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Symptom Clusters Change over Time in Women Receiving Adjuvant Chemotherapy for Breast Cancer

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Abstract

Context—Patients with breast cancer receiving chemotherapy (CTX) experience multiple concurrent symptoms, but little is known about how symptoms change during and after treatment. Knowledge of the identity and trajectory of symptom clusters (SCs) would enhance measurement and management.

Objectives—We aimed to identify SCs and their change over time from baseline to completion of breast cancer CTX.

Methods—SCs were identified and assessed for change in 219 women from Nebraska at four times: baseline, during cycles #3 and #4 of CTX, and one-month after finishing CTX. Ten symptoms were measured: two using the Hospital Anxiety and Depression Scale and eight using the Symptom Experience Scale. Exploratory factor analysis was conducted at each time point, then changes in SCs were evaluated at different times.

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Results—Two SCs were identified before and after initiating CTX: Gastrointestinal (GI) and Treatment-related (Tr). The number and type of symptoms in each cluster differed over time. Clusters were dynamic during CTX with changes in the number and type of symptoms. Only one Tr SC, which consisted of fatigue, pain, and sleep disturbance, was identified after CTX completion.

Conclusion—SCs during CTX appear to be dynamic, changing over time from before until after CTX completion. Repeated assessments of SCs reveal symptoms that are present and when patients are most burdened and in need of additional support.

Keywords

Breast cancer; symptom clusters; chemotherapy; symptom experience; longitudinal study; oncology

Introduction

In the United States (US), breast cancer is the most common cancer among women.[1] Approximately 246,660 women will develop invasive breast cancer in the US during 2016 and most of these women will receive adjuvant treatment.[1] Breast cancer and its treatment lead to multiple symptoms that are experienced simultaneously [2] and are highly distressing.[3] Symptom cluster research addresses multiple symptoms that co-occur and relate to each other. Because the symptoms within a symptom cluster are related, the treatment of one symptom may have a positive effect on the other symptoms in that cluster.[4] Identifying common symptom clusters presented in specific populations may lead to the discovery of new strategies in symptom management. Development of more targeted symptom intervention strategies can then reduce polypharmacy and decrease treatment side effects, leading to improved health outcomes, particularly, related to quality of life (QOL) and functional status.[5–8] The most common, stable and severe symptom clusters can be included in chemotherapy (CTX) clinic assessment protocols. Repeated assessments of symptoms will lead to a more comprehensive understanding of symptoms experienced by women undergoing CTX for breast cancer.

According to the Oncology Nursing Society (ONS), symptom cluster research is a priority in oncology nursing.[9] However, symptom cluster research on women with breast cancer remains limited and inconclusive. There are four published cohort studies that used an all-possible symptoms approach when assessing symptom clusters (SCs) and their change over time among women during treatment for breast cancer.[10–13]

In the first study of symptom clusters, Kim et al.[10] clustered symptoms based on severity using factor analysis. In their study, 44% of the women received CTX, 56% received radiation therapy (RT), and outcomes were measured at baseline (T1) and at two follow-up time points after treatment initiation (T2 and T3). At T1, one symptom cluster was identified and included cognitive disturbances, depressed mood, fatigue, insomnia, and pain. At T2, one symptom (hot flashes) was added to the symptom cluster. At T3, hot flash was removed from the symptom cluster and other symptoms remained stable. Additionally a

gastrointestinal (GI) cluster, composed of decreased appetite, nausea, and vomiting, appeared after the beginning of the treatment and remained unchanged between T2 and T3.

In the second study,[11] researchers wanted to determine whether nausea existed as a part of a symptom cluster. Three time points were evaluated: the day of the first cycle of CTX (T1), the end of cycle 1 (T2), and the end of cycle 2 (T3). When clustered by severity at T1, nausea clustered with dry mouth, feeling drowsy, lack of energy, and loss of appetite. The cluster changed after treatment initiation; nausea clustered with lack of energy and pain at T2, and with feeling bloated and lack of energy at T3.

In the third study,[12] researchers clustered symptoms by distress, not severity, before, during and after CTX. They found five SCs, some of which were stable across time points.

In the last study,[13] researchers evaluated the severity of SCs at middle, end, and 1-month after completion of RT. Only half (48.7%) of the patients had breast cancer. Mood-cognitive and sickness-behavior SCs were identified and remained relatively stable over time.

In summary, findings from these studies indicate little change in the number of SCs and symptoms within a cluster over time among patients with breast cancer before, during, and after adjuvant treatment. Although these studies have advanced our understanding of SCs, more knowledge is needed to draw conclusions about changes in SCs over time. The purpose of this study was to evaluate how SCs, clustered by severity, change over time from baseline to after completion of adjuvant breast cancer CTX in a homogeneous sample of women.

