Original Article

Symptom Clusters and Quality of Life over 1 Year in Breast Cancer Patients Receiving Adjuvant Chemotherapy

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ABSTRACT

Objective: Evidence is scant regarding symptom clusters and quality of life (QOL) over 1 year in women who receive adjuvant breast cancer chemotherapy (CTX). Our purpose was to identify the prevalence and severity of individual symptoms, symptom clusters, and QOL in women receiving adjuvant breast cancer CTX from baseline over 1 year. **Methods:** Symptoms were identified in a sample (n = 219) at three times: baseline (prior to the first adjuvant CTX treatment), 1 month after the last CTX (approximately 6 months after baseline), and 1 year after baseline. The Hospital Anxiety and Depression Scale and Symptom Experience Scale measured symptoms. The Medical Outcomes Study, Short-Form Survey, measured QOL. Exploratory factor analysis identified symptom clusters at each time and core symptoms in clusters over time. **Results:** The prevalence and severity of 10 symptoms decreased over time (P < 0.05). Fatigue, sleep disturbance, and pain were most prevalent; all were of mild severity. Two symptom clusters were identified at baseline and one met internal consistency reliability criteria at the later times. Core symptoms were identified. Both the physical and mental component scores of QOL improved over time (P < 0.01), but physical was below the general population norms 1 year after baseline. **Conclusions:** The symptom experience was dynamic, and symptom clusters changed over 1 year. Despite mild severity, core symptoms and clusters persisted over 1 year, and physical health was below the general population norms. Breast cancer survivors with persistent single and co-occurring symptoms need to be taught to manage the patterns of symptoms over time because they may not resolve by 1 year.

Key words: Breast cancer, chemotherapy, quality of life, symptom, symptom cluster

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Introduction

Breast cancer remains a major international public health problem. Survival rates have improved, but survivors frequently report multiple concurrent adverse physical and psychological symptoms. Symptoms associated with breast cancer treatments have a negative impact on the quality of life (QOL).[1,2] QOL is a major outcome measure in health care, along with morbidity and mortality, because it captures a patient's subjective view of health and is a prognostic factor.[3] Breast cancer survivors face several challenges to QOL due to the stresses of uncertainty surrounding a cancer diagnosis, adverse side effects of adjuvant chemotherapy (CTX),[4,5] and endocrine therapy.[6]

Approximately 25%–35% of disease-free breast cancer survivors report several co-occurring symptoms 1–10 years after breast cancer treatment.[7] Dodd *et al*. defined a symptom cluster as two or more concurrent symptoms that are related to each other but are not required to share the same etiology.[8] Physical and psychological symptoms tend to cluster together and may have natural associations and underlying mechanisms.[9,10] Assessment of symptoms as a cluster, in addition to individually, is beneficial because symptoms in a cluster have a synergistic effect on morbidity, mortality, prognosis, and QOL.[11,12]

Studies of symptom clusters in patients with breast cancer have shown that individual symptoms often change over time. Longitudinal studies have included symptom clusters at baseline and a variety of later times. Data collection has extended from baseline to (1) to times during CTX,[13] (2) to 1 month after the last CTX or radiotherapy,[10,14-16] (3) to 6 months after the first CTX,[17,18] (4) to 6 months and 1 year after starting CTX,[19,20] and (5) to 1 year after surgery.[21] Studies have reported symptoms by prevalence,[13] severity,[14,17,21] distress,[16,20] or combined frequency/severity/distress.[15,18,19] Studies with measurements 1 month after the last CTX or 6 months after the first CTX were combined and are referred to in this report as "1 month after the last CTX."

Only one study is available for comparison of symptom clusters in women with breast cancer at baseline and 1 month after the last CTX, but the study did not extend to 1 year.[18] A sample of Swedish women with primary and recurrent breast cancer reported symptom burden, comprised of occurrence, frequency, severity, and distress. Three clusters of burdensome symptoms were reported: emotional, gastrointestinal (GI), and unwellness. Additional symptoms were present in the emotional cluster 1 month after the last CTX.

