http://dx.doi.org/10.5665/sleep.1630

The Longitudinal Relationship between Fatigue and Sleep in Breast Cancer Patients Undergoing Chemotherapy

Lianqi Liu, MD[1]; Michelle Rissling, MS[1,2]; Loki Natarajan, PhD[3,4]; Lavinia Fiorentino, PhD[1]; Paul J. Mills, PhD[1,2,4]; Joel E. Dimsdale, MD[1,2,4]; Georgia Robins Sadler, PhD[4,5]; Barbara A. Parker, MD[4,6]; Sonia Ancoli-Israel, PhD[1,2,4,6]

[1]Department of Psychiatry, University of California, San Diego, La Jolla, CA; [2]SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA; [3]Department of Family and Preventive Medicine, University of California, San Diego, La Jolla, CA; [4]Moores UCSD Cancer Center, La Jolla, CA; [5]Department of Surgery, University of California, San Diego, La Jolla, CA; [6]Department of Medicine, University of California, San Diego, La Jolla, CA

Study Objective: Fatigue and sleep disturbances are two of the most common and distressing symptoms of cancer patients. A relationship between the two symptoms was reported in symptom cluster studies; however, only subjective measurements of sleep were examined and most studies were cross-sectional. In this study of women with breast cancer undergoing chemotherapy, we explored the longitudinal relationship between fatigue and sleep measured both subjectively and objectively.

Design: Prospective study. Data were collected at 7 time points: before (baseline) and during the 3 weeks of cycle 1 and cycle 4 chemotherapy.

Participants: Ninety-seven women with newly diagnosed stage I-III breast cancer who were scheduled to receive at least four 3-week cycles of chemotherapy.

Measurement and Results: Objective sleep parameters were measured with an Actillume actigraph (Ambulatory Monitoring Inc.). Subjective sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI). Fatigue was assessed with the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). Fatigue became worse during both cycles of chemotherapy (P-values < 0.01). Subjective sleep quality was poor at baseline and remained unchanged throughout treatment. Objective nighttime and daytime total sleep time increased compared to baseline during the treatment administration week of both cycles; daytime total wake time decreased during the treatment week of both cycles and during the last 2 week of cycle 4. Mixed model results revealed that fatigue was positively associated with total PSQI scores and with objective measures of total nap time, and negatively associated with total wake time during the day (all P-values < 0.01).

Conclusion: Fatigue was significantly associated with subjective reports of poor sleep and objective measures of daytime sleepiness, but not with nocturnal sleep as measured with actigraphy. This relationship between fatigue and sleep warrants further studies to explore their possible common underlying etiology.

Keywords: Breast cancer, fatigue, sleep, napping, chemotherapy

Citation: Liu L; Rissling M; Natarajan L; Fiorentino L; Mills PJ; Dimsdale JE; Sadler GR; Parker BA; Ancoli-Israel S. The longitudinal relationship between fatigue and sleep in breast cancer patients undergoing chemotherapy. *SLEEP* 2012;35(2):237-245.

INTRODUCTION

Cancer-related fatigue (CRF) is defined as a distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning.[1] CRF is one of the most common and distressing complaints among cancer patients. Seventy to eighty percent of cancer patients report experiencing fatigue not only during chemotherapy or radiotherapy, but also pre- and post-treatment.[2] One-third of breast cancer survivors suffer from persistent fatigue up to 10 years post-treatment.[3] Cancer-related fatigue interferes with daily life activities, reduces quality of life, and is often a significant reason for patients to discontinue treatment.[4] To address the importance of CRF, the National Comprehensive Cancer Network (NCCN) convened a panel of experts and has been publishing an annually updated guideline, the NCCN Cancer-Related Fatigue Guideline, since 2000.[5] Together with pain and depression, CRF has been identified as a priority by the National Institutes of Health, with recommendations for more research on the definition, occurrence, assessment and treatment of these cancer-related symptoms, as well as on the relationship of these symptoms with other coexisting conditions, such as sleep disorders.[6]

Sleep disturbance is another major complaint of cancer patients, yet is often neglected.[7] Many middle-aged women experience sleep problems, such as decreased total sleep time due to stressors (e.g., menopause, family, and career factors) and medical comorbidities.[8] Since most breast cancer first manifests in midlife, it is likely that some middle-aged women are already experiencing poor sleep before their cancer diagnoses, not to mention that cancer itself may also cause sleep disturbances. In fact, poor sleep has been reported among 30% to 75% of newly diagnosed or recently treated cancer patients.[9,10] Patients with cancer often complain of difficulty falling asleep, difficulty staying asleep, and non-restorative sleep, before, during, and for years after the end of treatment.[11,12]

Sleep and fatigue have been reported as important components of a symptom cluster in cancer.[13-15] Data from the majority of studies examining cancer-related symptoms indicate that fatigue and sleep disturbances are related to each other.[9,16] A few studies, however, failed to show this relationship. Savard and colleagues found that there was no relationship between fatigue and insomnia in men with prostate cancer.[17] Curran et al. reported that while breast cancer survivors reported significantly

