Patterns of Fatigue and Effect of Exercise in Patients Receiving Chemotherapy for Breast Cancer

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Purpose/Objectives: To examine daily fatigue patterns during the third cycle of chemotherapy in women with breast cancer and predict whether fatigue trajectories differ by exercise or chemotherapy regimens.

Design: A secondary data analysis.

Setting: Five cancer centers in the San Francisco Bay area.

Sample: 98 female outpatients with breast cancer receiving chemotherapy.

Methods: The data were collected as part of a randomized clinical trial to test the effectiveness of a systematic exercise intervention on fatigue. Participants were classified as exercisers or nonexercisers according to the Surgeon General's Guideline for Physical Activity criteria. Average and worst fatigue levels in the prior 24 hours were measured on a 0–10 numeric rating scale at bedtime for 21 consecutive days beginning on the day of chemotherapy.

Main Research Variables: Average and worst levels of fatigue, exercise status, and chemotherapy regimens.

Findings: Average and worst levels of fatigue peaked immediately after chemotherapy and declined gradually over time. The decreases were significant ($p < 0.001$) but not different between exercisers and nonexercisers. Fatigue of doxorubicin and cyclophosphamide (AC) regimens was more severe, especially for the first three days after chemotherapy, and more prolonged than those of non-AC regimens.

Conclusions: The patterns of change in fatigue were similar between exercisers and nonexercisers, but nonexercisers consistantly reported higher fatigue levels during the third cycle of chemotherapy. The patterns of fatigue differed by chemotherapy regimens.

Implications for Nursing: The information of fatigue trajectories is crucial in preparing patients for chemotherapy and determining the timing of interventions and measurement of outcomes.

Key Points . . .

- ➤ Cancer-related fatigue (CRF) peaks in the days immediately after IV chemotherapy and declines gradually over time.
- ➤ Exercise has an impact on levels of CRF.
- ➤ Fatigue patterns vary depending on the type of chemotherapy regimen patients receive.

Cancer-related fatigue (CRF) is a significant and highly prevalent clinical problem. It is long lasting and characterized by a significant temporal variability. The symptom often is not continually present but comes and goes in a somewhat roller coaster fashion (Berger, 1998). CRF affects all aspects of patients' lives and decreases quality of life. Although fatigue is one of the most impairing cancer-related symptoms, it has not been controlled fully. The unknown mechanisms and the fluctuating nature of CRF add to obstacles in studying and managing this symptom.

Patterns of Fatigue in Patients Receiving Chemotherapy

CRF fluctuates over time and peaks in the days immediately after IV chemotherapy administration. Richardson, Ream, and Wilson-Barnett (1998) revealed that patients with cancer who were treated by conventional three- or four-week regimens reported high levels of fatigue for the first four to five days after chemotherapy. Fatigue decreased steadily in subsequent days until around day 15, when a temporary

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rise was common. In a review of five studies on fatigue patterns in patients receiving cancer treatments, Schwartz et al. (2000) concluded that CRF peaked two to five days after chemotherapy and resolved over time but never reached pretreatment status. Similar patterns were observed in studies of patients with breast cancer. Pusztai et al. (2004) reported that fatigue, nausea, and muscle aches all increased transiently after paclitaxel chemotherapy. These symptoms reached a peak two to four days after chemotherapy and resolved by the end of the cycle. Other studies showed that after receiving the third chemotherapy treatment, most patients experienced peak fatigue levels within five days (Berger & Higginbotham, 2000; de Jong, Kester, Schouten, Abu-Saad, & Courtens, 2006). The highest fatigue was reported two days after chemotherapy (de Jong et al., 2006; Molassiotis & Chan, 2001). Schwartz (2000) further concluded that the most common pattern of fatigue in women with breast cancer who were receiving adjuvant treatment was a sharp increase in the first 24–48 hours after chemotherapy.

The timing associated with a circadian rhythm of CRF has been explored. Molassiotis and Chan (2001) discovered that fatigue started to elevate in the late afternoon (4 pm) on the day chemotherapy was administered. Fatigue was more pronounced in the evening (10 pm) among women than men on their treatment day (Molassiotis & Chan). The periods of day when patients were most frequently affected by fatigue were the early afternoon, late afternoon, and early evening (Richardson et al., 1998). CRF levels were higher in the afternoon and evening compared to the morning assessment (Molassiotis & Chan).

CRF peaks during the first days after IV chemotherapy. Inconsistent results have been reported in regard to whether CRF increases around hematologic nadir, usually around cycle midpoint. A common perception held by many healthcare providers is that CRF intensifies during nadir. Richardson et al. (1998) observed an abrupt increase in fatigue scores near the nadir period. However, discrepant findings appear in the literature. Berger (1998) reported that fatigue scores were higher 48 hours after chemotherapy than during cycle midpoints. The findings were consistent through three consecutive chemotherapy cycles. Other studies of women with breast cancer receiving adjuvant chemotherapy also failed to demonstrate an increase in fatigue during nadir (Schwartz, 2000; Schwartz et al., 2000). Another study measured CRF on a daily basis throughout the third chemotherapy cycle. The course of CRF in the 21-day doxorubicin group was characterized by a sharp increase one day after chemotherapy followed by a gradual decline and then a slight rise before the next cycle of chemotherapy (de Jong et al., 2006); CRF did not increase during the hematologic nadir.

Patterns of Fatigue and Associated Factors

Treatment-Related Characteristics

CRF patterns vary depending on the type of chemotherapy patients receive and the route used to deliver the chemotherapy (de Jong, Candel, Schouten, Abu-Saad, & Courtens, 2004; de Jong et al., 2006; Greene, Nail, Fields, Dudgeon, & Jones, 1994; Payne, 2002; Pusztai et al., 2004; Richardson et al., 1998). An early study (Greene et al.) comparing fatigue among three chemotherapy regimens for breast cancer reported a significant interaction of treatment regimen by time; in other words, levels of fatigue changed across the four measurement points and fatigue patterns varied across the three drug regimens.