In two studies of participants with mixed cancer diagnoses, symptom clusters were reported at baseline, 1 month after the last CTX, and 1 year. Women with breast cancer were 15.4% of the 219 in the first study[20] and 28.8% of the 143 in the second study.[19] A third study reported symptom clusters prior to surgery and 1 year later (n = 392), but there was no measurement at 6 months and only one-third received CTX during the year. This study reported three clusters based on occurrence and severity prior to surgery and five clusters 1 year later.

The aim of the primary study was to determine the effect of a four-component behavioral intervention on sleep quality and fatigue in women with breast cancer undergoing adjuvant CTX.[22,23] The same database was used to examine the patterns of 10 symptoms and symptom clusters at baseline, during, and 1 month after the last CTX.[14] At baseline, two symptom clusters were identified; treatment related (Tr) and GI, but Tr was the only reliable symptom cluster identified 1 month after the last CTX. The type and specific symptoms in each cluster were dynamic, yet similar over time. We extend these results and fill a gap in knowledge by reporting symptoms, symptom clusters, and QOL in this longitudinal sample from baseline to 1 month after the last CTX, to 1 year after baseline, with emphasis on the 1-year results. We hypothesized that symptoms would decrease in severity, symptom clusters would decrease in number, and QOL would improve by 1 year.

Methods

Study design

This secondary data analysis examined a prospective, longitudinal, randomized clinical trial database to fill the gaps regarding the patterns of symptoms, symptom clusters, and QOL.[22,23] The time span for this analysis was extended to 1 year after baseline. The experimental and control groups were combined for this analysis as there were no significant differences between the groups on any of the independent variables. However, bowel pattern was significantly different between the two groups at 1 year. This was judged to not be related to study participation, and a decision was made to include bowel pattern in this analysis.

Sample and setting

In the primary study, a sample of US women with breast cancer (n = 219) were recruited from two cancer centers and ten community oncology clinics in the Midwestern United States. Inclusion and exclusion criteria and detailed characteristics of the sample at baseline and at 1 year have been reported.[14,22] All participants were postoperative and received anthracycline-based CTX. Approximately 50% also received taxanes and 60% also received radiation therapy. Available data decreased over time because of missing data or participant dropout; most occurred between consent and baseline data collection.

Approvals for the study were obtained from the University of Nebraska Medical Center Institutional Review Board and all clinical sites, and informed consent was obtained from all participants.

Variables, instruments, and timing

Demographic data were obtained by questionnaire including age, education, marital status, menstrual status, ethnicity, race, employment status, weekly working hours, body mass index (BMI), income, and activity level. Patients' medical records were reviewed for disease stage and treatment information. Information on symptoms were extracted from self-report questionnaires: Hospital Anxiety and Depression Scale (HADS), Symptom Experience Scale (SES), and Medical Outcomes Study, Short-Form Survey (SF-36 v2). For this study, 10 symptom variables were assessed: anxiety and depression (HADS); appearance, appetite, bowel pattern, concentration, fatigue, nausea, pain, and sleep pattern (SES) and two QOL variables: physical and mental component scores (MCSs) (SF-36 v2). Three data collection times were included: baseline (prior to starting CTX), 1 month after the last CTX (approximately 6 months after baseline), and 1 year after baseline (approximately 6 months after the last CTX).

Methods and variables

Hospital anxiety and depression scale

The HADS is a 14-item self-assessment scale, with seven items measuring anxiety and seven measuring depression symptoms.[24] A 4-point Likert scale measures the intensity of each symptom. The total score range (0–21) for each symptom is interpreted as normal (0–7), mild (8–10), moderate (11–14), or severe (15–21). Cronbach's alpha was 0.85 for anxiety and 0.80 for depression at 1 year in this study.

Symptom experience scale

The SES measures eight symptoms associated with the treatment of breast cancer and each symptom is measured for frequency, intensity, and distress (total = 24 items).[25] A 5-point Likert scale measures items from 0 (most positive result) to 4 (most negative result). Cronbach's alphas were 0.66–0.74 in this study.

The medical outcomes study, short-form survey

The 36-item survey measures general health-related QOL.[26] Eight multi-item scales are aggregated into a physical component score (PCS) and a MCS. Scores range from 0 (poorest) to 100 (best health status). US general population 1998 criterion differentiates QOL scores between healthy (≥50.0, standard deviation [SD] 10) and diseased (<50.0, SD 10).

