# Predictors of Fatigue 30 Days After Completing Anthracycline Plus Taxane Adjuvant Chemotherapy for Breast Cancer

Kimberly K. Wielgus, PhD, APRN, BC, Ann M. Berger, PhD, RN, AOCN®, FAAN, and Melody Hertzog, PhD



**Purposes/Objectives:** To identify the predictors of fatigue 30 days after completing adjuvant chemotherapy for breast cancer and whether differences are observed between a behavioral sleep intervention and a healthy-eating attention control group in predicting fatigue.

**Design:** Descriptive, exploratory, secondary analysis of a randomized clinical trial.

**Setting:** Outpatient oncology patients in a midwestern U.S. city.

**Sample:** 96 women, ages 29–83 years, 72% married, 95% white, diagnosed with stage I–IIIA breast cancer, receiving adjuvant anthracycline and taxane chemotherapy.

**Methods:** Participants were randomized to a behavioral sleep intervention group or an attention control group. Participants completed data collection prior to and during the peak and rebound days of the initial chemotherapy treatment cycle and after the last treatment.

**Main Research Variables:** Fatigue, circadian rhythms of activity, objective and subjective sleep-wake, and objective and subjective activity-rest.

**Findings:** Predictors of fatigue were less total sleep time prior to treatment, higher fatigue prior to treatment and at the peak, and less energy upon awakening on rebound days. In the control group, predictors of higher fatigue were higher fatigue prior to treatment, higher body mass index, higher number of positive lymph nodes, and less daytime dysfunction. For the intervention group, lower peak activity at the peak of initial treatment differentially predicted fatigue.

**Conclusions:** Results suggest the sleep intervention group participants who maintained activity balanced with sleep at the peak of the initial treatment benefited most from the intervention.

**Implications for Nursing:** Nurses should screen for fatigue prior to initial chemotherapy treatment and at regular intervals, further assess for poor sleep in patients who report fatigue of 4 or higher (on a 0–10 scale), and use evidence-based guidelines to select appropriate interventions.

Breast cancer is the most common type of cancer in women in the United States (Jemal et al., 2008). Women treated with adjuvant chemotherapy for breast cancer of all stages have an 89% five-year survival rate (Jemal et al). Taxane chemotherapy increasingly is used to improve survival (Ferguson, Wilcken, Vagg, Ghersi, & Nowak, 2007); however, chemotherapy can result in distressful, debilitating fatigue in approximately a third of survivors that persists for years after completing treatment (Bower et al., 2006; National Comprehensive Cancer Network [NCCN], 2008). As the number of breast cancer survivors who have received adjuvant chemotherapy increases, improving fatigue and other symptoms becomes increasingly important to optimize quality of life (Andrykowski, Schmidt, Salsman, Beacham, & Jacobsen, 2005; Janz et al., 2007; Lee, Cho, Miaskowski, & Dodd, 2004).

Fatigue is defined by NCCN (2008) as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness, or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (p. FT1). Cancer-related fatigue has been associated with disrupted circadian rhythms, disturbed sleep-wake, and activity rest (Ancoli-Israel et al., 2006; Berger & Farr, 1999). Gaps exist in knowledge regarding the predictability of these rhythms and patterns prior to and during the initial chemotherapy treatment as they affect fatigue after treatment.

The current study attempted to answer a clinically significant question: At the initiation of chemotherapy, can clinicians predict who will experience greater fatigue 30 days after completing chemotherapy? This knowledge is important for clinicians to identify women with breast cancer who are most in need of interventions to prevent persistent, debilitating fatigue. Currently, the strongest evidence-based intervention that has been recommended for practice by the Oncology Nursing Society's (ONS's) Putting Evidence into Practice® (PEP) card (Mitchell, Beck, Hood, Moore & Tanner, 2006) and NCCN (2008) to treat fatigue is exercise and activity enhancement. Interventions to promote healthy circadian rhythms of activity, sleep-wake, activity-rest patterns potentially may reduce fatigue's dramatic effect on

women's physical and social functioning, quality of life, and disability (NCCN; Prue, Rankin, Allen, Gracey, & Cramp, 2006). This randomized controlled trial (RCT) was developed after pilot testing the feasibility and outcomes and revision of a behavioral sleep intervention (Berger et al., 2002, 2003).

## Conceptual Framework

The conceptual framework for the current study (see Figure 1) was derived from the Integrated Fatigue Model (IFM) (Piper et al., 1998; Piper, Lindsey, & Dodd, 1987). The components from the IFM that were proposed to influence fatigue were regulation and transmission (circadian rhythms of activity), sleep-wake, and activity-rest patterns.

The purposes of the study were to identify the predictors of fatigue 30 days after completing anthracycline plus taxane adjuvant chemotherapy for breast cancer using fatigue, circadian rhythms of activity, sleep-wake, activity-rest, and demographic and medical variables measured prior to and during the peak and rebound of the initial chemotherapy treatment and to determine whether differences exist between a behavioral sleep intervention group and a healthy eating attention control group in predicting fatigue 30 days after completing chemotherapy treatments.

## Methods

The current descriptive, exploratory study was a secondary analysis of data from an RCT that tested a behavioral sleep intervention compared to a healthy eating attention control in women with stages I–IIIA breast cancer at initiation of chemotherapy. For the secondary analysis, participants completed data collection prior to (days –2 to –1) and during the peak (days 2–4) and rebound (days 5–7) of the initial chemotherapy treatment and for 7 days 30 days after the last chemotherapy treatment.

### Setting and Sample

The RCT recruited participants (N = 219) from outpatient oncology clinics in a large midwestern city. Inclusion criteria for the RCT were women ages 19 and older who were diagnosed for the first time with stage I, II, or IIIA breast cancer; were post-breast cancer surgery (lumpectomy or mastectomy with or without reconstruction); were scheduled to begin adjuvant anthracycline-based IV chemotherapy for breast cancer; were English-speaking; and had a Karnofsky Performance Scale (KPS) score of greater than or equal to 60. Exclusion criteria were unstable comorbidities and an erratic sleep schedule (rotating shift worker).

Only findings from the participants who received anthracyclines plus taxanes are reported in the secondary analysis. Of the 103 eligible participants, 96 who provided data prior to and at peak and rebound days of the initial chemotherapy treatments, are included in the analysis.