Submitted for publication March, 2011
Submitted in final revised form September, 2011
Accepted for publication September, 2011

Address correspondence to: Sonia Ancoli-Israel, PhD, Professor of Psychiatry, Department of Psychiatry. University of California, San Diego; 9500 Gilman Drive, # 0733, La Jolla, California 92093-0733; Tel: (858) 822-7710; Fax: (858) 822-7712; E-mail: sancoliisrael@ucsd.edu

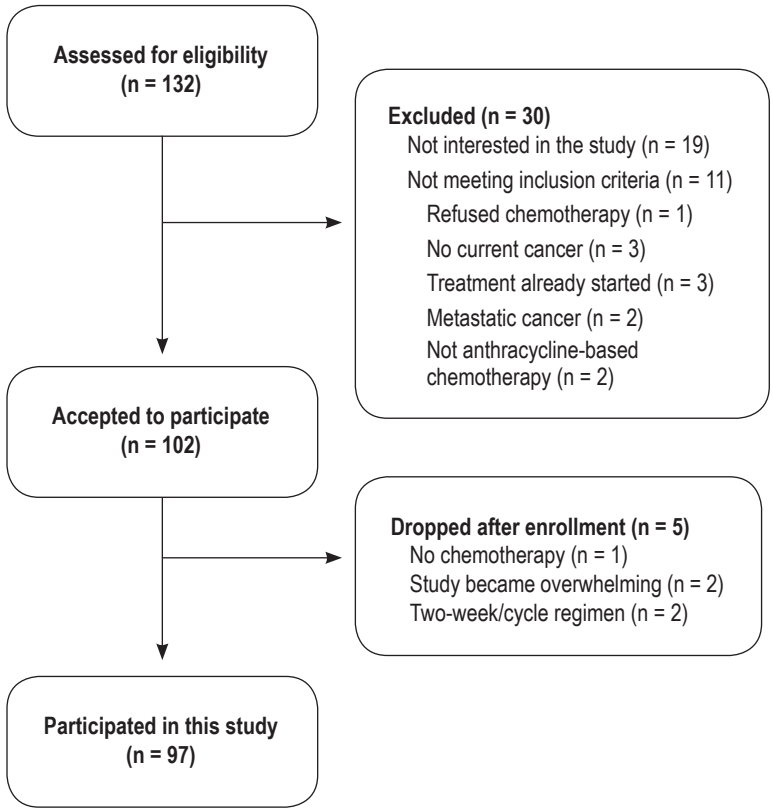

Figure 1—Screening and enrollment flowchart.

higher levels of fatigue than both healthy controls and women with benign breast problems, there were no group differences in self-reported sleep duration.[18]

As discussed in the review paper by Roscoe et al.,[16] the relationship between fatigue and sleep disturbances has only been reported as part of symptom clusters and most of the studies were cross-sectional surveys. Furthermore, few studies have explored the relationship between fatigue and objectively measured sleep, except in two small-sized reports which found weak associations.[19,20] Reported sleep duration and sleep onset latency are often overestimated when compared to polysomnographic (PSG) or actigraphic sleep data.[21,22] Therefore, there is still a need to understand the underlying connections of fatigue and sleep problems, including objective sleep disturbances in cancer patients. Longitudinally designed studies would help in better understanding the extent to which fatigue and sleep may have a common evolution and underlying etiology.

This study examined the relationship between fatigue and sleep in a sample of patients with breast cancer who were followed over four cycles of chemotherapy. We hypothesized that increased fatigue would not only be associated with subjective reports of poor sleep quality, but also with objectively measured poor sleep throughout treatment.

METHODS

Participants

Ninety-seven women with newly diagnosed stage I-III breast cancer and no previous exposure to chemotherapy were enrolled in this study (see Figure 1). All participants were scheduled to receive at least four 3-week cycles of adjuvant or neoadjuvant anthracycline-based chemotherapy. Women who were pregnant, undergoing bone marrow transplants, receiving radiotherapy, with confounding underlying medical illnesses, with 2-week cycle chemotherapy regimen, with significant preexisting anemia or with other physical or psychological impairments, and all men were excluded. Potential participants were referred by their oncologists at the Moores UCSD Cancer Center and from oncologists in the San Diego, California, and Yakama, Washington areas.

The study was approved by the University of California, San Diego (UCSD) Committee on Protection of Human Subjects and by the Moores UCSD Cancer Center's Protocol Review and Monitoring Committee.