Statistical analysis

At baseline, descriptive statistics were calculated to summarize demographic and clinical characteristics. An exploratory factor analysis using a Promax rotation was conducted to identify the number of symptom clusters based on symptom severity at each time.[27] Given the exploratory nature of this study, the number of factors was based on (1) eigenvalue ≥0.8, (2) factor loadings ≥0.3, and (3) each should account for at least 1% of the total variance. These criteria were selected in order to include the largest number of symptoms in the analysis. A symptom cluster was identified if symptom total correlation with Cronbach's alpha was ≥0.60. A Cronbach's alpha coefficient <0.60 was interpreted with caution. The best fit of symptom grouping was determined according to the following criteria: simple structure, total variance explained by the symptom clusters, and internal reliability of the symptom clusters measured by Cronbach's α. Core symptoms were defined as those with the highest interfactor correlation coefficient (Item-total *r*) at each time. Stable clusters were defined as those that have similar core symptoms across times.[19]

Repeated-measures ANOVA was used to analyze the longitudinal symptoms and PCS and MCS scores to examine changes over time, with a Bonferroni correction for multiple comparisons. Mauchly's sphericity test was used to examine the sphericity assumption of the ANOVA. If the sphericity assumption was violated, then Greenhouse–Geisser correction was used. A significance level of alpha of ≤0.05 (two sided) was considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM, Armonk, NY, US).

Ethical approval

The study has been approved by the appropriate institutional ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

Demographic and clinical characteristics of participants

Participants' demographic and clinical characteristics at baseline included mean age of 52 (range: 29–83) years; mean BMI of 28.7 (SD 6.1); most patients were Non-Hispanic Whites (96%); married (72%); had

some postsecondary education (75%); were diagnosed at Stage I or Stage II breast cancer (86%); and were moderately active (89%). History of treatments has been reported.[14]

Symptom prevalence and severity patterns over time

Symptom prevalence and severity patterns are displayed in Table 1. Fatigue, sleep disturbance, and pain were the most prevalent symptoms at all times. Depression was the least prevalent symptom at baseline and 1 month after the last CTX. Most symptoms prevalent at baseline gradually decreased over time and all diminished at 1 year. Symptoms with a prevalence ≥20% were included for further analysis. Exclusions due to prevalence <20% were depression at baseline; depression and nausea at 1 month after the last CTX; and appearance, appetite, depression, and nausea at 1 year.

The mean severity scores were variable for eight symptoms. Fatigue was the only symptom with a mean severity >1.00 at all times. There was no evidence of a difference in mean severity for pain and sleep disturbance when comparing scores 1 month after the last CTX to 1 year after baseline. The mean severity scores of fatigue, concentration, and appearance were higher 1 month after the last CTX than at baseline and at 1 year. The mean severity scores for anxiety and depression were within normal range at all times. Anxiety was highest at baseline and decreased over time, but the mean depression score was higher 1 month after the last CTX than at baseline and 1 year. Mauchly's test of sphericity was violated for appetite and appearance; therefore, Greenhouse–Geisser correction was used.

Overall, there was a statistically significant difference ($P < 0.05$) in the mean severity score of each of the symptoms over time. Symptoms of fatigue, sleep disturbance, pain, concentration, bowel pattern, and anxiety were still prevalent at >20% and reported as mild at 1 year.

Symptom clusters at each time and patterns over time

Time 1

Factor loading scores of symptom clusters based on symptom severity are summarized in Table 2. At baseline, two viable symptom clusters were identified. Cluster 1 was labeled as Tr and consisted of three symptoms: sleep disturbance, concentration, and anxiety. Cluster 2 was labeled as GI and consisted of four symptoms: fatigue, pain, bowel pattern, and nausea. Anxiety was the core symptom in the Tr and pain in the GI cluster. Cronbach's α of internal consistency reliability ranged from 0.62 to 0.70.

