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Changes in Fatigue, Psychological Distress, and Quality of Life After Chemotherapy in Women with Breast Cancer

A Prospective Study

Background: Chemotherapy leads to various symptoms and psychological distress, which contribute to a significant decrease in the quality of life of the patients. **Objectives:** The aim of this study was to identify changes and interrelationships in the fatigue-depression-anxiety symptom cluster and quality of life during the cancer care trajectory in women with breast cancer. **Methods:** Fifty women participated in the study and completed questionnaires at 3 different times: prechemotherapy, postchemotherapy, and 6 months after the completion of chemotherapy. The assessment tools were the Functional Assessment of Cancer Therapy–Fatigue Scale, Hospital Anxiety and Depression Scale, and Functional Assessment of Cancer Therapy–Breast Cancer version 4 Scale. Data were analyzed using descriptive and repeated-measures analysis of variance statistics. **Results:** A significant increase in fatigue ($F = 41.95$, $P < .001$) and psychological distress ($F = 26.55$, $P < .001$) from prechemotherapy to postchemotherapy was noted. Improvement was observed 6 months after the completion of chemotherapy. A positive or negative change in fatigue was associated with the same in psychological distress. Quality of life ($F = 65.22$, $P < .001$) also showed similar change patterns as observed with fatigue and psychological distress. Fatigue had a greater impact on quality of life at postchemotherapy, but psychological distress had a greater impact at prechemotherapy and at the 6-month follow-up. **Conclusion:** These results suggest that chemotherapy is highly associated with the fatigue-depression-anxiety symptom cluster and quality of life in women with breast cancer. **Implications for Practice:** Nursing

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intervention is needed to relieve the intensity of the fatigue-depression-anxiety symptom cluster and thus improve the quality of life of patients undergoing chemotherapy from before treatment to follow-up.

Chemotherapy, an adjuvant therapy, is commonly applied to most patients with breast cancer and has contributed to the increase in cancer survival rates.[1] However, chemotherapy leads to various physical symptoms (eg, vomiting, hair loss, pain, and fatigue) and psychological distress (eg, depression and anxiety).[2,3] Fatigue, pain, depression, and anxiety are reported to be most commonly experienced by patients with breast cancer.[2,3] Although these symptoms are alleviated over time, they have been associated with reduced quality of life and treatment adherence.[4–6] In patients with cancer, particularly breast cancer, cancer-related fatigue is among the most frequently occurring and distressing symptoms that persist after treatment[7] and are reported to be the most potent predictor of negative influences on health-related quality of life (HRQOL).[8] The mechanism of fatigue is as follows: Chemotherapy causes toxicity to the cells, and the resulting inflammatory response can cause fatigue due to excessive cytokine production.[9] Moreover, the low level of hemoglobin and loss of appetite can make fatigue more severe. In view of its prevalence and negative effect on quality of life, fatigue is an important symptom to target in the treatment of cancer survivors.[10] Symptom clusters may be more informative than single symptoms and could help direct goals of care.[11,12] Symptom clusters are defined as 2 or more symptoms that co-occur and are related to each other.[13] Although research on symptom clusters is progressing,[11,12] fatigue-pain-depression is recognized as a consistent cluster across studies.[14] This symptom cluster (fatigue-pain-depression) commonly occurs during chemotherapy. However, longitudinal studies have revealed inconsistent findings on the evolution of these symptoms during the cancer care trajectory.[15] Cluster variability over time and changes with chemotherapy need to be examined. Because chemotherapy will sometimes decrease cancer pain,[16] we focused on fatigue-depression-anxiety cluster in this study.

The diagnosis itself leads to 42.5% to 57% of the patients experiencing depression and anxiety.[11] Psychological symptoms, especially depression, have been found to have relatively high correlations with cancer-related fatigue.[10] However, most studies on this subject did not evaluate the impact of reducing fatigue on the psychological well-being of patients over time.[10]

Given the gap in literature, this study aims to identify the changes and its interrelationships in fatigue-depression-anxiety symptom cluster during the cancer care trajectory (from before to follow-up of chemotherapy) and to identify the influence of these variables (fatigue and psychological distress) on quality of life. The results from this prospective study will provide basic data in providing timely, customized interventions for patients with breast cancer receiving chemotherapy.