As an exploratory study, choice of predictors was driven by the data as well as by theory. Probability values (and significance tests) are not accurate in this situation, but power still was estimated to help identify a reasonable model size. A model with 28 predictors (up to 14 predictors and their product variables) that explains 40% of the variance will have power of 0.80 to test individual predictors that uniquely explain at least 3% of the variance if using a liberal alpha level of 0.20.

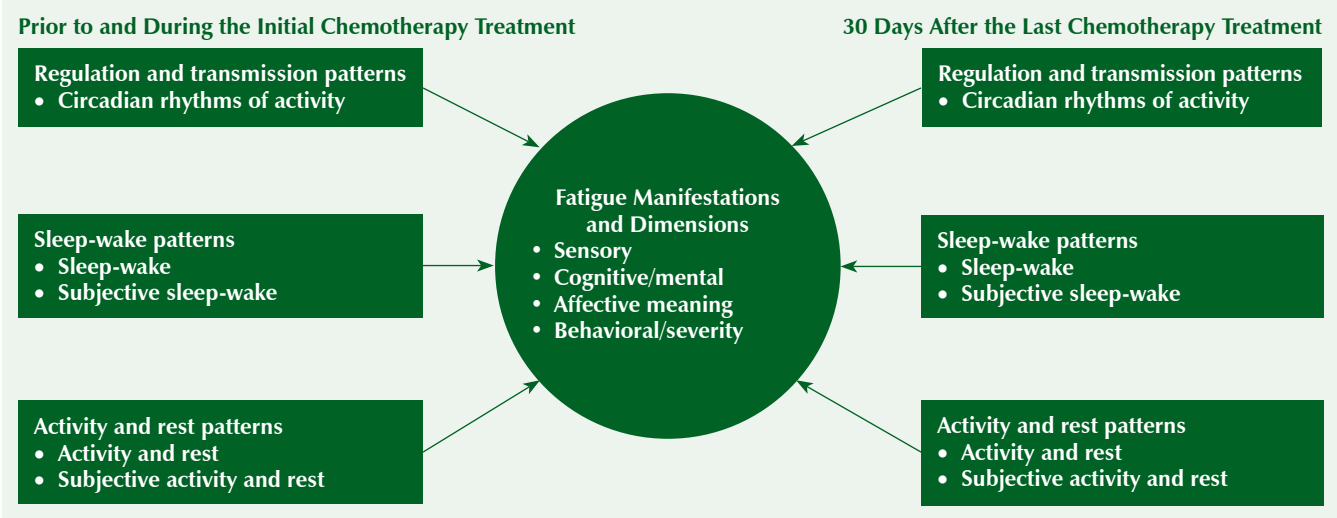


**Figure 1. Conceptual Model of Factors Influencing Fatigue Experienced by Women With Stage I, II, or IIIA Breast Cancer**

*Note*. Copyright 1987 by Barbara F. Piper. Adapted with permission.

## Measurement of Variables

Measurements and timing of the key variables used in the current study are shown in Table 1.

**Fatigue:** Fatigue was measured using the 22-item multidimensional revised **Piper Fatigue Scale (PFS)** (Piper et al., 1998). The 22 numerically scaled (0–10) items with word anchors measure four dimensions of subjective fatigue (behavioral/severity, sensory, cognitive/mood, and affective meaning). Excellent validity and reliability have been reported (Fu, LeMone, McDaniel, & Bausler, 2001; Piper et al., 1998). High estimates of internal consistency reliability (Cronbach alpha) have been reported for the subscales and total PFS scores in women with early-stage breast cancer (Berger, 1998; Berger et al., 2002). Cronbach alpha in the study for the total PFS score ranged from 0.97–0.98.

**Circadian rhythms of activity and objective sleep-wake and activity-rest: Octagonal Motionlogger™ actigraphs** (Ambulatory Monitoring, Inc.) were used to quantify the movements of the wrist to yield circadian rhythms of activity, sleep-wake, and activity-rest indicators (Mormont et al., 2000). They determine sleep versus activity based on the assumption that individuals move less when asleep and more when awake (Ambulatory Monitoring, Inc., 2005; Ancoli-Israel et al., 2003). The device is the size of a man's wristwatch and is worn on the nondominant wrist. The actigraphs recorded activity counts in one-minute epochs (intervals) per recent guidelines (Littner et al., 2003). Actigraphs have been reported to have 88% accuracy at distinguishing wakefulness from sleep when compared to the gold standard of polysomnography (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992; Mullaney, Kripke, & Messin, 1980). The definitions of specific actigraphy variables are shown in Figure 2.

**Subjective sleep-wake:** An item from the daily diary, measuring "energy upon awakening," was used to measure subjective sleep-wake. The item asked the participants to rate from 1–5 "When I got up this morning, I felt___" (1 = exhausted, 5 = refreshed). Each morning of data collection, information about the prior night's bed time and morning wake time also were recorded in the daily diary, and the times were used to distinguish day and night intervals in actigraphy files (Littner et al., 2003).

**Table 1. Data Collection Timetable**

| Variable Group | Measurement | Prior[a] | Peak[b] | Rebound[c] | Completion[d] |
|---|---|---|---|---|---|
| **Fatigue** | PFS | Day –2 | Day 3 | – | Day 1 |
| **Circadian rhythms of activity** | Actigraphy[e] | 48 hours | 72 hours | 72 hours | 168 hours |
| Peak activity | | | | | |
| 24-hour autocorrelation | | | | | |
| **Objective sleep-wake** | Actigraphy[e] | 48 hours | 72 hours | 72 hours | 168 hours |
| Total sleep time | | | | | |
| **Subjective sleep-wake** | | | | | |
| Energy upon awakening | Daily diary | Two days from daily diary[f] | Three days from daily diary[f] | Three days from daily diary[f] | Seven days from diary[f] |
| Daily dysfunction | PSQI | Day –2 | – | – | Day 1 |
| **Objective activity-rest** | Actigraphy[e] | 48 hours | 72 hours | 72 hours | 168 hours |
| Sleep percent (day) | | | | | |
| **Subjective activity-rest** | | | | | |
| PCS | PCS | Day –2 | – | – | Day 1 |
| **Demographic or medical characteristics** | | | | | |
| Body mass index | Medical record | Day 0 | – | – | – |
| Hemoglobin | Medical record | Day 0 | – | – | – |
| Lymph node status | Medical record | Day 0 | – | – | – |
| KPS | KPS | Day –2 | – | – | – |

[a] Two-day measurement period prior to receiving the initial chemotherapy treatment
[b] Three-day measurement period during days 2–4 of the initial chemotherapy treatment; PFS measured on day 3
[c] Three-day measurement period during days 5–7 of the initial chemotherapy treatment
[d] Seven-day measurement period 30 days following completion of the last chemotherapy treatment
[e] Wrist actigraphy—worn continuously
[f] Mean of daily values
KPS—Karnofsky Performance Scale; PCS—Physical Component Summary of the SF-36®, version 2; PFS—Piper Fatigue Scale; PSQI—Pittsburgh Sleep Quality Index

**24-Hour Autocorrelation**
The extent to which activity levels within 24 hours correlate with levels of another 24 hours (Lentz, 1990); this serves as an index of robustness of the circadian rhythm (Ambulatory Monitory, Inc., 2005; Rich et al., 2005).