Time 2

One month after the last CTX, only one reliable symptom cluster was identified. Cluster 1 (Tr) consisted of four symptoms: fatigue, sleep disturbance, pain, and concentration, with good internal consistency reliability. Anxiety dropped out and two new symptoms (fatigue and pain) joined this cluster. Fatigue was the core symptom in the Tr cluster. Cluster 2 consisted of three symptoms: concentration, appearance, and anxiety, with an internal consistency reliability of 0.59 that did not meet the criteria of >0.60.

Time 3

One year after the first CTX, only one reliable symptom cluster was identified. Cluster 1 (Tr) consisted of five symptoms: fatigue, sleep disturbance, pain, concentration, and anxiety, with good internal consistency reliability. This symptom cluster was similar to Cluster 1 (Tr) at 1 month after the last CTX, except that anxiety returned and was the core symptom as at baseline. Cluster 2 consisted of pain and bowel pattern, but the internal consistency reliability (0.58) did not meet criteria of >0.60.

The symptom experience was dynamic; thus, the number and specific symptoms included in each symptom cluster

Table 1: Symptom prevalence and severity at baseline[a], 1 month after last chemotherapy, and 1 year after baseline

Symptoms	Baseline[a] (n=202-204)		1 month after last CTX (n=180-182)		1 year after baseline (n=173)		P
	Prevalence (%)	Severity, mean (SD)	Prevalence (%)	Severity, mean (SD)	Prevalence (%)	Severity, mean (SD)	
Nausea[b]	22.1	0.32 (0.68)	13.7	0.16 (0.44)	11.6	0.16 (0.50)	0.025
Pain[b]	84.8	1.28 (0.79)	61.0	0.88 (0.86)	60.1	0.88 (0.88)	<0.01
Appetite[b]	41.2	0.45 (0.62)	28.6	0.34 (0.62)	8.7	0.12 (0.47)	<0.01
Sleep disturbance[b]	76.0	1.25 (0.91)	64.8	0.90 (0.89)	62.4	0.90 (0.86)	<0.01
Fatigue[b]	89.2	1.21 (0.64)	94.5	1.32 (0.64)	86.1	1.20 (0.68)	0.02
Bowel pattern[b]	37.7	0.46 (0.70)	29.2	0.37 (0.64)	25.4	0.31 (0.58)	0.03
Concentration[b]	54.7	0.66 (0.69)	59.9	0.74 (0.71)	42.8	0.53 (0.68)	<0.01
Appearance[b]	24.5	0.26 (0.49)	33.5	0.42 (0.70)	13.3	0.14 (0.40)	<0.01
Anxiety[c]	38.3	6.58 (3.87)	22.4	4.62 (3.75)	23.2	4.69 (3.61)	<0.01
Depression[c]	10.9	3.25 (3.00)	13.5	3.99 (3.28)	9.8	2.52 (2.71)	<0.01

[a]Baseline defined as prior to starting CTX, [b]Scores range from 0 (most positive result) to 4 (most negative result), [c]Scores range from 0 (least severe) to 21 (most severe). Bonferroni-adjusted P value reflects changes over time. CTX: Chemotherapy

were variable [Table 3]. Cluster 1 (Tr) had sleep disturbance and concentration present at all times. Cluster 1 (Tr) also had the most symptoms 1 year after baseline, with the highest variance and Cronbach's α value. The number of symptom clusters did not decrease between 1 month after the last CTX and 1 year after baseline.

Table 2: Factor loading scores of symptom clusters based on symptom severity (n=202)