Measures

Fatigue

Fatigue was assessed with the 30-item Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), which has been shown to be a valid and reliable tool for the multidimensional assessment of cancer-related fatigue.[23,24] The items of the MFSI-SF group into 5 subscales of fatigue-dimensions: General, Emotional, Physical, Mental, and Vigor. Each subscale includes 6 items, and each item is rated on a 5-point scale indicating how true the statement was during the last week (0 = not at all, 4 = extremely). Higher scores indicate more severe fatigue, except for the Vigor subscale, where a higher score indicates less fatigue (more Vigor). The sum of General, Physical, Emotional, and Mental subscale scores minus the Vigor subscale score generates a total fatigue score. The range of possible scores for each subscale is 0 to 24, and the range for total fatigue score is -24 to 96.

Subjective sleep quality

Subjective sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI).[25] The PSQI is a 19-item questionnaire which rates patients' reports of sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The total PSQI scores range from 0-21 with high scores reflecting poor sleep quality. Although the traditional cut-off for the PSQI has been 5, some studies have suggested that a cut-off score of 8 may be more appropriate to indicate poor sleep with daytime fatigue in clinical populations, including in cancer patients.[26,27]

Objective sleep quality

Objective sleep quality was measured with the Actillume actigraph (Ambulatory Monitoring Inc, Ardsley, New York). Actigraphy has been validated and shown to be reliable in the recording of sleep and wake in multiple studies.[28-30] The Actillume actigraph is a small device approximately 1x3x6 cm in size, which contains a piezoelectric linear accelerometer (sensitive to 0.003 g and above), a log-linear photometric transducer

(sensitive from < 0.01 lux to > 100,000 lux), a microprocessor, 32K RAM memory, and associated circuitry. A one-minute epoch was used. Once collected, data were downloaded onto a desktop computer and hand-edited with additional information from a sleep log completed by the participant where they recorded time to bed, time up in the morning, and other information needed for editing the actigraph data. The Action-3 software package for Actillume was used to score sleep and wake at night and during the day.

Total sleep time (TST), total wake time from time to bed to final awakening in the morning (TWT), total nap time (NAPTIME), and total wake time during the day (WAKE) were calculated. Total nap time was the sum of all naps (≥ 10 min of inactivity) per day.

Due to the difficulty of obtaining the exact time of lights out for actigraphy, the parameters of sleep onset latency (SOL) and sleep efficiency (SE) were not used in this study.

Procedure

Detailed procedural information can be found in Liu et al.[31] Briefly, after consent forms were signed, medical records were abstracted for medical history and current medication use. Questionnaire data were collected at the following 7 time points: before the start of the first cycle of chemotherapy (baseline or pre-treatment), during cycle 1 week 1 (C1W1; week of chemotherapy administration), cycle 1 week 2 (C1W2; week of lowest blood count), cycle 1 week 3 (C1W3; week of recovery), and during the 3 weeks of cycle 4 (C4W1, C4W2, C4W3). In general, baseline data collection began the week before chemotherapy, followed by data collection on the morning following chemotherapy administration (week 1 of both cycles). Data collected in each subsequent week (weeks 2 and 3 of both cycles) were collected on the same day of the week as during week 1. All questionnaires were completed once at each of the same 7 time points. Data of menopause status and utilization of medications other than chemotherapy were only collected during baseline and during C4W3.

Starting on the first day of each data collection time point, women also wore the Actillume for 3 consecutive days (i.e., 72 h) and completed a daily sleep log which was used for editing the Actillume data. While the ideal recording time for an actigraph is generally one week, due to potential subject burden, the minimum of 3 days suggested by the AASM practice parameters for actigraphy was used.[30]

Data Analysis

Pearson correlation analyses were performed between total and subscale scores of fatigue and sleep parameters. A mixed model analysis[32] was used to test the significance of possible confounding factors, to examine changes in fatigue and sleep (subjective and objective) over the course of chemotherapy, and to examine the longitudinal relationship between fatigue and sleep parameters. This modeling approach accounts for correlations in repeated measures within a subject, and also allows for partially missing data (i.e., subjects with missing data at some, but not all time points can be included in the model). A random intercept was included in each mixed model to account for subject-specific effects.In order to identify potential confounding factors, the following mixed models were developed: fatigue or sleep parameters were the response variables and demographic, disease or treatment characteristics were the main effect. Variables with $P < 0.1$ were determined to be confounders and were adjusted for in subsequent analyses.

In the mixed model analyses computed to examine changes of fatigue and sleep (subjective and objective) over time, chemotherapy week (time) was modeled as a fixed effect, and confounding factors were controlled accordingly. Due to multiple sleep measures (4 objective and 1 subjective) being tested, a Bonferroni adjusted significance level of $\alpha = 0.05/5 = 0.01$ was used for these analyses to control for inflated type I error.

Finally, a set of mixed models was developed to explore the longitudinal relationship between fatigue (outcome) and sleep parameters (predictors), with the sleep parameter included as a random effect, thereby allowing for subject-specific slope terms for sleep parameters in the model. These mixed models were adjusted with chemotherapy week (time) and confounding demographic, disease and treatment characteristic variables. Adjusted regression coefficients (β-value) with standard errors and associated P-values are presented. A Bonferroni adjusted significance level of $\alpha = 0.01$ was also used for these analyses.