Theoretical Framework

The HRQOL model revised by Ferrans et al[17] had mediators (individual and environmental characteristics) and critical elements for quality of life. The critical elements include biological function, symptoms, functional status, and general health perceptions which having the causal relationships among them. Among the elements, symptoms consist of the physical, emotional, and cognitive symptoms, and the reciprocal relationships among them have not been explained in the model. Chemotherapy results in various physical symptoms and psychological symptoms, which lead to a negative effect on the quality of life of the cancer patient.[2,3] Psychological symptoms have been found to have high correlations with cancer-related fatigue, which is one of the physical symptoms.[10] However, most studies on this subject were limited to cross-sectional associations.[10] Therefore, directionality needs to be further explored in longitudinal studies.[18]

Methods

Participants

Patients with breast cancer from a cancer hospital in Korea were invited to participate in the study before the start of their adjuvant chemotherapy. A total of 60 were approached and 55 consented to participate in the study. Of the 55 patients, 50 (90.9%) participated in the study, 2 died of their disease, and 3 did not complete the questionnaire.

Eligible participants included those 18 years or older and scheduled to receive an adjuvant chemotherapy regimen that included doxorubicin, cyclophosphamide, and taxol. Exclusion criteria included receiving neoadjuvant chemotherapy and history of depression. A sample size of 36 subjects was estimated for 90% power with an α of .05, and 3 measures to determine a medium effect size in repeated measures analysis of variance (ANOVA) in a group.

Procedure

The study had ethical approval from the institutional review board of a cancer hospital in Seoul, South Korea, and all the participants gave full written consent. The assessments were done in prechemotherapy (1-3 days before the start of the chemotherapy), postchemotherapy (1-2 days after the completion of chemotherapy), and the 6-month follow-up.

Questionnaires were administered individually, and clinical data were collected from electronic medical records.

Measures

FATIGUE

The Korean version of the Functional Assessment of Cancer Therapy–Fatigue (FACT-F) scale was used. It consisted of 13 items rated on a 5-point Likert scale, ranging from 0 ("not at all") to 4 ("very much"). Higher scores represented greater fatigue.

In the previous study, where it was originally developed for use with patients with cancer, the Cronbach's α was .93,[19] whereas in this study, it was .89 at prechemotherapy.

PSYCHOSOCIAL DISTRESS

Psychosocial distress was measured by the Korean version of the Hospital Anxiety and Depression Scale (HADS).[20] The 2 HADS subscales comprised 7 items on a 4-point scale, ranging from 0 to 3. The total score ranges between 0 and 21 per subscale. A higher score represented a higher level of symptomatology.[21] Scores from 8 to 10 indicate mild symptom, and from 11 to 21, moderate to severe. The Korean version of the HADS has been validated, with evidence supporting the universal cutoff points.[20] The HADS contains no somatic items, which could be confounded with medical symptoms. The total α reliability in this study was .87 at prechemotherapy.

QUALITY OF LIFE

The Functional Assessment of Cancer Therapy–Breast Cancer version 4 (FACT-B) was used to measure the quality of life in patients with breast cancer.[22] The instrument consisted of 37 items, including 5 subscales (ie, physical, social/family, emotional, functional well-being, and breast cancer). This measure included items from the FACT–General and 9 additional items specifically selected to evaluate the quality of life in breast cancer survivors. Each item can be scored on a 4-point scale (0 = "not at all" to 4 = "very much"), with scores ranging from 0 to 148. Higher scores indicate a better level of quality of life. This questionnaire has good validity and reliability properties.[23] Regarding internal consistency, the Cronbach's α was .91 in this study at prechemotherapy.

Statistical Analyses

The Statistical Package for the Social Sciences version 21.0 was used for all statistical analyses. Descriptive statistics were used to describe participant characteristics and assess the distribution of all variables. According to the general characteristics of the participant, fatigue, psychosocial distress, and quality of life at prechemotherapy were examined using t test and ANOVA. The Scheffe method was used as the post hoc test.

The effects of chemotherapy on fatigue, psychological distress, and quality of life were assessed at 3 time points, using repeated-measures ANOVA. A Bonferroni correction was used for post hoc comparisons. Bivariate associations between the variables were examined using Pearson correlation coefficients. Multiple regression analysis was used to test the changes of effects of psychological distress and fatigue on quality of life from prechemotherapy to follow-up 6 months after the treatment. A probability level of .05 was used for statistical significance.