In current practice, the standard treatment for stage I or II breast cancer includes doxorubicin- and nondoxorubicin-containing protocols. Protocols containing doxorubicin were associated with higher fatigue levels than those that did not contain doxorubicin at first chemotherapy treatment (Berger, 1998; Berger & Walker, 2001). Fatigue was more severe in patients who received 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) than for those who received paclitaxel (Pusztai et al., 2004). The courses of fatigue also were different by treatment protocols. Between the third and fourth chemotherapy cycles, the peak fatigue level was significantly higher in patients treated with the doxorubicin-based regimens every 21 days than for those who were treated with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) (de Jong et al., 2006). Fatigue reported by those receiving doxorubicin increased over time and then started to decline four weeks after the completion of chemotherapy, whereas the intensity of fatigue reported by those receiving CMF was stable throughout the treatment period with a significant increase four weeks after the completion of chemotherapy (de Jong et al., 2004). In contrast, in some studies, no significant relationship was observed between fatigue and type of chemotherapy (Can, Durna, & Aydiner, 2004; Schwartz, 2000). Although the women receiving doxorubicin protocols experienced lower activity levels across three chemotherapy cycles than women who did not receive doxorubicin, the doxorubicin group reported higher fatigue only on the first cycle of chemotherapy (Berger, 1998).

Exercise

Studies have shown that women with breast cancer who were less active reported higher fatigue (Berger & Higginbotham, 2000). Mock et al. (1994) developed a rehabilitation program consisting of a walking program and a support group for patients with breast cancer receiving chemotherapy. The participants demonstrated an improvement in physical functioning, with a decrease in fatigue and emotional distress. Improved physical functioning and less fatigue, anxiety, and difficulty sleeping also were reported by those who participated in a walking program during the radiation treatment (Mock et al., 1997). Another study showed that women who adopted exercise experienced fewer days of high fatigue. Levels and ranges of fatigue in the exercisers decreased over three cycles of chemotherapy (Schwartz, 2000). A significant improvement in fatigue was evident among patients with breast cancer who participated in a moderate-intensity exercise program during cancer treatments (Mock et al., 2005; Schwartz, Mori, Gao, Nail, & King, 2001). Exercise is an effective intervention for CRF. However, only a few studies have examined the daily course of fatigue in patients with cancer who participate in exercise activities.

Limited conclusions can be drawn from the previously identified studies because of several methodologic issues. The use of heterogeneous samples in terms of types and stages of cancer can limit usefulness in seeking information about fatigue in patients treated with a specific regimen for a particular cancer. Some longitudinal studies have followed patients over a period

of time but CRF was measured and compared at different time points (e.g., before treatment and 10 days after; 48 hours after treatment and at cycle midpoints), for limited periods (e.g., before treatment and 7–10 days after treatment), or at fixed intervals (e.g., every week). A noticeable time lag exists between each measurement and changes in fatigue that may occur between measurements are largely ignored, providing little information about the overall pattern across time. The time of day for instrument completion, which is related to the biologic rhythms of fatigue, usually is not addressed or standardized.

A variety of instruments, including multidimensional and unidimensional fatigue measurements, have been used to investigate the patterns of fatigue. Some studies investigate fatigue intensity while others study prevalence. Various combinations of measured dimensions (e.g., physical, emotional, cognitive fatigue) and characteristics (e.g., severity, frequency) limit conclusions that can be drawn across the studies. Inconsistent reference periods (e.g., right now, in the previous 24 hours, in the past seven days) of the instruments have added other methodologic concerns. The reference period used to measure CRF and the time when fatigue instruments are administered are critical in determining the timing associated with treatments or other events. However, findings usually are interpreted without considering the time referenced in the measurement. Moreover, a variety of statistical approaches have been used in analyzing fatigue patterns and their correlates. Some studies have used hypothesis testing to compare the impact of fatigue on selected factors cross-sectionally or longitudinally. Some studies established a set of factors to estimate levels of fatigue while others simply have examined the strength of the association between fatigue and its correlates. Fatigue studies mainly have employed the analyses with cross-sectional assumptions. Longitudinal conclusions often are drawn from the analyses designed for the cross-sectional data.

The purposes of this secondary data analysis were to examine daily fatigue patterns during the third cycle of chemotherapy in women with breast cancer and explore whether fatigue trajectories differ according to exercise activities. The effect of different chemotherapy regimens on the course of fatigue also was examined.

Methods

The data described in this article were collected as part of a large, single-blind, randomized clinical trial to test the effectiveness of a systematic exercise intervention on fatigue, the Pro-Self: Fatigue Control Program. A prospective, longitudinal, repeated-measures design adopted to meet the objectives entailed the use of a diary in which patients recorded their daily fatigue experiences over a course of chemotherapy. The third cycle of chemotherapy was chosen because of the observation that a most patients have experienced marked treatment-related morbidity (e.g., more sleeping and napping) by the third chemotherapy treatment (Piper, 1993).

Settings and Participants

The study took place in five cancer centers in the San Francisco Bay area. To be eligible, participants had to be age 21 or older, diagnosed with breast cancer and receiving chemotherapy, expected to survive at least 12 months, have Karnofsky Performance Status scores of 60 or higher, be mentally competent to consent, be able to communicate in English, and be willing to participate. Patients diagnosed with AIDS-related malignancies or leukemia, experiencing uncontrolled hypertension or diabetes mellitus, had received chemotherapy within the past year, were receiving radiotherapy or bone marrow transplantation, had a known history of major depression or sleep disorders, had pain scores of 3 or higher on a 0–10 scale, had orthopedic limitations, or had absolute contraindications for exercise as established by the American College of Sports Medicine (1995) were excluded because those conditions may affect fatigue experiences or prevent regular exercise activities.