All analyses were performed using version 9.2 of SAS (SAS Institute Inc. 2008).

RESULTS

As summarized in Table 1, the mean age of the 97 women was 50.7 years; 73% were Caucasian; 68% were married; 77% had at least some college; and 71% reported an annual income > $30,000. Eighty-six percent of the women were treated with doxorubicin and cyclophosphamide (AC), or AC plus fluorouracil, AC plus docetaxel, or AC plus paclitaxel; the rest were either treated with cyclophosphamide, epirubicin and fluorouracil (CEF), or their therapy was not clearly documented and marked as "other regimen."

The following variables listed in Table 1 were tested as potential confounders in relation to fatigue and sleep: age, BMI, race, education, income, marital status, menopause status, use of different medications, cancer stage, adjuvant or neoadjuvant treatment, chemotherapy regimen, and surgery type. According to the STRAW criteria,[33] menopausal status was defined as pre-menopause, peri-menopause, and post-menopause; due to this particular study sample, one extra group, hysterectomy, was also included as a type of menopausal status. In addition to their chemotherapy, women also used other medications to treat other symptoms, such as analgesics, antacids, antidepressants, antihypertensives, stimulants, and sleeping medications. Sedating medications included antihistamines, major tranquilizers, minor tranquilizers, OTC hypnotics, and sedative hypnotics.

Confounding factors were identified at the $P < 0.1$ level. Confounders for higher total MFSI-SF scores were non-Caucasians ($P = 0.04$) and use of antacids ($P = 0.06$); confounders for higher total PSQI scores were use of sleep medications ($P = 0.006$) and non-Caucasians ($P = 0.01$); confounders for shorter TST were higher BMI ($P = 0.01$), not using analgesics ($P = 0.07$), and non-Caucasians ($P = 0.09$); confounders for longer TWT were higher BMI ($P = 0.02$) and non-Caucasians ($P = 0.03$). No confounders were found for objective daytime sleep variables

Table 1—Demographic, disease, and treatment characteristics of the participants (n = 97)

Variable	Value
Age (years)	
Mean (SD)	50.7 (9.8)
Range	34 – 79
BMI	
Mean (SD)	28.8 (6.8)
Range	17.4 – 51.8
Race [n (%)]	
Caucasian	71 (73.2)
Non-Caucasian	26 (26.8)
Education [n (%)]	
Some or completed high school	22 (22.7)
Some college	26 (26.8)
Completed college and above	49 (50.5)
Marital Status [n (%)]	
Never married	10 (10.3)
Divorced/separated/widowed	21 (21.7)
Married	66 (68.0)
Household Annual Income [n (%)]	
≤ $30,000	15 (15.5)
> $30,000	69 (71.1)
Refused to answer	14 (13.4)
Menopausal Status [n (%)]	
Baseline	
Pre-menopause	37 (38.1)
Peri-menopause	19 (19.6)
Post-menopause	23 (23.7)
Hysterectomy	18 (18.6)
Cycle 4 Week 3	
Pre-menopause	4 (4.9)
Peri-menopause	12 (14.6)
Post-menopause	51 (62.2)
Hysterectomy	15 (18.3)
Unknown	16
Cancer Stage [n (%)]	
Stage I	29 (30.2)
Stage II	48 (50.0)
Stage III	19 (19.8)
Not available	1
Surgery Type [n (%)]	
Lumpectomy	40 (41.7)
Mastectomy	39 (40.6)
Double mastectomy	4 (4.2)
No surgery before chemotherapy	13 (13.5)
Not available	1
Chemotherapy Regimen [n (%)]	
AC	30 (30.9)
AC + docetaxel	31 (32.0)
AC + paclitaxel	18 (18.6)
AC + fluorouracil	4 (4.1)
ECF	8 (8.3)
Other	6 (6.2)
Sleeping Medications [n (%)]	
Baseline	
Yes	46 (48.9)
No	48 (51.1)
Not available	3
Cycle 4 week 3	
Yes	28 (45.9)
No	33 (54.1)
Not available	37
Analgesics [n (%)]	
Baseline	
Yes	56 (59.6)
No	38 (40.4)
Not available	3
Cycle 4 week 3	
Yes	15 (24.6)
No	46 (75.4)
Not available	37
Antacids [n (%)]	
Baseline	
Yes	29 (30.9)
No	65 (69.1)
Not available	3
Cycle 4 week 3	
Yes	27 (44.3)
No	34 (55.7)
Not available	37

AC, Doxorubicin + Cyclophosphamide; ECF, Epirubicin + Cytoxan + Fluorouracil.