■ Results

Table 1 represents the demographic and clinical characteristics of the participants. A total of 50 patients participated in this study and completed the questionnaires. Most participants were aged

Table 1 • Participants' Characteristics by Psychological Distress, Fatigue, and Quality of Life (N = 50)

Variables	Category	n (%) or M ± SD
Age, y	≤40	7 (14.0)
	41–50	21 (42.0)
	51–60	19 (38.0)
	≥61	3 (6.0)
		48.92 ± 7.79
Marital status	Married	47 (94.0)
	Not married	3 (6.0)
Education	Middle school or lower	7 (14.0)
	High school	26 (52.0)
	College or higher	17 (34.0)
Occupation	Employed	19 (38.0)
	Unemployed	31 (62.0)
Menopause	No	25 (52.1)
	Menopausal	18 (37.5)
	Chemotherapy-induced menopause	5 (10.4)
Comorbidity	Yes	12 (24.0)
	No	38 (76.0)
Cancer stage	I, II	38 (76.0)
	III	12 (24.0)
ECOG performance status	0	14 (28.0)
	1	30 (60.0)
	2	4 (8.0)
	3	2 (4.0)
Type of surgery	Total mastectomy	16 (32.0)
	Partial mastectomy	27 (54.0)
	No response	7 (14.0)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

41 to 50 years (mean age, 48.92 years; standard deviation [SD], 7.79) and were married. In addition, 52.0% of the participants obtained a high school education, whereas 34% graduated from college or higher; 62.0% did not have a job; 52.1% were not in menopausal phase; and 76% had no comorbidity.

Of the total 50 participants, 76.0% were at clinical stages I and II at the time of diagnosis, with a proportion of 24.0% for stage III; 88% were over grade 1 Eastern Cooperative Oncology Group performance status, ambulatory, and able to conduct work of a light or sedentary nature. Partial mastectomy was a frequently performed procedure (54.0%) than total mastectomy (32.0%).

There were no significant differences in fatigue, psychological distress, and quality of life depending on the demographic and clinical characteristics of the participants at the 3 time points.

Changes in Fatigue, Psychological Distress, and Quality of Life

Table 2 shows the changes in the number of participants experiencing depression and anxiety from prechemotherapy to the follow-up 6 months after chemotherapy. Four percent of patients in prechemotherapy, 30% in postchemotherapy, and 12%

Table 2 • Changes in Number of Participants Experiencing Depression and Anxiety From Prechemotherapy to Follow-up (N = 50)

Outcome Variables	Category	Prechemotherapy n (%)	Postchemotherapy n (%)	Follow-up n (%)
Depression	0-7	42 (84.0)	21 (42.0)	35 (70.0)
	8-10	6 (12.0)	14 (28.0)	9 (18.0)
	11-21	2 (4.0)	15 (30.0)	6 (12.0)
Anxiety	0-7	36 (72.0)	19 (38.0)	32 (64.0)
	8-10	11 (22.0)	13 (26.0)	10 (20.0)
	11-21	3 (6.0)	18 (36.0)	8 (16.0)

in 6-month follow-up experienced moderate to severe depression and anxiety in their daily lives. In case of anxiety, 6% in prechemotherapy, 36% in postchemotherapy, and 16% in 6-month follow-up experienced moderate to severe symptoms.

Table 3 and the Figure show the results of repeated-measures ANOVA with 3 time points. Fatigue showed a significant effect of time point ($F = 41.95$, $P < .001$). Participants revealed higher mean scores of fatigue at postchemotherapy (22.77) than at prechemotherapy (12.36) and 6-month follow-up (10.28). Psychological distress also had a significant main effect of time point ($F = 26.55$, $P < .001$). The mean scores of psychological distress were initially lower at prechemotherapy (10.91), rising significantly at postchemotherapy (16.34), before dropping at 6-month follow-up (12.02). Quality of life also showed a significant effect of time point ($F = 65.22$, $P < .001$). Quality of life mean scores were initially higher at prechemotherapy (102.09), dropping at postchemotherapy (65.85), before rising at 6-month follow-up (98.43).

Correlations among the variables at the 3 time points were as follows. Higher fatigue scores were significantly correlated with higher psychological distress ($r = 0.45$, $P = .001$; $r = 0.49$, $P < .001$; $r = 0.38$, $P = .009$, respectively) and lower quality of life ($r = -0.54$, $P < .001$; $r = -0.68$, $P < .001$; $r = -3.8$, $P = .009$, respectively). Increased psychological distress scores were significantly correlated with lower quality of life ($r = -0.59$, $P < .001$; $r = -0.69$, $P < .001$; $r = -0.62$, $P < .001$, respectively).