Procedures and Measures

The study was approved by the Human Subjects Committee at the University of California, San Francisco, and at each of the study sites. Patients who met the study criteria and were scheduled to begin chemotherapy were told about the study by the referring oncologists and nurses at each study site and approached by the research staff. After informed consent, the patients were instructed to complete a daily fatigue diary throughout the third cycle of chemotherapy. Treatment-related information was gathered from the medical record by the research staff.

The fatigue diary contained two questions: "What was your average level of fatigue/tiredness over the last 24 hours?" and "What was your worst level of fatigue/tiredness over the last 24 hours?" Each question was measured using an 11-point rating scale, ranging from 0 (no fatigue/tiredness) to 10 (overwhelming fatigue/tiredness). Descriptive numeric rating scales have been used in previous studies (Miaskowski et al., 2004) and the diary format has been proven efficient in measuring fatigue in patients with cancer (Richardson, 1994) with minimial burden. Internal consistency reliability of the two items in the fatigue diary ranged from $\alpha = 0.87–0.95$ in the present study. Average and worst fatigue were measured daily for the entire treatment cycle beginning on the first day chemotherapy was administered. The patient was instructed to complete the diary at the same time each night before going to bed and to record the time of day to ensure consistency and compliance with study protocol. An exercise physiologist instructed the patients to fill out the diary and describe their adherence via phone on a weekly basis. To determine if women were exercisers or nonexercisers, the Surgeon General's Guideline for Physical Activity (U.S. Department of Health and Human Services, 1996) of at least three days a week, 20 minutes per session, at an intensity of "somewhat hard" was used. Exercise frequency, duration, and intesity were self-reported by the participants.

Statistical Analysis

SPSS® 14.0 statistical software was used for data management and analyses. Average and worst fatigue on each day were plotted over time to summarize patterns of change in fatigue during the treatment cycle. Graphic displays of daily plots were examined for each patient and categorized according to the pattern. Chi-square tests and t-tests were used to examine whether characteristics between exercisers and nonexercisers and between those who were receiving doxorubicin and cyclophosphamide (AC) and non-AC chemotherapy protocols differed. Multilevel models, known variously as individual growth models, random coefficient models, mixed models, and hierarchical linear models, were used to estimate how

fatigue had changed over time and with exercise behaviors. Although the length of treatment intervals varied depending on chemotherapy regimens, the analyses were limited to the first 21 days after treatment. Multilevel modeling technique enables researchers to (a) describe changes within individuals over time and (b) examine interindividual differences in change. The multilevel statistical models also allow using the estimated values of parameters to draw conclusions about the direction and the magnitude of hypothesized effects in the population (Singer & Willett, 2003). In this article, day 0 represented the day chemotherapy was administered, day 1 represented the first day after treatment and so on.

Results

Sample

Table 1 summarizes the demographic, disease, and treatment-related characteristics of study participants. Ninety-eight female outpatients with breast cancer, ages 28–72 ($\bar{X}$ = 49.5, SD = 9.3), were evaluated in this secondary analysis. Most women were white (74%), well educated (88% had more than 12 years of education), married or partnered (72%), living with someone (85%), and unemployed (53%). The women primarily were premenopausal (42%) and being treated for stage I (40%) and II (45%) breast cancer. A majority (79%) were receiving AC chemotherapy. Most of the women had previous surgery (93%), and none received radiotherapy before the third course of chemotherapy. More than half of the women (57%) were classified as nonexercisers.

Overall Fatigue Patterns

Based on the cutoff levels of fatigue as none, mild, moderate, or severe (National Comprehensive Cancer Center, 2008), the average levels of fatigue reported by participants were moderate ($\bar{X}$ = 3.6–4.6, SD = 2.1–2.4) for the first eight days and mild ($\bar{X}$ = 2.7–3.4, SD = 1.7–2.2) for the rest of the cycle. The worst levels of fatigue were moderate ($\bar{X}$ = 3.8–6.0, SD = 2.3–2.7) throughout the third chemotherapy cycle. The highest levels of fatigue were observed on day 1 to day 3 for average ($\bar{X}$ = 4.3–4.6) and worst ($\bar{X}$ = 5.8–6.0) fatigue. Variation in average (SD = 1.7–2.4) and worst (SD = 2.3–2.7) levels of fatigue were noted on each day.

Average fatigue and worst fatigue on each day were plotted over the course of the third chemotherapy cycle. Smooth nonparametric trajectories were superimposed on empirical growth plots to illustrate the overall patterns of change in fatigue. Fatigue patterns were categorized visually based on the plots of 81 patients who had few data points missing. The average fatigue usually corresponded to the worst fatigue daily. The trends of average and worst fatigue were similar overall. Both scales demonstrated irregular patterns of fatigue over the course of chemotherapy. Five distinct trajectory patterns of CRF were identified. The most common pattern across all plots demonstrated one sharp increase in fatigue immediately after chemotherapy followed by a gradual decline over time (n = 28) (see Figure 1). In this pattern, fatigue reached a peak between day 0 and day 3. The second most common pattern was a concave-shaped pattern that displayed an early peak between day 0 and day 2 with a decline afterward and then a sharp increase right before the next cycle of chemotherapy (n = 17) (see Figure 2). The third pattern showed small variations

Table 1. Demographic Characteristics

Characteristic	$\bar{X}$	SD	Range
Age (years)	49.5	9.3	28–72
Characteristic	**n**		**%**
Ethnicity			
White	72		74
Black	11		11
Asian-Pacific Islander	12		12
Hispanic	1		1
Other	2		2
Education			
12 years or less	11		12
More than 12 years	85		89
Relationship status			
Single	27		28
Married or partnered	70		72
Live alone			
Yes	15		16
No	82		85
Employment			
Full-time	32		35
Part-time	12		13
Unemployed and other	50		53
Menopausal status			
Premenopausal	38		42
Perimenopausal	17		19
Postmenopausal	36		40
Stage of disease			
I	34		40
II	39		45
III	13		15
Treatment regimen			
Non-AC	21		21
AC	77		79
Initial cancer treatment			
Surgery	83		93
Chemotherapy	5		6
Combination	1		1

AC—doxorubicin and cyclophosphamide

Note. Because of missing data, not all n values total 98. Because of rounding, not all percentages total 100.

