al., 2016). Relatedly, the most distressing symptom in the current study was "I don't look like myself." In a study of symptom clusters in patients with ovarian cancer undergoing chemotherapy, dissatisfaction with one's appearance was rated as the most intense symptom and was second only to fatigue in terms of prevalence (Hwang et al., 2016). Conversely, in the longitudinal study by Huang et al., 2016, "I don't look like myself" was reported by only 28% of patients at any time point and was not rated among the most severe symptoms. Although it is unclear why patients' experiences of appearance-related symptoms differ across studies, some variation may be attributed to differences in the chemotherapy regimens and linguistic or cultural differences in the populations from which the study samples were drawn.

The inclusion of distress ratings in the current study highlights the negative impact of disease- and treatment-related side effects on body image. Concerns about body image, such as feeling less attractive or feminine, are common among patients with gynecologic cancer (Wilson et al., 2020) and may be associated with decrements in emotional well-being (Teo et al., 2018). Clinicians who care for these patients can promote their emotional well-being by normalizing body image concerns, offering the use of cold caps, and assisting patients to manage appearance-related side effects of treatment.

This study is the first to identify and compare symptom clusters in patients with gynecologic cancer using ratings of occurrence, severity, and distress. The results of this study build on what is known about symptom clusters in patients with gynecologic cancer. In a longitudinal study of patients with ovarian cancer receiving chemotherapy (Huang et al., 2016), a menopausal symptom cluster was identified using severity ratings. This symptom cluster may be attributed to treatment-induced menopause, which may occur in premenopausal patients following bilateral oophorectomy, chemotherapy, or pelvic radiation (del Carmen & Rice, 2017; Shifren & Gass, 2014). Symptoms of induced menopause may appear days to weeks after treatment initiation and may be more severe than those that occur during natural menopause (del Carmen & Rice, 2017). Patients with severe menopausal symptoms may be candidates for hormonal therapy or other symptom management interventions.

This study is the first to identify a respiratory symptom cluster in patients with gynecologic cancer that included difficulty breathing, shortness of breath, and cough across all three symptom dimensions. Respiratory symptoms in patients with gynecologic cancer may be attributed to pleural effusion, malignant ascites, tumor burden, anxiety, pneumonitis, thromboembolism, or infectious processes (Landrum et al., 2015). Although specific management strategies may vary by diagnosis and stage of disease, treating the underlying cause of respiratory symptoms in these patients may relieve several co-occurring symptoms.

TABLE 3. Comparison of Symptom Clusters Prior to Initiation of Chemotherapy Using Ratings of Occurrence, Severity, and Distress (N = 232)

Cluster and Symptoms	Occurrence	Severity	Distress
Gastrointestinal			
Diarrhea	0.482	NI	NI
Abdominal cramps	0.435	NI	NI
Constipation	0.36	NI	NI
Sweats	–0.318	NI	NI
Itching	–0.401	NI	NI
Hot flashes	–0.505	NI	NI
Total number of symptoms in cluster	6/6	NI	NI
Gastrointestinal/epithelial			
Lack of appetite	NI	0.856	0.479
Change in the way food tastes	NI	0.669	0.526
Weight loss	NI	0.58	–
Changes in skin	NI	0.543	0.654
Constipation	NI	0.537	–
Nausea	NI	0.452	0.309
Dizziness	NI	0.44	0.593
Itching	NI	0.387	0.626
"I don't look like myself."	NI	0.382	0.688
Hair loss	NI	0.317	0.616
Dry mouth	NI	–	0.324
Feeling irritable	NI	–	0.302
Total number of symptoms in cluster	NI	10/12	10/12
Hormonal			
Sweats	0.855	0.932	0.75
Hot flashes	0.801	0.904	0.992
Problems with sexual interest or activity	0.8	0.539	0.425
Abdominal cramps	0.652	–	–
Difficulty concentrating	0.555	0.314	–
Feeling irritable	0.469	–	–
Feeling drowsy	0.468	–	–
Pain	0.433	0.305	0.33
Feeling bloated	0.343	–	–
Total number of symptoms in cluster	9/9	5/9	4/9
Psychological			
Worrying	0.702	0.764	NI
Hair loss	0.579	–	NI
Feeling sad	0.571	0.738	NI
"I don't look like myself."	0.492	–	NI
Changes in skin	0.492	–	NI
Weight loss	0.462	–	NI
Change in the way food tastes	0.441	–	NI
Itching	0.411	–	NI
Lack of appetite	0.405	–	NI
Dizziness	0.354	–	NI
Feeling irritable	0.35	0.397	NI

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TABLE 3. Comparison of Symptom Clusters Prior to Initiation of Chemotherapy Using Ratings of Occurrence, Severity, and Distress (N = 232) *(Continued)*

Cluster and Symptoms	Occurrence	Severity	Distress
Psychological *(continued)*			
Feeling nervous	0.323	0.724	NI
Abdominal cramps	–	0.427	NI
Total number of symptoms in cluster	12/13	5/13	NI
Psychological/gastrointestinal			
Abdominal cramps	NI	NI	0.746
Feeling sad	NI	NI	0.618
Feeling bloated	NI	NI	0.585
Worrying	NI	NI	0.579
Feeling nervous	NI	NI	0.539
Diarrhea	NI	NI	0.493
Problems with sexual interest or activity	NI	NI	0.457
Difficulty concentrating	NI	NI	0.426
Feeling drowsy	NI	NI	0.405
Constipation	NI	NI	0.389
Feeling irritable	NI	NI	0.376
Itching	NI	NI	–0.314
Total number of symptoms in cluster	NI	NI	12/12
Respiratory			
Difficulty breathing	0.962	0.909	0.869
Shortness of breath	0.9	0.873	0.864
Pain	0.512	0.362	–
Cough	0.473	0.422	0.332
Dry mouth	0.455	–	–
Numbness/tingling in hands/feet	0.41	–	–
Feeling bloated	0.383	–	–
Dizziness	0.362	–	–
Difficulty sleeping	0.356	–	–
Total number of symptoms in cluster	9/9	4/9	3/9
Weight change			
Weight gain	0.902	0.907	0.897
Increased appetite	0.728	0.785	0.813
Lack of appetite	–0.416	–	–0.313
Weight loss	–0.474	–0.401	–0.356
Feeling bloated	–	–	0.304
Total number of symptoms in clyster	4/5	3/5	5/5