Table 4 shows the changes of effects of fatigue and psychological distress on quality of life from prechemotherapy to the 6-month follow-up.

In terms of time point, at prechemotherapy and follow-up, psychological distress ($\beta = -3.54$; $\beta = -4.52$) was a more significant predictor of quality of life than fatigue ($\beta = -2.79$; $\beta = -1.32$). These factors accounted for 38.8% to 41.7% of the patients' quality of life ($P < .001$). However, in case of postchemotherapy time point, fatigue ($\beta = -7.21$) was a more important factor of quality of life than psychological distress ($\beta = -4.65$), accounting for 74.0% of the variance in patients' quality of life ($P < .001$).

■ Discussion

This study confirmed the prechemotherapy and postchemotherapy changes in fatigue-depression-anxiety symptom cluster and the influence of these variables (fatigue and psychological distress) on quality of life.

The level of fatigue of patients with breast cancer in this study was in the middle range (mean, 22.77 score). This finding was similar to that in previous studies on patients with breast cancer that used the same scale.[24–26] Participants revealed higher mean scores of fatigue at postchemotherapy (22.77) than at prechemotherapy (12.36) and 6-month follow-up (10.28). These results support those found in previous studies, which reported that physical symptoms experienced by patients with cancer intensified with the increasing number of chemotherapy sessions and are later reduced 6 months after the end of the treatments,[5,27] but they still remain to have negative impacts on the quality of life.[5] Moreover, these results suggest that chemotherapy generate toxic effect to cells, and the resulting inflammatory response can cause fatigue.[9]

Our study showed that higher fatigue was associated with higher psychological distress (depression and anxiety). This study also confirmed a matching trend in the psychological distress of patients with cancer, in that it intensified after chemotherapy when compared with pretreatment and recovery 6 months after the treatment. This finding is similar to those founded in previous studies on patients with breast cancer, which reported that a decline in depressive symptoms occurred by 7 to 10 months after surgery and then remained stable.[15,28]

These results are in line with previous studies on cancer treatments[10,29]; a systematic review on fatigue and psychological distress revealed the average correlation between fatigue and depression at 0.56 and that between fatigue and anxiety at 0.46.[30] In truth, the relationship between fatigue and depression is rather unclear, as the former may be considered an aspect of depressive symptoms. The HADS–Depression subscale, which was used in this study to measure depression, did not include items on physical symptoms, such as "lack of energy" or "sleep disturbance."[13] The FACT Fatigue, which was used to measure fatigue, also did not include psychological items. Consequently, the results of this study seem to explain the relationship between fatigue and depression well.

Participants indicating moderate to severe depression, which requires specific medical therapy, increased from 4.0% before the start of chemotherapy to 30.0% after the end of chemotherapy. The number of participants needing treatment for anxiety increased from 6.0% before the start of chemotherapy to 36.0% after the end of chemotherapy. These phenomena were repeated in the ANOVA, indicating that psychological distress intensified along with the side effects of chemotherapy. These results are

Outcome Variables	Prechemotherapy[a] Mean ± SD	Postchemotherapy[b] Mean ± SD	Follow-up[c] Mean ± SD	Time effect F	P	Bonferroni
Anxiety/depression	10.91 ± 5.47	16.34 ± 7.25	12.02 ± 5.64	26.55	<.001	a, c < b
Fatigue	12.36 ± 8.22	22.77 ± 10.06	10.28 ± 6.86	41.95	<.001	a, c < b
Quality of life	102.09 ± 20.79	65.85 ± 25.61	98.43 ± 18.08	65.22	<.001	b < a, c
Physical	10.32 ± 8.19	10.32 ± 8.19	23.94 ± 5.36	103.29	<.001	a, b < c
Social/family	17.77 ± 6.66	15.70 ± 6.01	16.49 ± 5.71	4.52	.013	b < a
Emotional	17.81 ± 4.20	13.09 ± 5.74	18.02 ± 4.58	31.66	<.001	b < a, c
Functional	16.89 ± 7.06	10.55 ± 5.75	15.70 ± 5.69	19.33	<.001	b < a, c

a, b, c: Bonferroni post hoc test.

similar to the finding (32.0%) of a study on patients with colorectal cance.[31] However, they show a higher degree of depression compared with the finding (17.2%) of a previous study that used a same scale to measure patients with breast cancer with moderate to severe depression.[32] Regarding the depression of patients with cancer as a behavioral side effect to the diagnosis itself and the treatment, the level of depression in this study would have been impacted by the large number of participants experiencing physical fatigue, as measurement occurred immediately after the completion of chemotherapy. This finding suggests that fatigue may be casual in fatigue-depression-anxiety symptom interrelationships.