**Peak Activity**
Mean activity level plus the highest activity level of an individual's circadian rhythm of activity (Lentz, 1990)

**Sleep Percent (Day)**
The total number of minutes of sleep during the day divided by the total wake time (Young-McCaughan et al., 2003).

**Total Sleep Time**
The number of minutes asleep while in bed (Berger et al., 2005)

**Figure 2. Definitions of Variables Obtained by Actigraphy**

Subjective sleep-wake during the prior month was measured using the **Pittsburgh Sleep Quality Index (PSQI)** (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). A 19-item questionnaire, the PSQI yields a global score and seven component scores, one of which is daytime dysfunction. Each item is rated on a 0–3 scale with global scores ranging from 0–21. Higher scores indicate poorer sleep quality. Excellent internal reliability consistency (Cronbach alpha range 0.73–0.94) and construct validity (convergent, discriminant, and divergent) have been reported for a sample that included women with early-stage breast cancer (Berger et al., 2002; Carpenter & Andrykowski, 1998).

**Subjective activity-rest:** The **Physical Component Summary (PCS) of the SF-36®, version 2** (Ware, Kosinski, & Dewey, 2000) was used to measure subjective activity-rest. Internal consistency (Cronbach alpha) was calculated for each of the SF-36 subscales because it is inappropriate to calculate internal consistency on the PCS with its positive and negative weighting. In the sample, Cronbach alpha for the subscales ranged from 0.69–0.93.

**Demographic and medical characteristics:** This form included the demographic and medical characteristics of the sample. Medical charts were reviewed by research nurses to obtain height, weight, and hemoglobin.

## Procedure for Data Collection

The study was approved by a university institutional review board. Participants were randomized to the behavioral sleep intervention group or the healthy-eating, attention control group. Group randomization was stratified by number of planned chemotherapy treatments (4 or > 4) and self-identified type of sleeper (good or poor), using item number 6 from the PSQI. Data collection procedures were identical for the two groups with the exception of the forms used for delivery of the intervention. The intervention group received the behavioral sleep intervention from a trained research nurse. The behavioral sleep intervention involved developing an Individualized Sleep Promotion Plan (ISPP) that consisted of sleep restriction, stimulus control, relaxation therapy, and sleep hygiene counseling. The intervention was implemented at the first visit, reinforced on day 8 of each treatment, and revised 2 days prior to each subsequent treatment and at 30, 60, and 90 days after completing chemotherapy. Additional intervention details are described in the pilot study reports (Berger et al., 2002; 2003). Participants in the control group were given equal time and attention and new information about healthy eating and general conversation at each visit.

## Statistical Analysis

SPSS® 13.0 for Microsoft® Windows® was used to perform the statistical analysis. To address the first purpose of the study, zero-order correlations were used to evaluate predictors for inclusion. Hierarchical multiple regression was used for exploratory model building to predict the levels of fatigue 30 days after completing chemotherapy treatment from predictors chosen from the study variables and sample characteristics.

To address the second purpose of the study, the regression model was extended by adding calculated product variables for each of the continuous predictors. To reduce the multicollinearity likely to occur with inclusion of product variables, predictors were centered by subtracting the mean of a variable from the variable's value (Cohen, Cohen, West, & Aiken, 2002) prior to multiplication by the dummy-coded grouping variable.

# Results

The 96 women included in the sample ranged in age from 29–83. The typical participant was married, living with someone who was not a dependent, and White non-Hispanic. All received anthracycline-based (doxorubicin) adjuvant chemotherapy regimens for breast cancer plus a taxane; some received standard dosing (every three weeks) and others received dose dense (every two weeks) chemotherapy. Demographic characteristics of the sample are shown in Table 2. The two groups did not significantly differ prior to starting chemotherapy treatment.

The correlation of each study variable with total PFS score at treatment completion was evaluated to select predictors. A significance level of $p \leq 0.20$ for the correlation was used as a cutoff for inclusion, following a model-building strategy outlined by Hosmer and Lemeshow (2000). Attention was given to selecting variables from each variable group included in the study. As indicated in the power analysis, the sample size of the secondary analysis constrained the number of predictors that could be included in the model. Multicollinearity among available variables presented an additional limitation. When