(range usually ≤ 2) among the daily fatigue scores that were characterized by a single or some high and low points interwoven with uniform fatigue levels (n = 16) (see Figure 3). A chaotic pattern was characterized by erratic and wide swings in fatigue levels with significant changes of highs and lows over time (n = 14) (see Figure 4). The final pattern showed a step-up elevation in fatigue after chemotherapy. Fatigue reached a peak around day 10 and gradually declined over the rest of the cycle (n = 6) (see Figure 5). The five exemplar plots were selected to represent the prototypes of five change trajectories of fatigue in the study sample.

The first step in multilevel modeling was to assess individual differences in rates of change in average and worst fatigue. Individual average and worst levels of fatigue were modeled as functions of time (i.e., day of chemotherapy) during the 21-day period. The sample intercept (average initial fatigue level) and slope (expected rate of change over

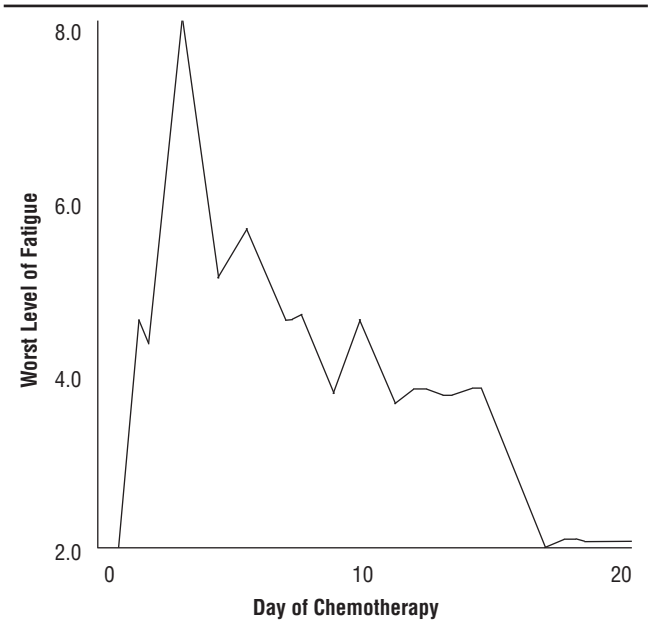


Figure 1. Immediate and Sharp Increase Followed by a Gradual Decline

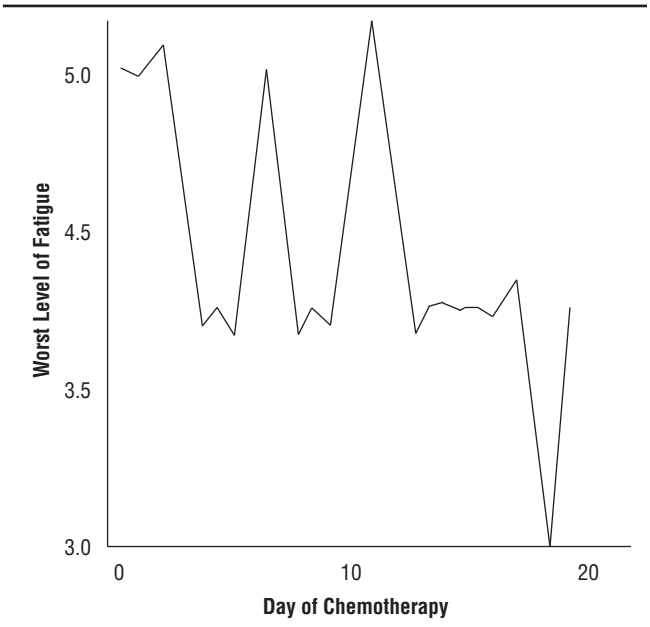


Figure 3. Small Variations Among Daily Scores

time) were generated based on the observed data. As in a simple linear regression model, the statistical models allow unknown population parameters to be estimated. Additional variables, such as exercise status and treatment regimens, were then added as predictors of population intercepts and slopes. Significance tests were performed on the predictors to determine whether the inclusion of variables in the model results in reduction of unexplained variance. Various models were tested and rejected during the process. The results of selected models are presented in Table 2.

Results of multilevel modeling for the entire sample, regardless of exercise status and treatment regimens, showed a strong linear change in average fatigue over time (see Table 2, Model A). The estimated average level of fatigue on the treatment day for women with breast cancer receiving the third cycle of chemotherapy was 4.3. The predicted daily rate of change in average fatigue was –0.086 ($p < 0.001$), meaning that average levels of fatigue declined as the days went by. The effect of time also demonstrated a cubic change trajectory in average fatigue over time (see Table 2,