This study confirmed a matching trend in the quality of life of patients with cancer compared with fatigue and psychological distress, in that those intensified immediately after the completion
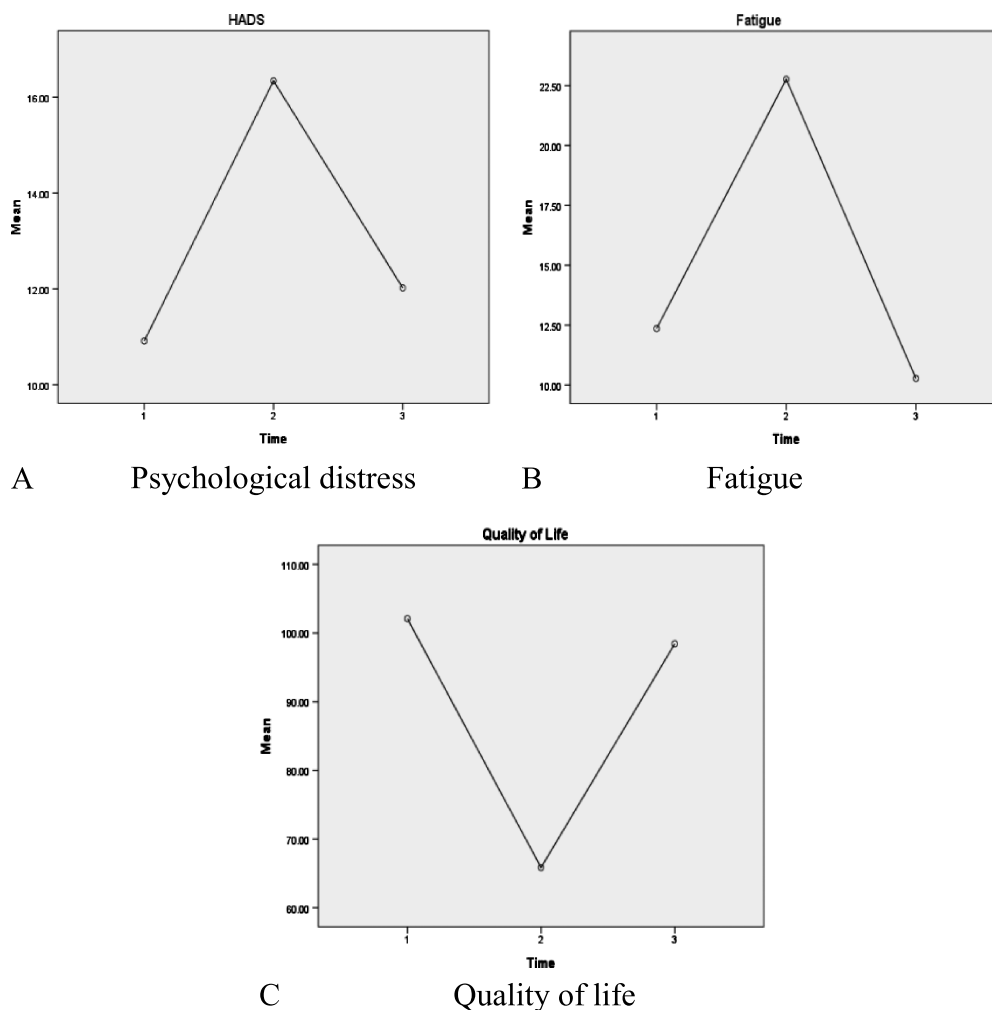
A   Psychological distress

B   Fatigue

C   Quality of life

Figure. Changes in psychological distress, fatigue, and quality of life from prechemotherapy to follow-up.