Methods

Study Design

This study is a secondary analysis of data obtained from a randomized clinical trial entitled, *Fatigue in Breast Cancer: A Behavioral Sleep Intervention*.[14] The purpose of the trial was to test the effectiveness of an individualized sleep promotion plan compared to a healthy eating control condition in women with breast cancer before, during, and after breast cancer adjuvant CTX. This trial was approved by the Institutional Review Board at the University of Nebraska Medical Center (UNMC). Four time points were used for this analysis: T1: baseline (two days before first CTX), T2 and T3: cycles three and four of CTX (first seven days after CTX), and T4: 30 days after the last CTX. The experimental and control groups were combined in this secondary analysis study after determining no statistically significant differences between the two groups on any of the independent variables at baseline or on any of the symptoms, including sleep, for all time points and for all dimensions of the symptoms.

Setting and Sample

In the original study, 219 patients were recruited from two cancer centers and 10 community oncology clinics in the midwestern US. Inclusion criteria were: a) women 19 years and older; b) initial diagnosis of stages I to IIIA breast cancer; c) post-modified radical mastectomy or lumpectomy; d) scheduled to begin four anthracycline-based intravenous

CTX; and e) Karnofsky Performance Scale (KPS) score greater than 60. Exclusion criteria included self-reported history of diagnosis of co-morbidities associated with poor sleep and fatigue.

Variables and Measures

Ten symptoms were represented in the study: altered appearance, anxiety, appetite disturbance, concentration disturbance, depression, disturbed bowel pattern, fatigue, nausea, pain, and sleep disturbance. Two measures, described below, were used to assess these symptoms.

Hospital Anxiety and Depression Scale (HADS)—The HADS is a 14-item scale that assesses anxiety and depression in medically ill patients.[15] The intensity of each symptom is measured by seven items using a four-point Likert scale. The total score for each symptom ranges from 0 to 21 and is interpreted as normal (0–7), mild (8–10), moderate (11–14), or severe (15–21). It has well established validity and reliability.[16,17] Internal consistency reliability (Cronbach's alpha) ranged between .83 and .87 for anxiety and .81 and .87 for depression in the current sample.

Symptom Experience Scale (SES)—The SES measures women's symptomatic experiences associated with breast cancer treatment in three dimensions (frequency, intensity, and distress).[18] The scale consists of 24 items, rated on a five-point Likert scales from 0 to 4. The scale is valid and reliable.[18] In the current sample Cronbach's alpha ranged between .89 and .92.

Statistical Analysis

Data were analyzed using SPSS for Windows software version 17.0.1 (SPSS, Inc., Chicago, IL, USA). Exploratory factor analysis was used to identify SCs when clustered by the severity dimension. The sample structures were estimated using the method of principal axis factoring with promax (oblique) rotation.[19,20] The best fit of symptom grouping was determined according to the following criteria: 1) simple structure; 2) total variance explained by the SCs; and 3) internal reliability of the SCs measured by Cronbach's alpha. To increase clinical significance, symptoms with a prevalence of less than 20% were excluded from the analysis. This approach was used previously by researchers studying SCs in breast cancer.[13] The symptoms with a factor loading less than .30 were excluded from a cluster.[20] A symptom cluster was accepted if it had a Cronbach's alpha of .60 or greater, with symptom-total correlations greater than .25.[21]

Results

Sample characteristics

The demographic and clinical characteristics of the original sample for this secondary analysis are presented in Table 1.

Symptom prevalence and severity across time points

The most prevalent symptom was fatigue, which ranged from 89 % to 98%, followed by sleep disturbance, pain, and concentration problems, which all had a prevalence above 50% across all time points. The least prevalent symptoms were anxiety and depression and rated less than 50% across all time points. In general, symptoms were more prevalent during CTX except pain, which was more prevalent before and after CTX, and anxiety, which was most prevalent at T1. During CTX, all symptoms had a prevalence greater than 20% and therefore were included in the further analysis. At T1, depression was excluded because of its low prevalence (10.8%) and at T4, both depression (13.3%) and nausea (13.7%) were excluded.

During CTX, the mean symptom severity score (range = 0–4) for the SES symptoms ranged from 0.71 for appearance to 1.90 for fatigue. Six symptoms, namely nausea, appetite, sleep disturbance, fatigue, bowel pattern, and concentration, had mean symptom severity score greater than one during both CTX cycles. Pain, which had a mean severity score less than 1.0 during CTX, was the most severe symptom reported at T1. In addition, fatigue was the only symptom from the SES with a severity score greater than 1.0 across all time points.