## Table 2. Demographic and Medical Characteristics of Sample

| Characteristic | Intervention (n = 53) | | | Control (n = 43) | | | Total (N = 96) | | |
|---|---|---|---|---|---|---|---|---|---|
| | $\bar{X}$ | SD | Range | $\bar{X}$ | SD | Range | $\bar{X}$ | SD | Range |
| Age (years) | 49.3 | 9.1 | 29–71 | 52.4 | 11.4 | 35–83 | 50.7 | 10.3 | 29–83 |
| Body mass index | 27.9 | 6.9 | 16–49 | 29.4 | 5.0 | 20–39 | 28.6 | 6.2 | 16–49 |
| Hemoglobin day 1[a] | 13.0 | 1.2 | 10.3–15.2 | 12.9 | 1.2 | 10.3–15.1 | 12.9 | 1.2 | 10.3–15.2 |
| **Characteristic** | **n** | **%** | | **n** | **%** | | **n** | **%** | |
| **Race** | | | | | | | | | |
| Black | 2 | 4 | | 3 | 7 | | 5 | 5 | |
| White | 51 | 96 | | 40 | 93 | | 91 | 95 | |
| **Ethnicity** | | | | | | | | | |
| Hispanic | 1 | 2 | | 2 | 5 | | 3 | 3 | |
| Non-Hispanic | 52 | 98 | | 41 | 95 | | 93 | 97 | |
| **Marital status** | | | | | | | | | |
| Single or never married | 6 | 11 | | 4 | 9 | | 10 | 10 | |
| Married | 37 | 70 | | 32 | 74 | | 69 | 72 | |
| Separated or divorced | 9 | 17 | | 4 | 9 | | 13 | 14 | |
| Widowed | 1 | 2 | | 3 | 7 | | 4 | 4 | |
| **Employment** | | | | | | | | | |
| Professional | 25 | 47 | | 16 | 37 | | 41 | 43 | |
| Service | 13 | 25 | | 16 | 37 | | 29 | 30 | |
| Homemaker | 8 | 15 | | 2 | 5 | | 10 | 10 | |
| Retired | 5 | 9 | | 7 | 16 | | 12 | 13 | |
| Unemployed | 2 | 4 | | 1 | 2 | | 3 | 3 | |
| Student | – | – | | 1 | 2 | | 1 | 1 | |
| **Karnofsky Performance Scale score** | | | | | | | | | |
| 60 | 1 | 2 | | – | – | | 1 | 1 | |
| 70 | 2 | 4 | | 2 | 5 | | 4 | 4 | |
| 80 | 5 | 9 | | 5 | 12 | | 10 | 10 | |
| 90 | 17 | 32 | | 15 | 35 | | 32 | 33 | |
| 100 | 28 | 53 | | 21 | 49 | | 49 | 51 | |
| **Cancer stage** | | | | | | | | | |
| I | 3 | 6 | | 5 | 12 | | 8 | 8 | |
| II | 39 | 74 | | 27 | 63 | | 66 | 69 | |
| IIIA | 11 | 21 | | 11 | 26 | | 22 | 23 | |
| **Lymph node status** | | | | | | | | | |
| Negative | 12 | 23 | | 13 | 30 | | 25 | 26 | |
| Positive 1–3 | 32 | 60 | | 20 | 47 | | 52 | 54 | |
| Positive 4–9 | 9 | 17 | | 10 | 23 | | 19 | 20 | |
| **Surgical procedure** | | | | | | | | | |
| Lumpectomy | 20 | 38 | | 18 | 42 | | 38 | 40 | |
| Modified mastectomy | 13 | 25 | | 12 | 28 | | 25 | 26 | |
| Modified mastectomy with reconstruction | 20 | 38 | | 13 | 30 | | 33 | 34 | |
| **Chemotherapy protocol** | | | | | | | | | |
| Adriamycin and cytoxan times four followed by taxane times four every two weeks | 33 | 62 | | 26 | 61 | | 59 | 62 | |
| Adriamycin and cytoxan times four followed by taxane times four every three weeks | 13 | 25 | | 9 | 21 | | 22 | 23 | |
| Adriamycin and cytoxan times four every three weeks followed by taxane every week times 12 | 4 | 8 | | 4 | 9 | | 8 | 8 | |
| Adriamycin and cytoxan times four every two weeks followed by taxane every week times 12 | 2 | 4 | | 3 | 7 | | 5 | 5 | |
| Adriamycin and cytoxan times six followed by taxane times four every two weeks | 1 | 2 | | – | – | | 1 | 1 | |
| Adriamycin and cytoxan times four every two weeks followed by taxane times four every three weeks | – | – | | 1 | 2 | | 1 | 1 | |

[a] N = 82 because of missing data.

*Note*. Because of rounding, not all percentages total 100.

*Note*. No significant differences between groups on any variable at alpha = 0.05

predictors within a variable group and measured at the same time were highly correlated with each other, the one with the strongest correlation with fatigue 30 days after completing treatment was selected.

A total of 13 predictors were included in the prediction model along with a dummy-coded variable representing the RCT group assignment (0 = intervention). Predictor variables measured prior to chemotherapy were fatigue (PFS), body mass index (BMI), hemoglobin, lymph node status, daytime dysfunction (PSQI), PCS, KPS score, and total sleep time at night (actigraph).Variables measured at the peak were fatigue (PFS) and peak activity (actigraph). Variables measured at the rebound were 24-hour autocorrelation (actigraph), energy upon awakening (daily diary), and sleep percent during the day (actigraph). Table 3 details the descriptive statistics of the 13 predictors as well as the zero-order correlations of the predictors with the outcome of fatigue 30 days after completing treatment.

Of the 96 participants included in the secondary analysis, 60 had complete data; 35 cases were missing a few values, usually on 1 or 2 variables. One case had missing values on multiple variables and, therefore, was excluded. Those with missing data differed ($p < 0.20$) from those with complete data on day 1 hemoglobin ($p = 0.03$), PCS prior to treatment ($p = 0.13$), and amount of energy upon awakening at rebound ($p = 0.11$). Missing values were imputed using the expectation maximization in SPSS Missing Values Analysis 13.0 module, which assumes data are missing at random. To strengthen the imputation model, a small number of additional variables correlated with the predictors having incomplete data were included in calculation of missing values (Collins, Schafer, & Kam, 2001). To preserve possible interactions of the intervention group with other predictors, imputation was conducted for each group independently and then combined into a single dataset.

The list of predictors was organized temporally into four groups for entry into the hierarchical regression model, with the intervention group added at a fifth step. This allowed evaluation of whether factors occurring at later points added significantly to what could be explained by previously existing characteristics.

## Multiple Regression Results of Fatigue Regressed on Selected Predictors: Model 1

Because of the exploratory nature of the analysis, a liberal significance level of $p \leq 0.20$ was used to evaluate individual regression coefficients as well as changes in $R^2$ as sets of variables were added. Table 4 presents the model summary for each step of the model. Change in $R^2$ as sets of variables were added was significant only at step 1 ($p < 0.001$), in which variables measured prior to treatment were entered, and at step 3 ($p = 0.05$), in which fatigue and peak activity at the peak (days 2–4) were