Table 4 • Changes in Effects of Psychological Distress and Fatigue on Quality of Life

Variables	B	β	t	P	Dubin-Watson	Tolerance	VIF
Prechemotherapy							
Constant	130.00	–	24.78	<.001	2.06	0.800	1.25
Psychological distress	−1.65	−.44	−3.54	.001			
Fatigue	−0.85	−.34	−2.79	.008			
Adj R^2 = 0.417, F = 18.20, P < .001							
Postchemotherapy							
Constant	122.79	–	23.44	<.001	1.95	0.755	1.33
Psychological distress	−1.33	−.39	−4.65	<.001			
Fatigue	−1.53	−.61	−7.21	<.001			
Adj R^2 = 0.740, F = 70.75, P < .001							
Follow-up							
Constant	124.59	–	24.23	<.001	1.70	0.856	1.17
Psychological distress	−1.81	−.56	−4.52	<.001			
Fatigue	−0.43	−.17	−1.32	.193			
Adj R^2 = 0.388, F = 15.58, P < .001							

of chemotherapy compared with prechemotherapy and the 6-month follow-up. This finding supports the HRQOL model that explains that physical and emotional symptoms are the critical elements for quality of life.

These results are in line with other studies, which reported a decrease in quality of life after the end of treatment and a recovery to pretreatment levels after 6 months despite the existing symptoms from chemotherapy in patients with breast cancer.[33] In this study, the subdomain-specific level of quality of life indicated lowest postchemotherapy scores in physical and functional well-being. Moreover, after 6 months, the functional domain showed the lowest scores. These results are in line with previous studies on patients with colorectal cancer[31] and breast cancer,[32] which reported that quality of life posted the lowest score in the functional domain.

Quality of life was the lowest immediately after the completion of chemotherapy in this study. Fatigue was found to be a more significant influence compared with psychological distress, and these variables explained quality of life by 74%. Therefore, fatigue symptoms should be closely monitored and managed as soon as adjuvant treatments are started.[15]

Meanwhile, before the beginning of chemotherapy and 6 months after chemotherapy, the influence of psychological distress on quality of life was higher than that of fatigue. These phenomena are similar to reports on the quality of life of patients with hematopoietic stem cell transplant, in which physical symptoms are the most influential in changes to quality of life in the transplantation and early recovery periods, and psychological distress is influential in all periods (ie, before, during, and after transplantation).[33,34] These results indicate that the nursing strategies to improve the quality of life of breast cancer must differ before and after chemotherapy treatments Although existing studies on patients with breast cancer suggest that anxiety and depression are the most significant factors in quality of life,[32] it is important to focus nursing care on the management of physical symptoms, such as fatigue, rather than psychological distress immediately after the completion of chemotherapy. This indicates that during chemotherapy, patients with cancer undergo severe physical

symptoms, intensifying psychological distress; this process has a significant influence on quality of life.[34,35] Such psychological distress lowers the quality of life in patients with cancer[36] and influences recurrence of cancer.[37] Therefore, these outcomes require psychosocial support that can advance the psychological well-being of patients with cancer during chemotherapy.

The results of this study indicate that the fatigue and psychological distress experienced by patients vary significantly, and their influence on quality of life by period has significant implications. Therefore, along with managing fatigue, screening and management of psychological distress are important, and such nursing care can improve the quality of life of patients.

This study is a prospective study that tracked the influence of chemotherapy on fatigue-depression-anxiety symptom cluster and quality of life of patients with cancer. As the tracking ended 6 months after the treatment, this study was unable to analyze the late changes occurring after the treatment. This study also focused on identifying the experience of fatigue-depression-anxiety symptom cluster and changes in quality of life. Thus, other influential variables that could influence their changes were not examined.

This prospective study was conducted to identify the changes in the fatigue-depression-anxiety symptom cluster and quality of life at 3 time points (ie, prechemotherapy, postchemotherapy, and 6-month follow-up) in women with breast cancer. Fatigue and psychological distress (depression and anxiety) increased significantly at postchemotherapy and improved at 6-month follow-up. Changes in fatigue were associated with those in psychological distress. This finding suggests that fatigue may be casual in fatigue-depression-anxiety symptom interrelationships and support the existence of the symptom cluster.

At immediately after the completion of chemotherapy, 33.0% of the patients complained of moderate to severe psychological distress, and 14.4% exhibited moderate to severe psychological distress at 6-month follow-up. Similar patterns were observed in quality of life, fatigue, and psychological distress. Fatigue had a greater impact on quality of life, but psychological distress had a greater impact at prechemotherapy and 6-month follow-up.

These results suggest that chemotherapy is highly associated with fatigue, psychological distress, and quality of life in women with breast cancer. Nursing intervention is needed to relieve fatigue and psychological distress and thus improve the quality of life of patients undergoing chemotherapy from before the treatment to follow-up.

ACKNOWLEDGMENTS

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