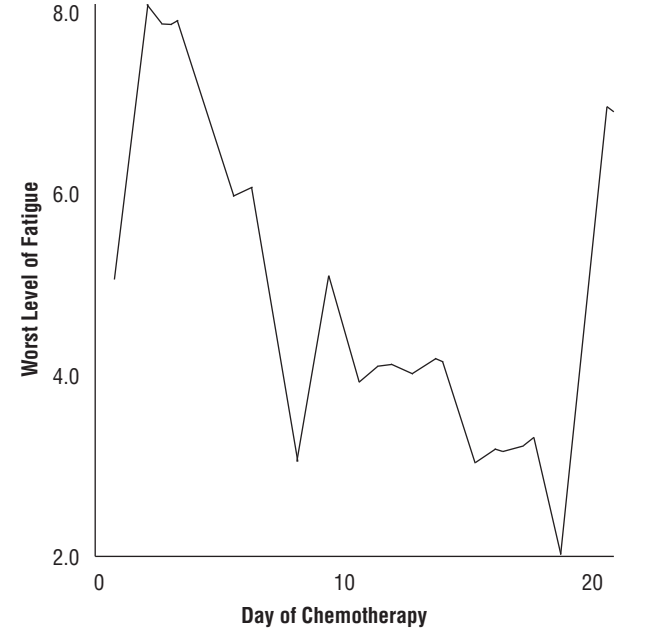


Figure 2. Early Peak, a Decline, and a Sharp Increase Toward the End of Cycle

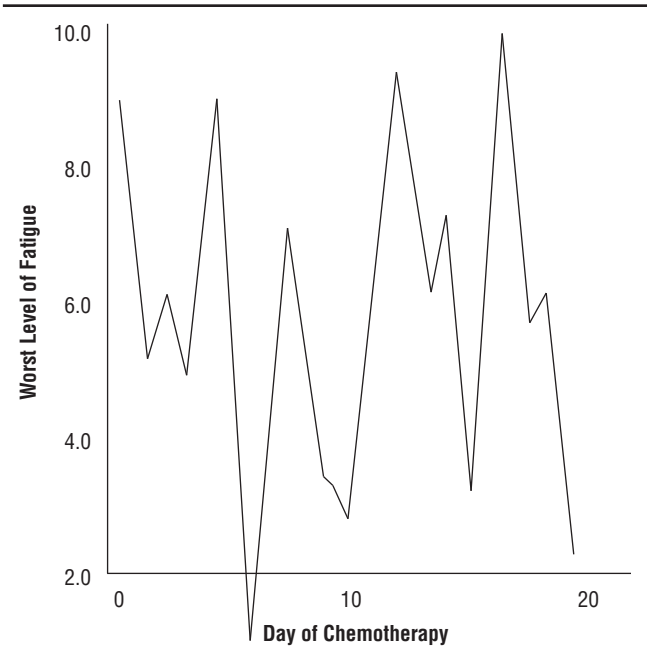


Figure 4. Chaotic Pattern

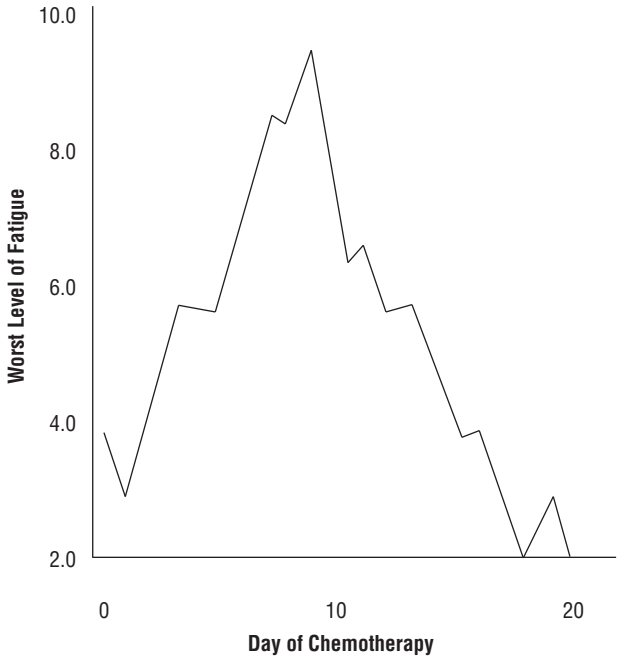


Figure 5. Step-Up Evaluation Followed by a Gradual Decline

Model B). The cubic change trajectory is characterized by having two stationary points; shown as one peak and one trough in Figure 6. The cubic function of time exhibited that fatigue peaked immediately (within 24 hours) after the chemotherapy administration, gradually declined over time, and then elevated slightly days before the next cycle of chemotherapy (see Figure 6).

A linear change trajectory in worst levels of fatigue also was observed in the entire sample (see Table 2, Model C). The estimated worst fatigue on the treatment day for the women was 5.7. The predicted daily rate of change in worst fatigue was –0.103 ($p < 0.001$). Similar to average fatigue, levels of worst fatigue declined over time but the rate of change was slightly greater. Results also demonstrated a quadratic change trajectory of worst fatigue during the third cycle of chemotherapy (see Table 2, Model D). The quadratic function of time suggested that rate of change in fatigue was either accelerated or decelerated over time. As shown in Figure 7, worst fatigue peaked right after chemotherapy and then decreased and decelerated over time.

Exercise and Fatigue

No significant differences were found between the women who exercised and those who did not exercise on a variety of characteristics, including age, education, marital status, living arrangement, employment status, menopausal status, cancer stage, and treatment regimen ($p > 0.05$). Exercise status was used as a factor to predict average and worst levels of fatigue during the third chemotherapy cycle. A significant linear change trajectory was observed in average and worst fatigue when using exercise as a predictor (see Table 2, Models E and F). The predicted average and worst level of fatigue on the day of chemotherapy for nonexercisers was 4.7 and 6.2, respectively. Nonexercisers experienced higher average fatigue ($p < 0.01$) and higher worst fatigue ($p < 0.01$) than exercisers. Average and worst fatigue declined over time ($p < 0.001$), but the decreases were not significantly different

Table 2. Results of Fitting Multilevel Model for Change to Average and Worst Fatigue