**Table 3. Descriptive Statistics and Pairwise Correlations of 13 Predictors With Fatigue Measured 30 Days Following Completion of Chemotherapy Treatment by Groups**

| Measurement Time | Key Variables and Measurements | Study Groups | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Total[a] | | | Intervention[b] | | | Control[c] | | |
| | | $\bar{X}$ | SD | r | $\bar{X}$ | SD | r | $\bar{X}$ | SD | r |
| Prior | Fatigue (PFS total score) | 2.73 | 1.99 | 0.39*** | 2.89 | 2.01 | 0.35* | 2.53 | 1.98 | 0.46** |
| | Body mass index | 28.59 | 6.16 | 0.15 | 27.92 | 6.92 | 0.08 | 29.42 | 5.01 | 0.27 |
| | Day 1 hemoglobin | 12.94 | 1.18 | –0.19 | 12.96 | 1.21 | –0.21 | 12.93 | 1.15 | –0.15 |
| | Lymph node status | | | 0.10 | | | –0.04 | | | 0.23 |
| | Daytime (PSQI) dysfunction | 0.58 | 1.02 | 0.23* | 0.90 | 0.63 | 0.36* | 0.98 | 0.74 | 0.10 |
| | Physical component summary | 43.58 | 9.58 | –0.28* | 43.56 | 9.73 | –0.22 | 43.60 | 9.51 | –0.35* |
| | KPS score | – | – | –0.21* | – | – | –0.23 | – | – | –0.20 |
| | Total sleep time | 421.39 | 9.03 | –0.24* | 430.26 | 83.66 | –0.17 | 410.30 | 95.22 | –0.30 |
| Peak | Fatigue (PFS total score) | 4.85 | 2.23 | 0.33** | 5.00 | 2.24 | 0.39** | 4.68 | 2.22 | 0.27 |
| | Peak activity | 176.46 | 46.17 | –0.13 | 176.94 | 49.34 | –0.31* | 175.90 | 42.86 | 0.08 |
| Rebound | 24-hour autocorrelation | 0.43 | 0.16 | –0.24* | 0.43 | 0.17 | –0.32* | 0.41 | 0.15 | –0.16 |
| | Energy upon awakening | 3.41 | 0.92 | –0.35*** | 3.31 | 0.93 | –0.44** | 3.54 | 0.91 | –0.26 |
| | Sleep percent (day) | 11.47 | 8.77 | 0.18 | 12.24 | 10.01 | 0.39** | 10.58 | 7.08 | –0.11 |

[a] Total sample (N = 96) range of sample sizes for correlations was 77–89.

[b] Intervention group (n = 53) range of sample sizes for correlations was 40–48.

[c] Control group (n = 43) range of sample sizes for correlations was 38–41.

*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

KPS—Karnofsky Performance Scale; PFS—Piper Fatigue Scale; PSQI—Pittsburgh Sleep Quality Index

**Table 4. Model 1: Summary of Multiple Regression Results for Fatigue Regressed on Selected Predictors at Treatment Completion**

| Step | $R^2$ | Adjusted $R^2$ | $R^2$ Change | p ($R^2$ change) |
|---|---|---|---|---|
| 1 | 0.206 | 0.171 | 0.206 | < 0.001 |
| 2 | 0.256 | 0.187 | 0.050 | 0.227 |
| 3 | 0.306 | 0.224 | 0.050 | 0.053 |
| 4 | 0.335 | 0.228 | 0.029 | 0.323 |
| 5 | 0.339 | 0.223 | 0.004 | 0.510 |

N = 95

entered. In some cases, individual predictors were significant even when the test of the set of variables added was not.

Coefficients for Model 1 with all 14 predictors are presented in Table 5. Four variables were significant predictors of fatigue at treatment completion: fatigue prior to treatment (p = 0.007), total sleep time prior to treatment (p = 0.13), fatigue at the peak (p = 0.12), and amount of energy upon awakening at rebound (p = 0.09). Each of these variables also had been a significant predictor at the step in which it entered the model and remained so as other variables were added. The remaining variables were not significant at any step, with the exception of BMI. BMI was not significant in the final model (p = 0.59), but was significant (p < 0.12) when it entered the model in the first step. It no longer made a unique contribution once step 2 variables were added.

### Multiple Regression Results of Fatigue Regressed on Selected Predictors and Product Variables: Model 2

To evaluate whether relationships of the predictors and fatigue 30 days after completing chemotherapy varied by group, product variables were added in a sixth step. This resulted in large variance inflation factors (VIF), indicating high multicollinearity. Removing product variables with p values greater than 0.20 reduced VIF values with little effect on the regression coefficients of the remaining predictors. The reduced model is presented as Model 2 in Table 6.

Adding the five product variables significantly increased the $R^2$ by 0.10 (p = 0.03) to 0.440 (adjusted $R^2$ = 0.299, p < 0.001), suggesting significant differences between the groups in the relationships of some of the predictors with fatigue 30 days after completing treatment, controlling for other predictors in the model.

The only variable in the reduced model from the earlier steps that was significant independently was the amount of energy upon awakening at rebound (p < 0.02). Those with less energy upon awakening at rebound (days 5–7) had higher fatigue at treatment completion with no difference between groups. Although peak activity at the peak (days 2–4) was significant (p < 0.07), it was not interpreted because of its significant interaction with the group.

To interpret the group differences in prediction, separate regression coefficients for each predictor were calculated. The unstandardized coefficient for the original variable represents the relationship of that variable to fatigue 30 days after completing treatment for the intervention group (coded 0). The regression coefficient for the associated product variable indicates the amount that the control group's coefficient differs from that of the intervention group. Adding the two values yields the coefficient for the control group (coded 1). By running the model again with the coding reversed, a p value for the coefficient for the control group was obtained.

Higher fatigue prior to treatment was related significantly to higher fatigue 30 days after completing treatment in the control group (0.484, p < 0.001) but not in the intervention group (0.123, p = 0.46). A similar pattern was observed for BMI prior to treatment, with a significant positive relationship for the control group (0.097, p = 0.19) but not for the intervention group (–0.016, p = 0.72). More positive lymph nodes predicted higher fatigue at treatment completion in the control group (0.935, p = 0.04), but not in the intervention group (–0.441, p = 0.34). Lower daytime dysfunction (PSQI) prior to treatment predicted higher fatigue in the control group (–0.744, p = 0.11), but not in the intervention group (0.492, p = 0.39). Peak activity at the peak of treatment in the intervention group had a coefficient of –0.012 (p = 0.07), indicating that in the group, lower peak activity during the peak of the initial treatment predicted higher fatigue at treatment completion. The coefficient in the control group was not significant (0.008, p = 0.31).

## Discussion

This secondary analysis was able to identify the predictors of fatigue 30 days after completing anthracycline-based plus taxane adjuvant chemotherapy for breast cancer. Four predictors of higher fatigue 30 days after completing treatment were identified. These predictors were less total sleep time prior to treatment, higher fatigue prior to and at the peak of treatment, and less energy upon awakening at rebound from the initial treatment. Fatigue prior to treatment was the strongest predictor of later fatigue.

This is the first report that identifies predictors of fatigue 30 days after completing chemotherapy from measurements collected prior to and during the initial week of treatment.