(WAKE and NAPTIME). The medication confounders, i.e., sleep medications, analgesics, and antacids are listed in Table 1. These identified confounding factors were adjusted accordingly in the mixed models (also see Figure 2 and Table 4 for adjusted confounders).

Changes in Fatigue over the Course of Chemotherapy

There was a significant overall time effect ($P < 0.0001$) for MFSI-SF total scores. As seen in Figure 2A, total MFSI-SF scores increased significantly from baseline to C1W1, C1W3, C4W1, C4W2, and C4W3 (P-values range from < 0.0001 to 0.005). The means and standard deviations of the changes from baseline at each time point are listed in Table 2.

Changes in Sleep over the Course of Chemotherapy

Subjective sleep

Table 2 shows the means and standard deviations of the changes compared to baseline. There was no significant overall time effect ($P = 0.89$) for PSQI scores. Figure 2B shows that there were also no significant changes of total PSQI scores from baseline to any week of each cycle (all P-values > 0.01). However, the mean total PSQI scores were all in the pathological range (i.e., > 5) at all 7 time points. At baseline, 61% of the women reported a PSQI > 5, and 32% reported PSQI > 8, while at the end of treatment (C4W3), 76% reported a PSQI > 5 and 42% reported a PSQI > 8.

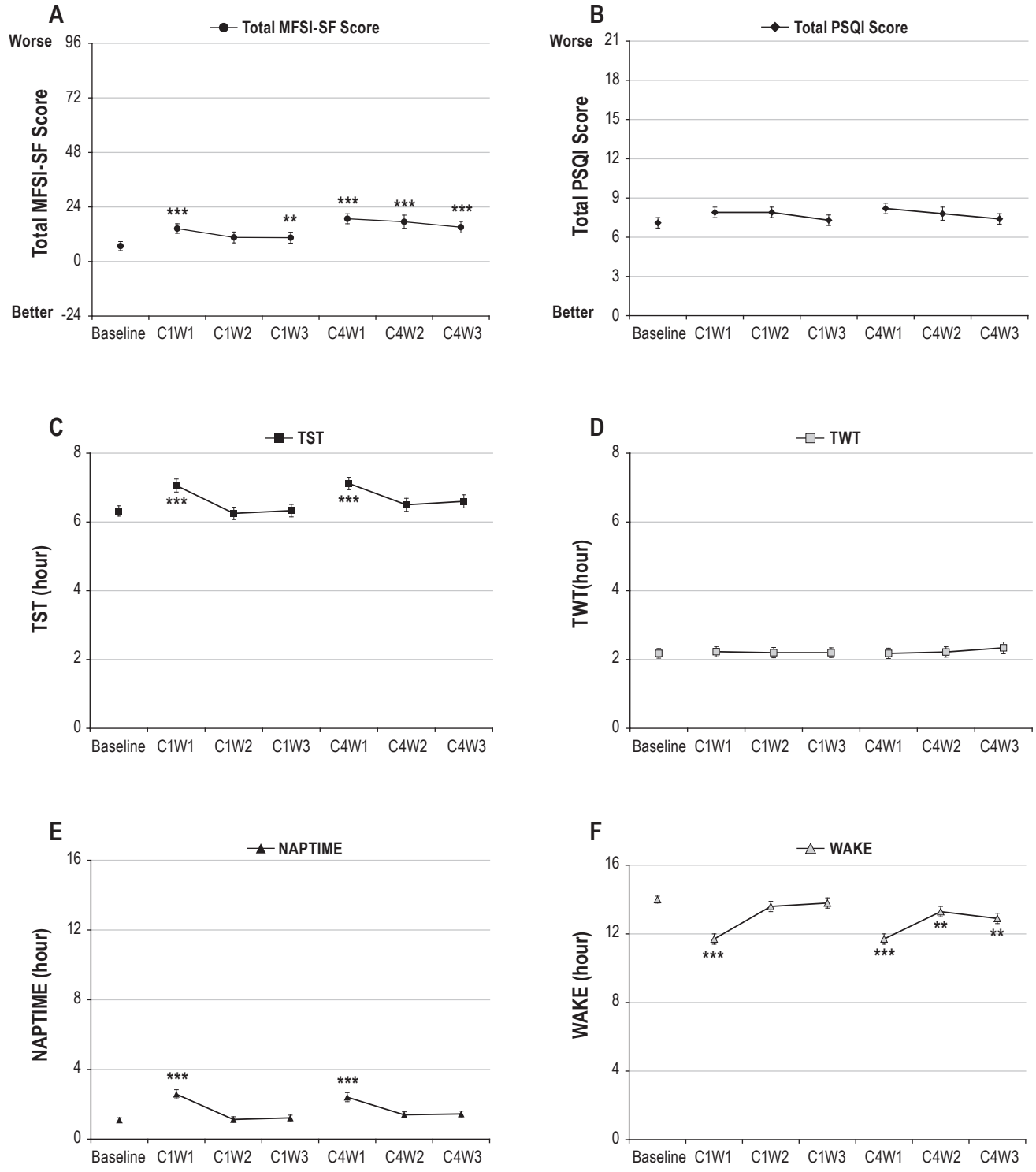

Figure 2—Total Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) scores, total Pittsburgh Sleep Quality Index (PSQI) scores, nighttime total sleep time (TST), nighttime total wake time (TWT), daytime total nap time (NAPTIME) and daytime total wake time (WAKE) before and during chemotherapy (mean ± SE). C1W1, Cycle 1 Week 1; C1W2, Cycle 1 Week 2; C1W3, Cycle 1 Week 3; C4W1, Cycle 4 Week 1; C4W2, Cycle 4 Week 2; C4W3, Cycle 4 Week 3. Significant differences between each treatment time point and baseline (time effect) are indicated by: **P < 0.01, ***P < 0.0001. **(A)** Total MFSI-SF scores. Race and use of antacids were adjusted. Note that total MFSI-SF scores increased significantly at C1W1, C1W3, C4W1, C4W2 and C4W3 compared to its baseline. **(B)** Total PSQI scores. Race and using of sleeping medications were adjusted. Note that although there were no significant changes of total PSQI scores during both cycles of chemotherapy compared to its baseline, the mean total PSQI scores were > 7 at all time points. **(C)** TST. Race, BMI, and use of analgesics were adjusted. Note that TST increased significantly during the treatment