	Parameter Estimate	Model A	Model B	Model C	Model D	Model E	Model F	Model G	Model H
Initial status	Intercept	3.428** (20.216)	3.362** (19.568)	4.710** (22.196)	4.585** (21.384)	3.892** (18.136)	5.205** (18.609)	2.806** (5.235)	4.213** (6.287)
	Exercise	–	–	–	–	–1.117** (–3.423)	–1.181** (–2.778)	–	–
	Chemotherapy type	–	–	–	–	–	–	0.456 (1.092)	0.303 (0.581)
Rate of change	Day (linear slope)	–0.086** (–6.821)	–0.115** (–7.066)	–0.103** (–7.646)	–0.101** (–7.426)	–0.085** (–6.532)	–0.103** (–7.435)	–0.038 (–0.956)	–0.041 (–0.981)
	Day x day (quadratic slope)	–	0.002* (2.428)	–	0.004** (3.788)	–	–	0.013** (4.967)	0.016** (5.407)
	Day x day x day (cubic slope)	–	0.0005* (2.921)	–	–	–	–	–	–
	Day by chemotherapy type interaction	–	–	–	–	–	–	–0.039 (–1.268)	–0.049 (0.142)
	Day x day by chemotherapy type interaction	–	–	–	–	–	–	–0.009** (–4.473)	–0.010** (–4.421)

* $p < 0.01$; ** $p < 0.001$

Note. Values in columns are estimated effects of predictors on the change trajectory; values in parentheses are t statistics; day, as a time predictor, is centered on day 10 to simplify interpretation of intercept

Note. Model A predicts change trajectories of average fatigue as a linear function of day. Model B predicts change trajectories of average fatigue as a cubic function of day. Model C predicts change trajectories of worst fatigue as a linear function of day. Model D predicts change trajectories of worst fatigue as a quadratic function of day. Model E examines whether linear change trajectory of average fatigue differs by exercise status. Model F examines whether linear change trajectory of worst fatigue differs by exercise status. Model G examines whether quadratic change trajectory of average fatigue differs by type of chemotherapy. Model H examines whether quadratic change trajectory of worst fatigue differs by type of chemotherapy.

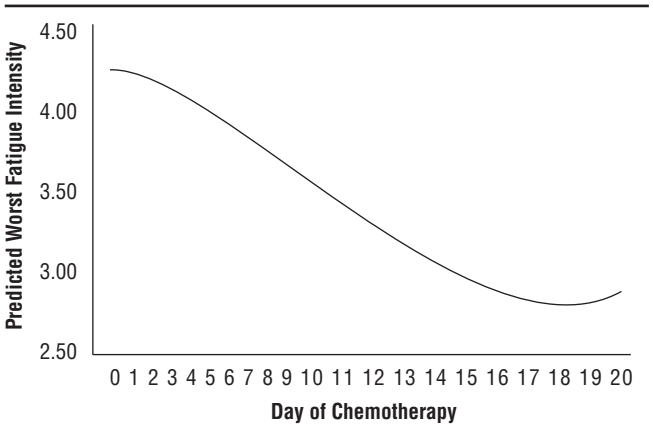


Figure 6. Overall Pattern of Average Fatigue

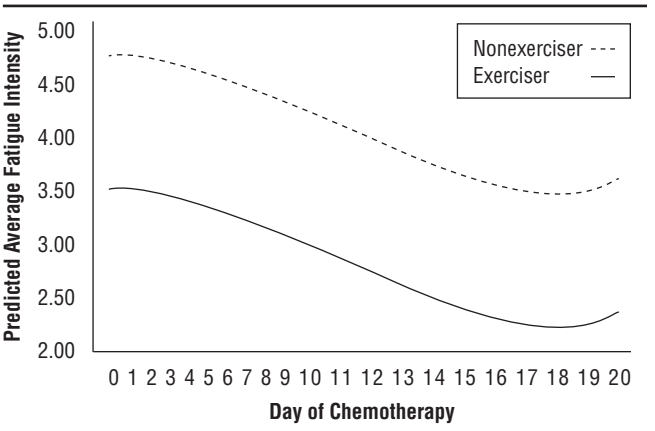


Figure 8. Average Fatigue by Exercise Status

between exercisers and nonexercisers. Results also demonstrated parallel cubic change trajectories of average fatigue in exercisers and nonexercisers (see Figure 8). Average fatigue peaked right after chemotherapy and a trough a few days before the next cycle. Similarly, parallel quadratic change trajectories of worst fatigue also were observed in exercisers and nonexercisers (see Figure 9). Worst fatigue reached a peak immediately after chemotherapy and then decreased and decelerated over time. Although overall patterns of change were similar, nonexercisers were consistantly higher in average and worst levels of fatigue than exercisers.

Chemotherapy Regimen and Fatigue

No significant differences were found between the women who were treated with AC and non-AC chemotherapy protocols on a variety of characteristics, including age, education, marital status, living arrangement, employment status, menopausal status, and cancer stage ($p > 0.05$).

Results of multilevel models, using chemotherapy regimen as a predictor, demonstrated a quadratic change trajectory of average and worst fatigue during the third cycle of chemotherapy (see Table 2, Models G and H). The estimated average and worst fatigue on day 10 did not differ significantly between women treated with AC versus non-AC regimens ($p = 0.277$ for average fatigue, $p = 0.562$ for worst fatigue). A significant interaction of chemotherapy regimen by time was observed in average and worst fatigue ($p < 0.001$). Average and worst levels of fatigue declined over time for all women but the patterns of change in fatigue varied depending on types of chemotherapy regimens the women received (see Figures 10 and 11). The overall patterns of change trajectory were similar between average and worst fatigue. The fatigue trajectories in the women treated with AC regimens were convex to the time axis, with a single trough toward the end of the cycle. The fatigue trajectories in the women treated with non-AC regimens were concave to the time axis, with a single peak near the beginning of the cycle.

Discussion

This study is among the first to report nonlinear effects of time on CRF supported by statistical evidence. A cubic and quadratic change trajectory summarized the daily average and worst levels of fatigue over the third chemotherapy cycle in women with breast cancer. The average levels of fatigue reached a peak on the treatment day followed by a gradual decline and a slight elevation two to three days before the fourth chemotherapy treatment. The worst levels of fatigue peaked immediately after chemotherapy and then decreased and decelerated over time. The patterns of change in fatigue were similar between exercisers and nonexercisers, but nonexercisers consistantly reported higher fatigue levels during the third cycle of chemotherapy.