Previous descriptive studies have reported associations between fatigue and other variables selected for inclusion in the secondary analysis. Ancoli-Israel et al. (2006) described patterns of fatigue, sleep, and circadian rhythms in 85 women with breast cancer prior to the

**Table 5. Model 1[a]: Multiple Regression Results of Fatigue Regressed on Selected Predictors 30 Days After Completing Chemotherapy Treatment**

| Step | Variable | Coefficient | | | |
|---|---|---|---|---|---|
| | | B | SE | Beta | p |
| Prior[b] | Fatigue (PFS Total) | 0.331 | 0.120 | 0.307 | 0.007** |
| | Body mass index | 0.021 | 0.038 | 0.058 | 0.587 |
| | Hemoglobin | –0.030 | 0.184 | –0.016 | 0.870 |
| | Lymph node status | 0.183 | 0.324 | 0.057 | 0.574 |
| Prior[b] | Daytime dysfunction (PSQI) | –0.120 | 0.353 | –0.037 | 0.735 |
| | PCS | –0.002 | 0.028 | –0.007 | 0.951 |
| | Karnofsky Performance Scale | –0.080 | 0.278 | –0.033 | 0.773 |
| | Total Sleep Time | –0.004 | 0.003 | –0.171 | 0.128* |
| Peak[c] | Fatigue (PFS Total) | 0.164 | 0.104 | 0.167 | 0.120* |
| | Peak activity | –0.004 | 0.005 | –0.087 | 0.423 |
| Rebound[d] | 24-hour autocorrelation | –1.009 | 1.852 | –0.071 | 0.587 |
| | Amount of energy upon awakening | –0.454 | 0.262 | –0.191 | 0.087* |
| | Sleep percent (day) | –0.007 | 0.034 | –0.028 | 0.832 |
| Grouping variable | Grouping variable | 0.272 | 0.412 | 0.062 | 0.510 |

N = 95

*p < 0.20; **p < 0.05

[a] $R^2_{(14,80)} = 0.339$, p = 0.001 (adjusted $R^2 = 0.223$)

[b] Two-day measurement period prior to receiving the initial chemotherapy treatment

[c] Three-day measurement period during days 2–4 of the initial chemotherapy treatment

[d] Three-day measurement period during day 5–7 of the initial chemotherapy treatment

PCS—Physical Component Summary of the SF-36®, version 2; PFS—Piper Fatigue Scale; PSQI—Pittsburgh Sleep Quality Index

*Note.* Table presents results for all predictors in model simultaneously in step 5.

initial chemotherapy treatment. Although no relationships were found between fatigue and circadian rhythms of activity and objective sleep-wake prior to initial treatment, significant relationships exist between fatigue and subjective sleep-wake and activity-rest measures. Berger (1998) described patterns of lower circadian rhythms of activity that were associated with higher fatigue during the first four days after the initial treatment. The current study is important because it adds to the understanding of the variables related to fatigue prior to and during initial chemotherapy that are predictive of fatigue after completion of chemotherapy treatment. This is an important area of study because receiving adjuvant chemotherapy, compared to radiation, has been shown to significantly predict higher fatigue at treatment completion (Andrykowski et al., 2005), and fatigue is the most common symptom reported by survivors (Janz et al., 2007).

The secondary analysis also determined the differences between a behavioral sleep intervention and a healthy-eating, attention control group in predicting fatigue 30 days after completing chemotherapy treatments. When group assignment was added to the key variables, five of the variables predicted higher fatigue based on the group. For control group participants, values prior to treatment of higher fatigue and daytime dysfunction, higher BMI, and more positive lymph nodes predicted higher fatigue 30 days after completing treatment. Individual factors prior to initiation of chemotherapy, such as fatigue levels, BMI, and lymph node status, appear to play a role above and beyond that contributed by the chemotherapy regimen in women's perceptions of fatigue after completing treatment.

For sleep intervention participants, lower peak activity (less activity during the day and more at night as measured by actigraphy) was the only predictor of higher fatigue 30 days after completing treatment. The result suggests that those in the sleep intervention group who were able to maintain day activity balanced with night sleep at the peak of the initial treatment benefited most from the intervention. In addition, these results suggest that the sleep intervention was able to decrease the effects of the factors that predicted higher fatigue in the control group at treatment completion. No other studies have used a behavioral sleep intervention to reduce fatigue in women with breast cancer; therefore, the findings cannot be compared. A limited number of small studies have used a behavioral sleep intervention to relieve fatigue in patients with cancer (Berger et al., 2002, 2003; Mitchell et al., 2007).

The results are useful for hypothesis generation and guiding future study. However, interpretation of the

**Table 6. Model 2[a]: Multiple Regression Results of Fatigue Regressed on Selected Predictors and Product Variables 30 Days After Completing Chemotherapy Treatment**

| | | Coefficients | | | |
|---|---|---|---|---|---|
| **Step** | **Variable** | **B** | **SE** | **Beta** | **p** |
| Prior[b] | Fatigue (PFS Total) | 0.123 | 0.165 | 0.114 | 0.459 |
| | Body mass index | –0.016 | 0.044 | –0.044 | 0.724 |
| | Hemoglobin | –0.142 | 0.186 | –0.075 | 0.448 |
| | Lymph node status | –0.441 | 0.459 | –0.138 | 0.340 |
| Prior[b] | Daytime dysfunction (PSQI) | 0.492 | 0.566 | 0.153 | 0.388 |
| | PCS | –0.006 | 0.027 | –0.024 | 0.835 |
| | Karnofsky Performance Scale | –0.253 | 0.274 | –0.104 | 0.360 |
| | Total sleep time | –0.003 | 0.003 | –0.111 | 0.327 |
| Peak[c] | Fatigue (PFS total) | 0.113 | 0.103 | 0.115 | 0.274 |
| | Peak activity | –0.012 | 0.006 | –0.250 | 0.065* |
| Rebound[d] | 24-hour autocorrelation | –0.354 | 1.852 | –0.025 | 0.849 |
| | Amount of energy upon awakening | –0.638 | 0.261 | –0.269 | 0.017** |
| | Sleep percent (day) | –0.033 | 0.036 | –0.130 | 0.366 |
| Grouping variable | Grouping variable | 0.269 | 0.396 | 0.062 | 0.498 |
| Product variables | Fatigue (PFS) prior times group | 0.361 | 0.220 | 0.219 | 0.105* |
| | Body mass index times group | 0.097 | 0.073 | 0.150 | 0.189* |
| | Lymph node status times group | 1.376 | 0.626 | 0.310 | 0.031** |
| | Daytime dysfunction (PSQI) times group | –1.236 | 0.749 | –0.280 | 0.103* |
| | Peak activity times group | 0.019 | 0.010 | 0.254 | 0.051* |

N = 95

*$p < 0.20$; **$p < 0.05$

[a] $R^2_{(19, 75)} = 0.440$, $p < 0.001$ (adjusted $R^2 = 0.299$)

[b] Two-day measurement period prior to receiving the initial chemotherapy treatment.