The mean severity score for both anxiety and depression was less than seven, which is the cut point for normal symptom severity according to the HADS. Anxiety was most severe at T1, and tended to decrease gradually with time. Depression was most severe during CTX and least severe during T1.

SCs trajectory over time

Based on the factor analysis results, there were moderate differences in SCs at different time points. To describe these differences, results are organized and presented in three parts.

1. Differences in SCs before and after initiating CTX—Two SCs were found when clustering nine to ten symptoms before (T1) and after (T2, T3) initiating CTX (Table 2). The first cluster was called gastrointestinal (GI) SC and consisted of five symptoms at T1: appetite, bowel pattern, fatigue, nausea, and pain. After initiating CTX, the cluster consisted of appetite and nausea at T2 and nausea, bowel pattern, pain, and sleep disturbance at T3. However, because of poor internal consistency reliability (Cronbach’s alpha = .55), the cluster at T3 was not considered reliable.

The second symptom cluster was called Treatment-related (Tr) SC and at T1 consisted of four symptoms: anxiety, appearance, concentration, and sleep disturbance. At T2, the same symptoms remained in the cluster. In addition, four new symptoms were added; three of the four (bowel pattern, fatigue, and pain) were part of the GI SC at T1 and the fourth symptom (depression), was not included at T1 because of its low prevalence. At T3, the cluster consisted of all symptoms from the Tr SC at T1 except sleep disturbance; additional symptoms included appetite, depression, and fatigue.

Differences were found between SCs before and after initiating CTX. Two SCs were formed at both time points. However, the number and type of symptoms included in each cluster differed.

2. Stability of SCs during CTX—Two time points (T2 and T3) were assessed to evaluate stability of SCs during CTX. At T2, two SCs were found: GI SC, consisted of appetite and nausea; Tr SC, consisted of the other eight symptoms. At T3, GI SC had poor internal consistency reliability and therefore was not considered. Tr SC consisted of six symptoms, five of which were part of Tr SC at T2 (anxiety, appearance, concentration, depression, and fatigue) (Table 2). Appetite, which was the sixth symptom of Tr SC at T3, was part of GI SC at T1 and at T2. At T3, appetite has a clearly higher loading on Tr SC (Table 2). It is important to note that appetite had the lowest item-total correlation in the cluster, and thus the Cronbach's alpha coefficient would not be altered if appetite was deleted. In addition, there was a significant bivariate correlation between appetite and nausea ($r = .35$).

3. Differences in SCs during and after CTX—After CTX (T4), two symptoms (depression and nausea) were excluded from analysis because of low prevalence. Because nausea was one of the main symptoms in GI SC, this cluster no longer existed after CTX. Tr SC consisted of three symptoms: fatigue, pain, and sleep disturbance. Additionally, a new symptom cluster materialized from Tr SC and included three symptoms: anxiety, appearance, and concentration. However, because of low internal consistency reliability (Cronbach's alpha = .59), it was not considered reliable. Nonetheless, it is interesting to note that anxiety, appearance, and concentration clustered together at all of the time points. Table 3 summarizes the change in SCs over time.

Discussion

This study evaluated changes in breast cancer SCs before, during, and after CTX when prevalent symptoms were clustered by their severity dimension. Two prior studies [10,11] also evaluated SCs clustered by severity dimension over time in this population. However, the study by Kim et al.[10] included more than one treatment modality and only 44% of the women were receiving CTX. The second study was not specific to breast cancer and included only a nausea-related symptom cluster. No prior study compared a symptom cluster trajectory from before until after treatment. In contrast to previous studies [10,12,13] that found symptoms to be stable, we found them to be dynamically changing over time. Recognition of this dynamic change is important for symptom management interventions to support the patient throughout the treatment experience. This discussion describes similarities and key differences between our findings and prior literature.

At baseline, two SCs were found. The GI SC consisted of five symptoms: appetite, bowel pattern, fatigue, nausea, and pain. This cluster was also found during CTX, but only contained appetite and nausea. In the Kim et al.[10] study, a GI SC was found only during treatment. Molassiotis et al.[11] found a nausea-related cluster both at baseline and during treatment. The cluster differed in number and type of symptoms at different time points. Our results support Molassiotis et al. and provide evidence that GI-related symptoms, are present in women with breast cancer after surgery but before beginning CTX. However, there are differences in GI SCs before and during CTX.