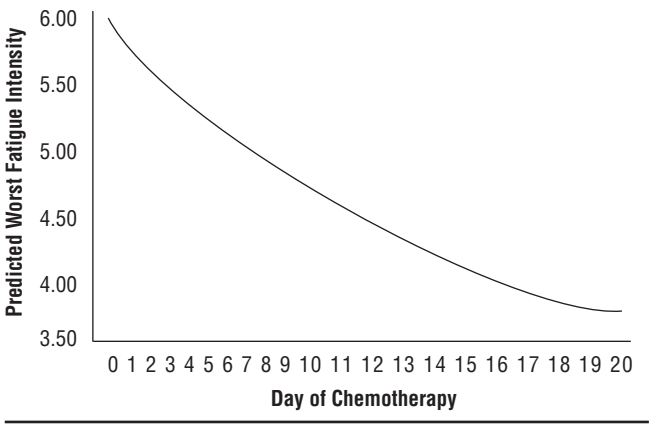


Figure 7. Overall Pattern of Worst Fatigue

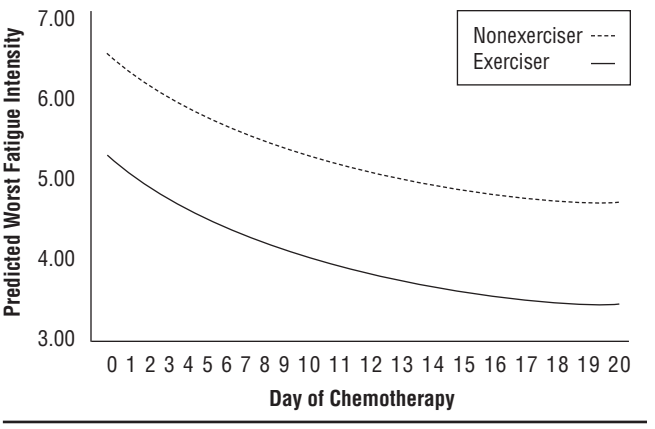
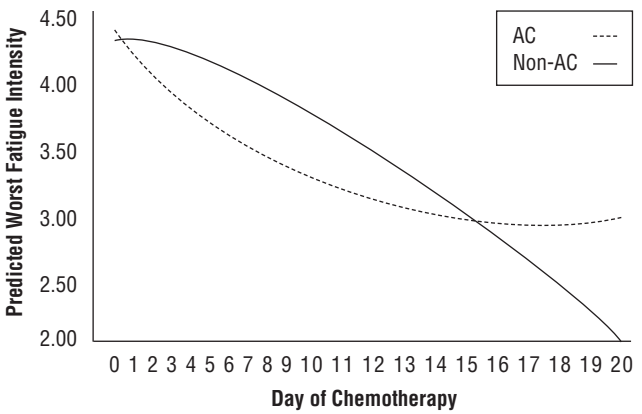


Figure 9. Worst Fatigue by Exercise Status



AC—doxorubicin and cyclophosphamide

Figure 10. Average Fatigue by Chemotherapy Regimen

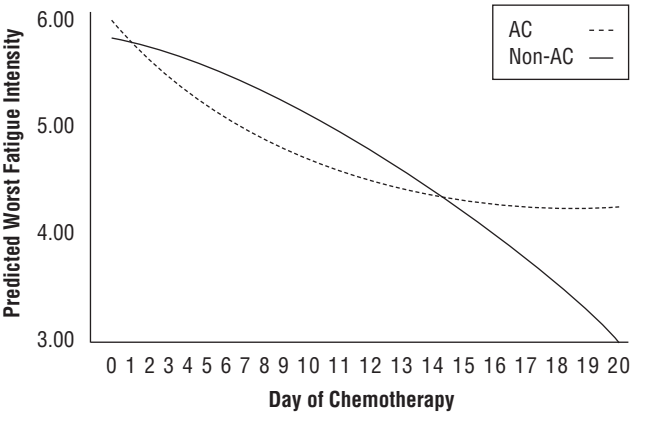
The linear multilevel models also allow researchers to predict the direction and magnitude of hypothesized effects of time on fatigue in the population. The predicted average and worst levels of fatigue on the treatment day for the patients receiving chemotherapy was 4.3 and 5.7 on a 0–10 scale. Levels of fatigue decreased by 0.1 each day during the third chemotherapy cycle. The results indicate that women with breast cancer experience moderate fatigue on the day they receive chemotherapy. The average levels of fatigue steadily decrease and become mild after two weeks. Although the worst levels of fatigue also decline as days go by, the intensity remains moderate. When exercise status is considered, the women who did not exercise experienced average and worst fatigue of 4.7 and 6.2 on the day of chemotherapy. Nonexercisers generally scored 1.1 and 1.2 higher in average and worst fatigue than exercisers.

The most common pattern showed by the graphic displays was an immediate increase in fatigue after chemotherapy followed by a gradual decline over time, which was statistically confirmed by multilevel models. Consistent with previous studies, the level of fatigue is most intense in the first two days (the first 24–48 hours) after chemotherapy (Berger, 1998; Schwartz, 2000) and then gradually decreases in subsequent days (de Jong et al., 2006; Miller, Maguire, & Kearney, 2007; Molassiotis & Chan, 2001). In contrast to the common perception (Richardson et al., 1998), fatigue in this sample was not increased at hematologic nadir. The finding that average levels of fatigue start to increase 2–3 days before the next chemotherapy cycle has been documented in the literature (de Jong et al., 2006; Richardson et al.). Psychological factors and patients' anticipation were suggested to play a part in experiencing increased fatigue before subsequent cycles of chemotherapy (Richardson et al.). Women who have multiple roles may be busy completing tasks or making arrangements prior to their treatment because they expect to be less energetic for a few days after chemotherapy.