week of both cycles (C1W1 and C4W1) compared to baseline. **(D)** TWT. Race and BMI were adjusted. Note that there were no significant changes of TWT during chemotherapy compared to baseline. **(E)** NAPTIME. Note that NAPTIME increased significantly during the treatment week of both cycles (C1W1 and C4W1) when compared to baseline. **(F)** WAKE. Compared to baseline, WAKE decreased significantly during the treatment week of cycle 1 (C1W1) and all weeks of cycle 4 (C4W1, C4W2 and C4W3).

Table 2—Changes of fatigue and subjective/objective sleep at each time point compared to baseline (mean ± SD)

	C1W1	C1W2	C1W3	C4W1	C4W2	C4W3
Total MFSI-SF score	9.0 ± 12.9	4.7 ± 16.9	4.7 ± 14.2	13.4 ± 16.5	12.5 ± 22.5	9.5 ± 17.2
Total PSQI score	0.6 ± 3.3	0.6 ± 3.3	-0.1 ± 3.5	0.7 ± 3.6	0.3 ± 3.8	0.0 ± 3.8
Total sleep time (TST, hh:mm)	0:44 ± 1:25	-0:3 ± 1:14	0:0 ± 1:4	0:47 ± 1:14	0:8 ± 1:20	0:11 ± 1:25
Nighttime total wake time (TWT, hh:mm)	0:2 ± 1:1	0:2 ± 0:54	0:3 ± 0:50	-0:5 ± 1:2	0:8 ± 1:26	0:15 ± 1:12
Total nap time (NAPTIME, hh:mm)	1:18 ± 1:43	-0:2 ± 1:9	0:5 ± 0:58	1:25 ± 2:10	0:25 ± 1:46	0:19 ± 1:35
Daytime total wake time (WAKE, hh:mm)	-2:6 ± 2:28	-0:17 ± 1:50	-0:11 ± 2:7	-2:17 ± 2:29	-1:1 ± 2:59	-1:4 ± 2:32

C1W1, Cycle 1 Week 1; C1W2, Cycle 1 Week 2; C1W3, Cycle 1 Week 3; C4W1, Cycle 4 Week 1; C4W2, Cycle 4 Week 2; C4W3, Cycle 4 Week 3. MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form, higher score indicates more fatigue. PSQI, Pittsburgh Sleep Quality Index, higher score indicates poorer sleep quality.

Table 3—Correlation coefficients between MFSI-SF total and subscale scores and total PSQI scores before and during chemotherapy

	Total PSQI Score						
MFSI-SF score	**Baseline**	**C1W1**	**C1W2**	**C1W3**	**C4W1**	**C4W2**	**C4W3**
Total	0.397**	0.453**	0.559**	0.524**	0.607**	0.661**	0.512**
General	0.305**	0.409**	0.439**	0.440**	0.495**	0.517**	0.425**
Emotional	0.324**	0.421**	0.484**	0.472**	0.536**	0.592**	0.399**
Physical	0.300**	0.428**	0.519**	0.429**	0.492**	0.582**	0.432**
Mental	0.343**	0.294**	0.469**	0.438**	0.537**	0.609**	0.506**
Vigor	-0.319**	-0.245*	-0.439**	-0.417**	-0.493**	-0.529**	-0.356**

*P < 0.05, **P < 0.01. C1W1, Cycle 1 Week 1; C1W2, Cycle 1 Week 2; C1W3, Cycle 1 Week 3; C4W1, Cycle 4 Week 1; C4W2, Cycle 4 Week 2; C4W3, Cycle 4 Week 3. MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form, higher score indicates more fatigue. PSQI, Pittsburgh Sleep Quality Index, higher score indicates poorer sleep quality.