Prior to initiating CTX, the Tr SC includes anxiety, appearance, concentration, and sleep disturbance. After initiating CTX, these four symptoms remained clustered together;

however, new symptoms (appetite, bowel pattern, depression, fatigue, and pain) entered the cluster. These findings are in contrast to those of Kim et al.[10] who found that cognitive disturbance, depressed mood, fatigue, insomnia, and pain cluster remained the same before and after initiating treatment.

Three studies evaluated stability of SCs during treatment.[10,11,13] SCs remained stable in two studies.[10,13] In the current study, however, SCs were less stable. The GI SC (appetite, nausea) at T2 had different symptoms and low reliability at T3. Appetite had high factor loading on the GI SC in T2, but was no longer part of the cluster at T3. Disappearance of this symptom from the GI SC at T3, may be related to the decrease factor loading of nausea. At T2, nausea has the highest factor loading in the GI SC, while at T3 its factor loading decreased and pain became the key symptom in the cluster.

The dynamic nature of SCs, even with a homogeneous sample, may be related to several factors. First, the timing of symptom assessment may influence the results, as symptom severity can change during treatment and may fluctuate from day to day.[4] Second, there are complex relationships among symptoms within a cluster. Third, there are also relationships between different clusters. In the current study, there were moderate correlations between the clusters, indicating that the symptoms from one cluster are associated with the symptoms from another cluster, which increases the probability of clustering these symptoms together at different times. For example, appetite was in the GI SC at T2 and became part of the Tr SC at T3. Other studies supported this result; Molassiotis et al.[11] found appetite and nausea to be clustered together before treatment, yet appetite was no longer part of the nausea-related cluster after initiating CTX. Furthermore, two studies [10,22] included appetite in a GI SC, while one other study [23] included appetite in a Tr (sickness behavior) SC.

After CTX, Tr SC was divided into two clusters. The first cluster, consisted of fatigue, pain, and sleep disturbance and the second cluster consisted of anxiety, appearance, and concentration. The second cluster had low internal consistency reliability, however it is commonly observed in clinical practice. The differences between SCs during and after treatment may be related to fewer numbers of symptoms after completing CTX, which may affect how analysis of symptom clustering is determined. In the current study, depression and nausea were excluded from the final analysis due to their low prevalence. In addition, prevalence and severity of anxiety decreased gradually over time. This decrease had a negative effect on anxiety factor loading on Tr SC that decreased over time. Differences in the number of SCs and type of symptoms in each cluster were supported by other researchers.[13]

The limitations of this study are important to consider when interpreting the results. The biggest limitation was the limited number of symptoms assessed in the original study. One study [22] reported that women with breast cancer receiving CTX experience between 2 and 32 symptoms with a mean of 17. In this study, only 10 symptoms were available for analysis. Secondly, most symptoms were measured by a non-specific symptom scale, as the SES measures each symptom using a single item. This approach can decrease the validity of responses, as some symptom names may be misinterpreted by patients.[24] Finally, data

about women's comorbidities and any self-care strategies they used to manage their symptoms were not available.

Despite the limitations, the findings have implications for further research and clinical practice. Our findings support the complex interrelations among symptoms. Clinical determination of common SCs is beneficial, and statistical analysis can be used to determine symptom interactions to provide more accurate results. Despite using an accurate method of symptom clustering and a homogeneous sample, results showed that SCs can change over time. These findings are clinically important because they demonstrate that symptoms as well as SCs change during the trajectory of treatment and require effective management. Knowing what SCs are present and when they are more likely to appear will help clinicians to be prepared to intervene and decrease symptom burden. Ultimately, the goal is to provide comfort and relieve distress among patients affected by cancer and treatment protocols. More research must be conducted using prospective longitudinal design that fully capture the on-going dynamic symptom experiences and the SCs that are experienced during treatment. Understanding SCs is vital to the comprehensive assessment, prevention, and management of symptoms across diagnosis and treatment.

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Table 1

Demographic and Clinical Characteristics of the Sample *(N* = 211–219)

Characteristic	**Mean (*SD*)**	**Range**
Age (years)	52.2 (10)	29–83
Working Hours (weekly)	36.6 (12.9)	0–65
Body mass index	28.7 (6.1)	16–53
	Categories	***N* (%)**
Ethnicity	Hispanic Non-Hispanic	8 (3.7) 211 (96.3)
Race	White Non-White	209 (95.4) 10 (4.6)
Education	Up to High School Some College or more	55 (25.1) 164 (74.9)
Marital Status	Married Non-Married	158 (72.1) 61 (27.9)
Employment	Employed Non-Employed	165 (75.3) 54 (24.7)
Household Income (annual)	Less than $ 20,000 $ 20,000 – $ 40,000 Over $ 40,000	21 (10) 45 (21.3) 145 (68.7)
Surgical Procedure	Lumpectomy Modified Mastectomy	95 (43.6) 123 (56.4)
Breast Cancer Stage	I II IIIA	72 (33.2) 114 (52.1) 31 (14.2)
Menstrual Status	Regular Irregular	69 (32.5) 143 (67.5)
Karnofsky Score	60–70 80–100	10 (4.6) 209 (95.4)
Activity Level	Moderately-Active Non-Active	195 (89) 24 (11)