The patterns of fatigue differed by the chemotherapy regimens. The finding suggests that fatigue of AC regimens may be more severe, especially for the first three days after treatment, and more prolonged than those of non-AC regimens. The peak fatigue levels appeared to be higher in the women treated with AC regimens than those treated with non-AC regimens. Average and worst levels of fatigue in women treated with AC regimens decreased over time, but the decrease was not as great as for those treated with non-AC regimens. A noticeable difference was observed a few days before the next chemotherapy. Although levels of fatigue in the women with non-AC regimens continued descending, fatigue in women with AC regimens reached a plateau and stopped decreasing. The women treated with AC regimens experienced higher levels of fatigue by the end of the cycle. It should be noted that in the present study, the non-AC group was smaller, which might influence the results. However, types of chemotherapy may still contribute to the differences in fatigue. The effect of different chemotherapy regimens, such as doxorubicin-containing regimens, on the course of fatigue is not yet clear and should be examined further.

Changes in trajectories were different between average and worst fatigue over the third chemotherapy cycle. Although the levels of average and worst fatigue usually were highly related, they did not change in the same way over time. Perhaps average and worst fatigue are representing different aspects of the symptom and should not be analyzed and interpreted as the same entity. This study illustrates the importance of considering the trajectory of fatigue when descriptively or experimentally studying fatigue in patients receiving chemotherapy. Researchers who are seeking to document the severity or test the effectiveness of an intervention will gain different impressions depending on when fatigue is measured. In summary, the ability to detect changes in CRF is complicated by the characteristic of the instrument, frequency of measurement, and timing related to the disease and treatment trajectory when data are obtained.

This study confirmed the roller coaster pattern of CRF and also provided greater detail of the fluctuations in fatigue in relation to the chemotherapy administration. The longitudinal design adopted in the current study was successful in capturing the fatigue trajectory over time. To reduce the variability in time, the women completed the fatigue diary at the same time each day through out the study period. Simplicity of the diary successfully enabled the researchers to obtain numerous repeated measures of fatigue experienced by the patients undergoing chemotherapy. The daily measurement of fatigue over 21 days provided sufficient evidence to support the validity of the longitudinal conclusions. The detailed longitudinal data were analyzed descriptively in conjunction with the advanced statistical techniques. The findings contribute to the current knowledge in daily patterns of fatigue with exercise behaviors and with different chemotherapy regimens.



AC—doxorubicin and cyclophosphamide

Figure 11. Worst Fatigue by Chemotherapy Regimen

Limitations

Despite these strengths, the study did have some limitations. Like most of the studies in fatigue, the study sample consisted of female outpatients with breast cancer. Patients with other types of cancer and those with more advanced illness and possibly worse fatigue experiences were not recruited. The study did not explore the fatigue experience at different times during the day, which may result in an incomplete view of this symptom. With the absence of baseline fatigue data before chemotherapy, it is unknown whether fatigue had returned to the pretreatment levels by the end of the cycle. How much fatigue had increased after chemotherapy also is unknown. Fatigue was measured unidimensionally. Interpretations of the findings must be considered within this limitation. Filling in the diary each day can create a certain routine and patients may unconsciously reset their interpretation of fatigue over time. As a result, the data may not fully reflect the range of fatigue experienced by the women. Finally, lengths of a cycle of chemotherapy vary depending on type of regimen. In this analysis, comparisons were limited to the first 21 days. Some of the data (e.g., the data in 28-day regimens) (Med n = 16) were not fully analyzed, which may distort the results.

Findings in this study provide a beginning for future studies. This study examined the course of fatigue between the third and fourth treatments of chemotherapy. Future studies need to test whether the patterns of fatigue found in this study can be replicated in other chemotherapy cycles. Longitudinal studies of fatigue trajectories across chemotherapy cycles are needed to assist planning fatigue interventions. The effectiveness of exercise behaviors on fatigue requires further investigation. The dosage and timing of exercise therapy on CRF are to be determined. Exploring the change trajectory in pathophysiologic factors in relation to levels of fatigue may help in identifying the underlying mechanisms of CRF and developing interventions that are effective in relieving fatigue.

Nursing Implications

Recommendations for clinical practice can be drawn upon the findings of this study. Patients with breast cancer are likely to experience moderate levels of fatigue on the day they receive the third cycle of IV chemotherapy. In practice, multiple treatment-related and educational activities often are arranged for the day patients receive chemotherapy. Given the high level of fatigue on the day of treatment, oncology nurses need to be aware of patients' fatigue levels and arrange the activities accordingly. The effectiveness of patient education or instruction given on the treatment day needs to be evaluated. Oncology nurses may want to review the content with patients later in the cycle when patients are less fatigued.

Fatigue is at its worst during the first 24–72 hours after chemotherapy and then declines gradually in subsequent days. The average levels of fatigue become mild after two weeks while the intensity of worst levels of fatigue remains moderate over time. Patients may experience a slight increase in fatigue two to three days before the subsequent cycle of chemotherapy. This information should be communicated routinely to patients so that they have knowledge about what to anticipate and can make plans for the days when they are most at risk for experiencing fatigue. Furthermore, individual variation is observed among the five illustrated fatigue trajectories. The difference suggests that unified educational information may not be sufficient in preparing patients for chemotherapy. Given the findings that patterns of fatigue differed by chemotherapy regimens, a more valuable approach would involve tailoring information for individual patient with the consideration of treatment-related factors as well as other factors, such as exercise status, to provide individualized patient education.

This study furthers the understanding of the pattern of fatigue and the effect of exercise and chemotherapy. Understanding the trajectory of CRF is fundamental in determining the timing of interventions and measurement of outcomes. Information on the pattern of fatigue is crucial in preparing patients for chemotherapy. Patients will have knowledge about what to anticipate and they will be able to make plans for those days when they are most likely to experience fatigue.

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