Objective sleep

Nighttime Sleep: There was a significant overall time effect ($P < 0.0001$) for TST. As shown in Figure 2C, TST increased significantly from baseline to the treatment week of both cycles (C1W1 and C4W1, both P-values < 0.0001). However, there was no significant overall time effect ($P = 0.4$) for TWT (Figure 2D).

Daytime Sleep: There was a significant overall time effect ($P < 0.0001$) for NAPTIME. Figure 2E shows that NAPTIME increased significantly from baseline to the treatment week of both cycles (C1W1 and C4W1, both P-values < 0.0001). Unlike TWT, there was a significant overall time effect ($P < 0.0001$) for WAKE (Figure 2F) with significant decreases from baseline to the treatment week of cycle 1 (C1W1, $P < 0.0001$) and to all 3 weeks of cycle 4 (C4W1, C4W2 and C4W3; all P-values < 0.008).

The means and standard deviations of the changes of these objective sleep parameters from baseline to each time points are listed in Table 2.

Associations between Fatigue and Sleep

Fatigue and subjective sleep quality

MFSI-SF total score and all 5 subscale scores were significantly correlated with total PSQI scores at each of the 7 time points (r-values range from 0.309 to 0.661, P-values range from < 0.0001 to 0.007; see Table 3), except that Vigor was negatively correlated with total PSQI scores at the $\alpha = 0.05$ level ($r = -0.245$, $P = 0.03$). All correlations were positive except for Vigor which was negative, suggesting that fatigue was associated with reports of poor sleep.

Fatigue and objective nighttime sleep parameters

There were no significant correlations between MFSI-SF total score and nighttime sleep parameters. There were however, significant correlations between TWT and MFSI-SF General ($r = 0.362$, $P = 0.004$) and Physical subscale scores ($r = 0.326$, $P = 0.009$) during the last week of cycle 4 chemotherapy (C4W3), suggesting that more fatigue was associated with more wake at night at the end of chemotherapy. There were no other significant relationships between nighttime sleep and the fatigue subscale scores.

Fatigue and objective daytime sleep parameters

There were significant negative correlations between WAKE and MFSI-SF total score at C1W1 ($r = -0.342$; $P = 0.004$) and C1W2 ($r = -0.319$; $P = 0.009$). There were also significant negative correlations between WAKE and MFSI-SF General ($r = -0.355$; $P = 0.003$) and Physical ($r = -0.330$; $P = 0.005$) subscale scores at C1W1, and significant positive correlation between WAKE and MFSI-SF Vigor subscale scores ($r = 0.429$; $P = 0.0004$) at C1W2. NAPTIME was also significantly and positively correlated with MFSI-SF Mental subscale score at C1W3 ($r = 0.329$; $P = 0.006$). These results suggest that more fatigue was associated with more napping during the day during the first cycle of chemotherapy.

There were no significant associations between the total or subscale fatigue scores and NAPTIME or WAKE during cycle 4.

Longitudinal relationship between fatigue and sleep parameters

The longitudinal relationship between fatigue and sleep was assessed with mixed models (Table 4). All 7 time points were used in the models, with baseline as the reference. In these mixed models, fatigue was the response variable and subjective and objective sleep parameters were the primary variables, with adjustment for time (chemotherapy weeks) and confounding factors (race, income, and chemotherapy regimen). The results showed that changes in the total MFSI-SF scores were significantly associated with changes in the total PSQI scores, NAPTIME, and WAKE (all P-values < 0.01). Specifically, every increase of 1 point of total PSQI score was associated with an increase of 1.7 points of total MFSI-SF score, every increase of 1 hour of nap time was associated with an increase of 1.9 points of total MFSI-SF score, and every increase of 1 hour of total wake time during the day was associated with a decrease of 1.2 points of total MFSI-SF score. Changes in fatigue were not significantly associated with changes in objective nighttime sleep parameters (both P-values ≥ 0.01).

Table 4—Mixed model results with fatigue as the response variable and subjective/objective sleep parameter as main effect

	Total MFSI-SF Score			
Sleep Variable[a]	Adj. β-value	Standard Error	t	P value
Total PSQI score	1.694	0.261	6.50	**< 0.0001**
Total sleep time (TST)	1.358	0.694	1.96	0.054
Nighttime total wake time (TWT)	-0.109	0.838	-0.13	0.8
Total nap time (NAPTIME)	1.890	0.537	3.52	**0.0007**
Daytime total wake time (WAKE)	-1.233	0.329	-3.74	**0.0003**

[a]Adjusted with time, race, and use of antacids. Bold numbers in P values indicate significant associations between fatigue and sleep. MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form, higher score indicates more fatigue. PSQI, Pittsburgh Sleep Quality Index, higher score indicates poorer sleep quality.