[c] Three-day measurement period during days 2–4 of the initial chemotherapy treatment.

[d] Three-day measurement period during day 5–7 of the initial chemotherapy treatment.

PCS—Physical Component Summary of the SF-36®, version 2; PFS—Piper Fatigue Scale; PSQI—Pittsburgh Sleep Quality Index

*Note.* Table presents results for all predictors and five product variables in model simultaneously in step 6. Variable name X group refers to the product variable. Model results including 13 product variables were $R^2_{(27, 67)} = 0.466$, $p = 0.006$ (adjusted $R^2 = 0.250$). Product variables with $p > 0.30$ were removed. Model 2 represents the regression coefficients for the product variables retained.

model was limited by small sample size and multicollinearity. Another limitation is the lack of racial or ethnic diversity in the sample. A strength of the secondary analysis is that although missing data are inherent in studies of human subjects and present challenges, methods were used to maximize the use of available data for analysis.

## Recommendations for Research

Using the entire data set of 219 participants, the prediction model could be reanalyzed with increased power to determine stability of the predictors with additional participants who received only anthracycline-based chemotherapy treatments. Also, data analysis from one or all chemotherapy treatments and at later times (60 and 90 days after treatment completion and one year after the initial treatment) may further explain the relationships between circadian rhythms of activity, sleep-wake, activity-rest, demographic or medical characteristics, and fatigue.

## Implications for Practice

NCCN (2008) cancer-related fatigue guidelines recommended education and counseling regarding fatigue patterns as central to effective management. Results of the current study provided information regarding variables prior to treatment that predicted higher fatigue 30 days after completing treatment. The finding assists with identifying those most in need of early and intensive teaching on strategies to manage fatigue. The strongest predictor was the fatigue level of the individual prior to receiving the initial chemotherapy treatment. This supports the simple, and yet widely underused recommendation of the NCCN cancer-related fatigue guidelines to screen all patients for fatigue prior to treatment and at regular intervals.

NCCN (2008) suggested self-monitoring of fatigue levels. Because fatigue levels during the peak of treatment were found to be another strong predictor of fatigue at treatment completion, regular screening for fatigue should include an assessment of the patient's fatigue levels at the peak of treatment. The amount of energy upon awakening at rebound also predicted fatigue at treatment completion. A self-report diary could be completed for seven days after the initial treatment, including ratings of fatigue and an item assessing the energy upon awakening, to further focus teaching on promotion of quality sleep during the next visit to clinic as recommended by the NCCN guidelines.

Less total sleep time prior to treatment also predicted higher fatigue at treatment completion. An evidence-based intervention, such as the behavior sleep intervention tested in the current study, can be initiated in women who identify themselves as poor sleepers prior to treatment. Patient education to promote quality sleep for all women starting adjuvant chemotherapy for breast cancer is a first step. The ONS PEP card for sleep-wake disturbances provides the nurse clinician with information that can be taught to patients to improve their sleep quality (Page, Berger, & Johnson, 2006). Instruction at the initiation of chemotherapy may decrease the fatigue experienced at the peak, affect the amount of energy upon awakening at rebound, and encourage daytime activity (Mitchell et al., 2007). Ongoing assessment of fatigue and sleep quality will identify individuals who develop these problems after the initial chemotherapy treatment. Intervening as early as possible in the course of chemotherapy offers the potential for lower fatigue at treatment completion, thereby possibly decreasing the disability and quality-of-life issues associated with this distressful symptom.

*The authors greatfully acknowledge Barbara F. Piper, DNSc, RN, AOCN®, FAAN, Lynne Farr, PhD, Nancy Waltman, PhD, RN, and Amy Kessinger, MD, for their support in this work.*

Kimberly K. Wielgus, PhD, APRN, BC, is an assistant professor, Ann M. Berger, PhD, RN, AOCN®, FAAN, is an associate professor, and Melody Hertzog, PhD, is an assistant professor, all at the University of Nebraska Medical Center in Omaha. This research was funded by the Breast Cancer Training Program Fellowship, the U.S. Army Breast Cancer Research Program Award (2001–2002; DADM17-00-1-0361), an American Cancer Society Doctoral Scholarship in Cancer Nursing (2002–2004; DSCN-02-213-01-SCN), and the National Aeronautics and Space Administration Nebraska Space Grants Scholarships (2002, 2003) awarded to Wielgus and by a National Institutes of Health and the National Institute of Nursing Research (#5R01NR007762-05) grant awarded to Berger. No financial relationships to disclose. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Oncology Nursing Forum* or the Oncology Nursing Society. Wielgus can be reached at kwielgus@unmc.edu, with copy to editor at ONFEditor@ons.org. (Submitted December 2007. Accepted for publication April 1, 2008.)

Digital Object Identifier: 10.1188/09.ONF.38-48

## References

Ambulatory Monitoring, Inc. (2005). *Action4(c) procedure manual*. Ardsley, NY: Author.

Ancoli-Israel, S., Cole, R., Alessi, C., Chambers, M., Moorcroft, W., & Pollak, C.P. (2003). The role of actigraphy in the study of sleep and circadian rhythms. *Sleep, 26*(3), 342–392.

Ancoli-Israel, S., Liu, L., Marler, M.R., Parker, B.A., Jones, V., Sadler, G.R., et al. (2006). Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. *Supportive Care in Cancer, 14*(3), 201–209.

Andrykowski, M.A., Schmidt, J.E., Salsman, J.M., Beacham, A.O., & Jacobsen, P.B. (2005). Use of a case-definition approach to identify cancer-related fatigue in women undergoing adjuvant therapy for breast cancer. *Journal of Clinical Oncology, 23*(27), 6613–6622.

Berger, A.M. (1998). Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. *Oncology Nursing Forum, 25*(1), 51–62.

Berger, A.M., & Farr, L. (1999). The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. *Oncology Nursing Forum, 26*(10), 1663–1671.