Table 2

Symptom Clusters with Symptom Factor Loadings and Item-total Correlations (N = 178–202)

Baseline Symptoms	GI SC	Tr SC	Item-total *r* GI SC	Item-total *r* Tr SC
Nausea	**.59**	−.18	.39	
Appetite	**.48**	.04	.40	
Bowel Pattern	**.44**	.04	.35	
Pain	**.56**	.03	.45	
Fatigue	**.55**	.16	.50	
Sleep Disturbance	.11	**.54**		.47
Concentration	.01	**.70**		.55
Anxiety	−.15	**.79**		.56
Appearance	.29	**.30**		.38
Baseline SC Totals:				
Cronbach's alpha			.66	.70
Variance Explained (%)	6.75	27.91		

T2 Symptoms	GI SC	Tr SC	Item-total *r* GI SC	Item-total *r* Tr SC
Nausea	**.80**	−.13	.45	
Appetite	**.56**	.11	.45	
Sleep Disturbance	.22	**.33**		.44
Pain	.01	**.34**		.32
Fatigue	.15	**.54**		.56
Bowel Pattern	−.09	**.44**		.34
Concentration	−.06	**.72**		.60
Appearance	.08	**.56**		.54
Anxiety	−.04	**.72**		.59
Depression	.09	**.73**		.67
T2 SC Totals:				
Cronbach's alpha			.62	.80
Variance Explained (%)	4.64	33.38		

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T3 Symptoms	GI SC	Tr SC	Item-total *r* GI SC	Item-total *r* Tr SC
Nausea	**.49**	.13	.37	
Bowel pattern	**.30**	.18	.29	
Sleep Disturbance	**.53**	−.08	.31	
Pain	**.55**	−.06	.37	
Fatigue	−.13	**.70**		.52
Appetite	.10	**.40**		.39
Concentration	.23	**.37**		.46
Appearance	.12	**.52**		.53
Anxiety	.30	**.40**		.52
Depression	−.12	**.92**		.70
T3 SC totals:				
Cronbach's alpha			.55	.77
Variance Explained (%)	4.73	29.33		

T4 Symptoms	Factor	Tr SC (1)	Tr SC (2)	Item-total *r* Tr SC (1)	Item-total *r* Tr SC (2)
Fatigue	.09	**.60**	-.00	.48	
Sleep Disturbance	.05	**.62**	−.11	.39	
Pain	−.04	**.68**	−.13	.43	
Concentration	−.11	.37	**.39**		.42
Appearance	.09	−.25	**.66**		.32
Anxiety	−.05	.29	**.46**		.46
Appetite	**.73**	.02	.04		
Bowel Pattern	.27	.28	.08		
T4 SC Totals:					
Cronbach's alpha				.62	.59
Variance Explained (%)	5.29	26.78	6.39		

Note: SC, symptom cluster; GI SC, gastrointestinal symptom cluster, Tr SC, treatment-related symptom cluster (at T4, two Tr SCs were identified).

Bolded factor loadings indicate that the symptom loaded most strongly on this cluster.

Table 3

Summary of Symptom clusters at Different Time Points

SCs	T1	T2	T3	T4
GI SC	Appetite	Appetite	*Bowel pattern*	
	Bowel Pattern	Nausea	*Nausea*	
	Fatigue		*Pain*	
	Nausea		*Sleep disturbance*	
	Pain			
Tr SC	Anxiety	Anxiety	Anxiety	Fatigue
	Appearance	Appearance	Appearance	Pain
	Concentration	Bowel Pattern	Appetite	Sleep disturbance
	Sleep Disturbance	Concentration	Concentration	
		Depression	Depression	*Anxiety*
		Fatigue	Fatigue	*Appearance*
		Pain		*Concentration*
		Sleep Disturbance		
Total Variance (%)	34.66	38.02	29.33	26.78

Note: Symptom clusters in italics have Cronbach's alpha less than .60 and were therefore not considered reliable. GI SC, gastrointestinal symptom cluster; Tr SC, treatment-related symptom cluster (there were two Tr SC at T4); T1, baseline; T2, cycle three of chemotherapy; T3, cycle four of chemotherapy; T4, 30 days after the last chemotherapy.