NI—not identified
Note. Empty cells signify that factor loadings for these symptoms were less than 0.3.
Note. Extraction method: unweighted least squares; rotation method: geomin (oblique) rotation

The weight change symptom cluster identified in the current study included weight gain, increased appetite, and weight loss (loaded negatively) across all three symptom dimensions. Patients with gynecologic cancer may experience weight gain as a result of reduced activity secondary to fatigue, as a side effect of chemotherapy, or as a result of changes in eating habits (Hess et al., 2007; Mardas et al., 2017). In addition, weight gain may occur as a result of malignant ascites or pleural effusions. When weight changes

are a concern, patients may benefit from referral to a dietitian for nutritional counseling.

A psychological symptom cluster was identified using ratings of occurrence and severity that included worrying, feeling sad, feeling irritable, and feeling nervous. Patients with gynecologic cancer experience a range of psychological symptoms in response to diagnosis (Hill & Watkins, 2017; Norton et al., 2004; Roland et al., 2013), which may be compounded by loss of fertility, abrupt onset of surgical menopause, diagnosis at an advanced stage, and fear of cancer recurrence. A psychological symptom cluster was identified in several prior studies of patients with ovarian cancer (Fox & Lyon, 2007; Huang et al., 2016; Hwang et al., 2016; Nho et al., 2017). Taken together, these findings highlight the interplay of symptoms of psychological distress, some of which disproportionately affect patients with gynecologic cancer (Faller et al., 2017).

In the current study, the only symptoms common to the gastrointestinal, psychological/gastrointestinal, and gastrointestinal/epithelial symptom clusters were constipation and itching. One possible explanation is that the use of opioid analgesics may contribute to both symptoms. However, it is unclear why itching loaded negatively on the gastrointestinal symptom cluster identified using occurrence rates. In one study of patients with ovarian cancer receiving chemotherapy, an abdominal discomfort symptom cluster was comprised of feeling bloated, indigestion, pain, and weight loss (Hwang et al., 2016). Differences in the symptom clusters identified across studies may be attributable to the measures used to assess the symptoms. In the current study, gastrointestinal symptoms clustered with psychological and epithelial symptoms. In a study of symptom clusters in ovarian cancer survivors, gastrointestinal discomfort–related symptoms similarly clustered with nongastrointestinal symptoms (Kim et al., 2018). Additional research is needed to identify the common underlying mechanisms for gastrointestinal and nongastrointestinal symptoms in patients with gynecologic cancer.

The symptom clusters identified as part of this study are similar to those experienced by patients with other types of cancer. Members of the current study team identified similar hormonal, psychological, gastrointestinal, and epithelial symptom clusters in patients with breast cancer (Ward Sullivan et al., 2017); respiratory, psychological, and epithelial symptom clusters in patients with lung cancer (Wong et al., 2017); and weight change, psychological, and gastrointestinal symptom clusters in patients with gastrointestinal cancer (Han et al., 2019).

KNOWLEDGE TRANSLATION

- Lack of energy, hair loss, and "I don't look like myself" were the most common, severe, and depressing symptoms.
- On average, patients experienced 14 symptoms prior to their next cycle of chemotherapy.
- The hormonal symptom cluster was found across occurrence, severity, and distress dimensions of the symptom experience.

Limitations

Several limitations warrant consideration. The heterogeneity in the patients' gynecologic cancer diagnoses (e.g., ovarian, uterine), chemotherapy agents used, and types of previous cancer treatments could influence the number and type of symptom clusters. Another limitation is the lack of racial and ethnic diversity in the sample, which may limit the generalizability of the study findings. In addition, changes in symptom clusters during and after chemotherapy need to be evaluated.

Conclusion

Patients with gynecologic cancer experience multiple symptom clusters during chemotherapy. Additional research is needed to identify sentinel or core symptoms within each cluster as well as potential underlying mechanisms for these symptom clusters. More research is warranted to confirm these clusters in patients with gynecologic cancers. Interventions that target multiple co-occurring symptoms may need to account for potential differences in symptom clusters according to ratings of occurrence, severity, and distress.

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This work was supported by a grant from the National Cancer Institute (CA134900). Pozzar is supported by an American Cancer Society postdoctoral fellowship (133063-PF19-102-01-CPPB) and a Gordon and Betty Moore Foundation Society for Medical Decision Making Fellowship in Medical Decision Making (GBMF7853). Miaskowski is an American Cancer Society Clinical Research Professor. The funding sources were not involved in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the article for publication.

Pozzar, Kober, Levine, and Miaskowski contributed to the conceptualization and design. Hammer and Kober completed the data collection. Cooper, Paul, and Miaskowski provided statistical support. Pozzar, Cooper, Kober, Chen, Paul, and Miaskowski provided the analysis. Pozzar, Hammer, Cooper, Kober, Chen, Conley, Levine, and Miaskowki contributed to the manuscript preparation.

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