Berger, A.M., Parker, K.P., Young-McCaughan, S., Mallory, G.A., Barsevick, A.M., Beck, S.L., et al. (2005). Sleep/wake disturbances in people with cancer and their caregivers: State of the science [Online exclusive]. *Oncology Nursing Forum, 32*(6), E98–E126. Retrieved November 25, 2008, from http://ons.metapress.com/content/7244v4525u2j6408/fulltext.pdf

Berger, A.M., Von Essen, S., Kuhn, B.R., Piper, B.F., Agrawal, S., Lynch, J.C., et al. (2003). Adherence, sleep, and fatigue outcomes after adjuvant breast cancer chemotherapy: Results of a feasibility intervention study. *Oncology Nursing Forum, 30*(3), 513–522.

Berger, A.M., Von Essen, S., Kuhn, B.R., Piper, B.F., Farr, L., Agrawal, S., et al. (2002). Feasibility of a sleep intervention during adjuvant breast cancer chemotherapy. *Oncology Nursing Forum, 29*(10), 1431–1441.

Bower, J.E., Ganz, P.A., Desmond, K.A., Bernaards, C., Rowland, J.H., Meyerowitz, B.E., et al. (2006). Fatigue in long-term breast cancer survivors: A longitudinal investigation. *Cancer, 106*(4), 751–758.

Buysse, D.J., Reynolds, C.F., III, Monk, T.H., Berman, S.R., & Kupfer, D.J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research, 28*(2), 193–213.

Carpenter, J.S., & Andrykowski, M.A. (1998). Psychometric evaluation of the Pittsburgh Sleep Quality Index. *Journal of Psychosomatic Research, 45*(1), 5–13.

Cohen, P., Cohen, J., West, S.G., & Aiken, L.S. (2002). *Applied multiple regression/correlation analysis for the behavioral sciences* (3rd ed.). Mahwah, NJ: Lawrence Erlbaum Associated.

Cole, R.J., Kripke, D.F., Gruen, W., Mullaney, D.J., & Gillin, J.C. (1992). Automatic sleep/wake identification from wrist activity. *Sleep, 15*(5), 461–469.

Collins, L.M., Schafer, J.L., & Kam, C.M. (2001). A comparison of inclusive and restrictive strategies in modern missing data procedures. *Psychological Methods, 6*(4), 330–351.

Ferguson, T., Wilcken, N., Vagg, R., Ghersi, D., & Nowak, A.K. (2007). Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database for Systematic Reviews, 17*(4), CD004421.

Fu, M., LeMone, P., McDaniel, R.W., & Bausler, C. (2001). A multivariate validation of the defining characteristics of fatigue. *Nursing Diagnosis, 12*(1), 15–27.

Hosmer, D.W., & Lemeshow, S. (2000). *Applied logistic regression* (2nd ed.). New York: Wiley.

Janz, N.K., Muhahid, M., Chung, L.K., Lantz, P.M., Hawley, S.T., Morrow, M., et al. (2007). Symptom experience and quality of life

of women following breast cancer treatment. *Journal of Women's Health, 16*(9), 1348–1361.

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., Murray, T., et al. (2008). Cancer statistics, 2008. *CA: A Cancer Journal for Clinicians, 58*(2), 71–96.

Lee, K., Cho, M., Miaskowski, C., & Dodd, M. (2004). Impaired sleep and rhythms in persons with cancer. *Sleep Medicine Reviews, 8*(3), 199–212.

Lentz, M.J. (1990). Time-series analysis—cosinor analysis: A special case. *Western Journal of Nursing Research, 12*(3), 408–412.

Littner, M., Kushida, C.A., Anderson, W.M., Bailey, D., Berry, R.B., Davila, D.G., et al. (2003). Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: An update for 2002. *Sleep, 26*(3), 337–341.

Mitchell, S.A., Beck S.L., Hood L.E., Moore, K., & Tanner, E.R. (2007). Putting Evidence Into Practice®: Evidence-based interventions for fatigue during and following cancer and its treatment. *Clinical Journal of Oncology Nursing, 11*(1), 99–113.

Mormont, M.C., Waterhouse, J., Bleuzen, P., Giacchetti, S., Jami, A., Bogdan, A., et al. (2000). Marked 24-h rest/activity rhythms are associated with better quality of life, better response, and longer survival in patients with metastatic colorectal cancer and good performance status. *Clinical Cancer Research, 6*(8), 3038–3045.

Mullaney, D.J., Kripke, D.F., & Messin, S. (1980). Wrist-actigraph estimation of sleep time. *Sleep, 3*(1), 83–92.

National Comprehensive Cancer Network. (2008). *NCCN Clinical Practice Guidelines in Oncology™: Cancer-related fatigue* [v.1.2008]. Retrieved November 25, 2008, from http://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf

Page, M., Berger, A.M., & Johnson, L.B. (2006). Putting Evidence Into Practice®: Evidence-based interventions for sleep-wake disturbances. *Clinical Journal of Oncology Nursing, 10*(6), 753–767.

Piper, B.F., Dibble, S.L., Dodd, M.J., Weiss, M.C., Slaughter, R.E., & Paul, S.M. (1998). The revised Piper Fatigue Scale: Psychometric evaluation in women with breast cancer. *Oncology Nursing Forum, 25*(4), 677–684.

Piper, B.F., Lindsey, A.M., & Dodd, M.J. (1987). Fatigue mechanisms in cancer patients: Developing nursing theory. *Oncology Nursing Forum, 14*(6), 17–23.

Prue, G., Rankin, J., Allen, J., Gracey, J., & Cramp, F. (2006). Cancer-related fatigue: A critical appraisal. *European Journal of Cancer, 42*(7), 846–863.

Rich, T., Innominato, P.F., Boerner, J., Mormont, M.C., Iacobelli, S., Baron, B., et al. (2005). Elevated serum cytokines correlated with altered behavior, serum cortisol rhythm, and dampened 24-hour rest-activity patterns in patients with metastatic colorectal cancer. *Clinical Cancer Research, 11*(5), 1757–1764.

Ware, J.E., Kosinski, M., & Dewey, J.E. (2000). *How to score version two of the SF-36® Health Survey*. Lincoln, RI: QualityMetric.

Young-McCaughan, S., Mays, M.Z., Arzola, S.M., Yoder, L.H., Dramiga, S.A., Leclerc, K.M., et al. (2003). Change in exercise tolerance, activity and sleep patterns, and quality of life in patients with cancer participating in a structured exercise program. *Oncology Nursing Forum, 30*(3), 441–454.