Symptoms	Factor 1	Factor 2	Factor 3	Item-total r	
				Factor 1	Factor 2
Baseline					
Nausea	−0.17	0.48	0.15		0.36
Appetite	−0.05	0.22	0.55		
Bowel pattern	0.06	0.45	−0.02		0.34
Pain	0.05	0.54	0.03		0.42
Fatigue	0.17	0.51	0.07		0.46
Sleep disturbance	0.55	0.22	−0.15	0.45	
Concentration	0.72	−0.17	0.26	0.52	
Anxiety	0.74	−0.03	−0.10	0.54	
Appearance	0.29	0.27	0.05		
Cronbach α variance (%)	28.30	7.08	2.56	0.70	0.62
1 month after last CTX					
Fatigue	0.60	0.003	0.09	0.52	
Sleep disturbance	0.62	−0.11	0.05	0.43	
Pain	0.68	−0.13	−0.04	0.41	
Concentration	0.37	0.38	−0.11	0.40	0.44
Appearance	−0.25	0.66	0.09		0.31
Anxiety	0.29	0.46	−0.05		0.46
Appetite	0.02	0.04	0.73		
Bowel pattern	0.28	0.08	0.27		
Cronbach α variance (%)	26.78	6.39	5.29	0.66	0.59
One year after baseline					
Pain	0.40	0.33		0.48	0.40
Sleep disturbance	0.40	0.22		0.42	
Fatigue	0.52	0.09		0.44	
Bowel pattern	−0.09	0.82			0.40
Concentration	0.64	−0.08		0.47	
Anxiety	0.75	0.09		0.55	
Cronbach α variance (%)	34.25	7.38		0.73	0.58

Not all columns add up to n=202 due to missing value. CTX: Chemotherapy

Table 3: Summary of symptom clusters based on severity scores at different times

Cluster	Baseline	1 month after last CTX	1 year after baseline
Cluster 1 Treatment Related (Tr)	Sleep disturbance Concentration Anxiety	Fatigue Sleep disturbance Pain Concentration	Fatigue Sleep disturbance Pain Concentration Anxiety
Cluster 2 Gastrointestinal GI	Fatigue Pain Bowel pattern Nausea	Concentration Appearance Anxiety	Pain Bowel pattern

Symptom clusters in italics did not quite meet the criteria of Cronbach's α ≥0.60. Underlined symptoms were present in clusters at all times. Core symptoms are shown in bold font. CTX: Chemotherapy

Quality of life over time

Scores on the eight QOL scales improved over time [Table 4]. At baseline, the role emotional scale was highest, followed by social functioning, and vitality was lowest. At 1 month after the last CTX, role emotional was highest, followed by mental health and social functioning, and vitality remained lowest. One year after baseline, social functioning was highest, followed by role emotional, physical functioning, and mental health. Vitality repeated as lowest. Repeated-measures analysis indicated that there was a statistically significant improvement in the mean PCS and MCS scores over time, but the PCS remained lower than the general population norm score.[26]

Discussion

This study is an expansion of a previous work on the prevalence and severity of symptoms, symptom clusters, and QOL in a large, longitudinal sample of women with breast cancer from baseline to 1 year later. Results support the hypothesis that symptom severity and symptom clusters decrease and QOL improves over 1 year. We identified the dynamic unstable nature of symptoms and symptom clusters over 1 year. Anxiety was the core symptom at baseline and 1 year and fatigue at 1 month after the last CTX. Physical health did not reach general population norms 1 year after baseline. These results are vital to symptom cluster science because they verify that this sample did not return to prediagnosis "normal."

This sample reported experiencing several symptoms at baseline, similar to prior studies in patients with breast cancer.[13,15-21] The high prevalence and severity of several symptoms at baseline is likely due to prediagnosis health status, recent cancer diagnosis, and surgical procedure(s). Persistent symptoms are likely due to CTX regimens and inadequate time for return to prediagnosis health status.[2]

A major finding at 1 year was the prevalence and severity of fatigue, sleep disturbance, pain, concentration, bowel pattern, and anxiety in over 20% of the sample. Previous studies reported that symptoms returned to baseline 1 year after CTX but were higher than in cancer-free controls.[1,28] Symptoms may be due to age, menopausal symptoms, uncertainty,[29] other age-related diseases, and/or side effects of oral anti-estrogen therapy.[6]

At baseline, Cluster 1 (Tr) comprised of sleep disturbance, concentration, and anxiety, and Cluster 2 (GI) comprised of fatigue, pain, bowel pattern, and nausea. These results are similar to those of previous reports and suggest that these symptom clusters are likely due to the patient's recent cancer diagnosis and surgery.[13,15-21]

Cluster 1 (Tr) was dynamic, with fatigue and pain joining sleep disturbance and concentration about 1 month after

Table 4: Short-Form-36 v2 health survey: Eight health scales, physical component score[a], and mental component score[b] at three times (n=205)

Scales	Mean (SD)			*P*
	Baseline	1 month after the last CTX	1 year after baseline	
Physical functioning	70.6 (22.4)	70.2 (24.5)	80.5 (21.7)	<0.001
Role physical	59.0 (28.0)	61.8 (26.7)	78.0 (23.7)	<0.001*
Bodily pain	60.2 (23.3)	72.3 (24.2)	74.7 (23.2)	<0.001
General health	71.0 (16.9)	70.0 (19.5)	74.6 (18.5)	0.003
Vitality	56.1 (20.1)	52.4 (21.3)	62.7 (20.9)	<0.001
Social functioning	74.9 (23.6)	76.5 (23.2)	86.3 (18.7)	<0.001*
Role emotional	76.8 (22.4)	79.0 (25.3)	82.9 (23.8)	0.008*
Mental health	69.6 (17.6)	76.8 (17.4)	80.4 (15.8)	<0.001
PCS	44.6 (9.6)	45.5 (9.3)	49.3 (8.8)	<0.001
MCS	47.5 (10.4)	49.1 (10.3)	51.3 (10.0)	0.002*

[a]PCS comprised of items from first four scales above, norm is 50.0 (SD: 10.0), [b]MCS comprised items from second four scales, norm score is 50.0 (SD: 10.0), [c]Higher values on scales indicate a higher level of functioning and QOL (0-100), *Greenhouse-Geisser for the *P* value as the Mauchly's test indicated violation of the sphericity assumption. Not all columns add up to n=205 due to missing values. Bonferroni-adjusted *P* values represent longitudinal analysis of change over time. QOL: Quality of life, SD: Standard deviation, CTX: Chemotherapy, PCS: Physical Component Score, MCS: Mental Component Score

the last CTX, similar to a previous report.[16] Another team found three clusters that remained stable from baseline, with core symptoms of lack of energy, feeling sad, difficulty sleeping, difficulty concentrating, worrying, and pain.[15] Clusters labeled emotional, unwellness, and GI[18] included similar symptoms, but another team[19] reported different clusters. Results may be the effect of recent CTX or because the core symptom was triggering other symptoms in the clusters.

One year after baseline, anxiety rejoined Cluster 1 (Tr) and, surprisingly, was the core symptom. This cluster includes known side effects of CTX and oral anti-estrogen therapy.[6] The dynamic nature of the symptoms in Cluster 1 (Tr) is supported by other longitudinal studies of clusters at 1 year.[19-21] However, these studies measured prevalence, distress, or combined frequency/severity/distress, and this study measured the severity of symptoms.

Physical health was lower than the general population norms at all times. Mental health was lower than the general population norms at the first two times but reached norm values at 1 year. These findings are similar to those of a previous study.[1] Results infer that by 1 year, women recovered from mental health challenges more than from physical health challenges. Fatigue and vitality were notable influences on QOL. Another rationale is women's premorbid psychological characteristics and coping style were related more to lower physical and mental health than to cancer stage and treatment.[3] These results align with a prior report that patients with higher severity of pain, fatigue, sleep disturbances, and depression had lower QOL at baseline, at the end of CTX, 1 year after baseline, and over time.[28]

The strengths of this study include a large sample with longitudinal data over 1 year. All of the sample completed surgery and anthracycline-based CTX; approximately 50% received taxanes and 60% received radiation therapy. Limitations include the length of time between data collection and this secondary data analysis. We justify reporting these results because despite the passage of time, anthracycline-based CTX with or without taxanes is a current regimen. In addition, no other longitudinal study has reported on symptom severity clusters from baseline, to 1 month after the last CTX, and at 1 year. Comparing our results with prior studies was challenging because of variety of settings, selection and timing of measurements, and statistical methods used.

Implications for research include the need to develop and test interventions for the most commonly occurring symptom clusters in women with breast cancer during the 1st year after starting adjuvant therapies. Personalized clinical assessment and interventions for symptoms and symptom clusters are needed to reduce this public health problem and enhance QOL during survivorship. Early intervention is recommended because symptoms and symptom clusters present at baseline persist and impact survivors' QOL 1 year later.

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Conflicts of interest

There are no conflicts of interest.

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