DISCUSSION

To our knowledge, this is the first study to examine the relationship between fatigue and objectively measured sleep parameters over time in women undergoing chemotherapy. The results confirmed that fatigue was worse during chemotherapy, with the increase during cycle 1 being temporary and the increase at cycle 4 being more persistent. Objective sleep measurements showed that, compared to pre-chemotherapy, patients spent more time sleeping both at night and during the day during the weeks of chemotherapy administration than during pre-treatment. Conversely, patients spent less time awake during the day during the two treatment weeks and during the last two weeks of cycle 4 chemotherapy. These results suggest that patients need more sleep during chemotherapy, especially during the treatment administration weeks, perhaps to cope with fatigue and other treatment-induced side effects.

Reports of sleep quality did not change significantly from pre-treatment to chemotherapy weeks; however, baseline levels of the PSQI score were already in the pathological range. The percentage of patients with PSQI scores above threshold also increased at the end of cycle 4 chemotherapy, with 76% patients reporting PSQI > 5 and 42% reporting PSQI > 8. Therefore, the nonsignificant change of subjective sleep quality suggests that the majority of women were already experiencing poor sleep before treatment, and this poor sleep continued throughout chemotherapy.

The relationship between fatigue and sleep quality reported previously in cancer symptom studies[9,16] was confirmed in this study. There was a significant association between fatigue (total and subscales) and reported sleep quality over the course of four cycles of chemotherapy, which remained significant after controlling for confounding factors.

Although fatigue worsened and total sleep time increased at night, only the General and Physical fatigue subscale scores significantly correlated with nighttime total wake time and only during the last week of cycle 4 chemotherapy. There were no associations with total sleep time. It is possible that the association between sleep and fatigue increases gradually over time and only manifests as significant at the end of chemotherapy. Since both sleep and fatigue complaints continue for months and sometimes years after the end of chemotherapy, this association during the last week of the last cycle might explain this phenomenon. Additional studies examining the associations between fatigue and objective measures of sleep immediately post chemotherapy are needed to answer this question.

On the other hand, total and most subscales of fatigue (General, Mental, Physical, and Vigor) were significantly associated with napping. This association remained significant after controlling for confounding factors. Short naps of no more than 30 minutes have been shown to have multiple health benefits, but frequent, longer naps have been shown to lead to adverse long-term outcomes.[34] Women in this study napped more than 1 hour at all seven time points (mean daily nap time 1.1-2.6 h, data not shown); this longer naptime may indicate poor sleep habits and lower sleep quality, thus it is not surprising that fatigue was associated with total nap time in this group of women. This significant relationship between fatigue and napping rather than between fatigue and total nocturnal sleep, might be due to the fact that fatigue is a subjective feeling during daytime, and fatigued women might therefore nap more to try to ease that fatigue.

The relationship between fatigue and reports of poor sleep in cancer patients has been well documented, although causality has not been determined.[16,35] Data from the current study adds further evidence to the existence of this relationship, with both subjective and objective sleep parameters. Although fatigue was not significantly associated with objective nighttime sleep variables, the objective nighttime sleep variables were significantly correlated with daytime sleep parameters, with longer nighttime sleep correlating with longer daytime sleep (data not shown). One interpretation of these findings is that women undergoing chemotherapy for breast cancer are sleepier both during the day and night, an indication of increased general sleepiness.

Overall, the close relationship between fatigue and sleep in cancer patients suggests that these two symptoms might have some underling behavioral and/or biological connections. Behaviorally, as discussed above, patients with more fatigue tend to nap more; biologically, fatigue and sleep disturbances might share some common mechanisms, such as a cytokine-based etiology, as suggested in some studies.[36-38] If fatigue and sleep disturbances do share a common etiology, clinical intervention studies treating both symptoms would provide identical effects to the two symptoms. To date, few intervention studies have targeted both fatigue and sleep, and those that have been done have generated inconsistent results. While some interventions improved both fatigue and sleep,[39-41] others improved sleep but not fatigue or did not improve either.[42,43] Therefore, additional clinical studies, such as studies examining if aiming at one symptom using clinically proved strategies will improve the other, as suggested in a review by Zee and Ancoli-Israel,[35] are highly needed. Studies examining biological connections of the two symptoms are also warranted.

This study defined naps as inactivity for at least 10 minutes between the final up time in the morning and bedtime. There have been no standard definitions published for actigraphic naps. A few studies used any short sleep episode (1 min) during the out-of-bed time as a nap,[44-46] while other studies defined at least 5 minutes of no activity as a nap.[47,48] In a study comparing two actigraphic devices for assessing sleep/wake and nap in an aged sample (mean age 62 years), a minimum duration of 10 minutes was used to define a nap.[49] The results showed that the agreement of identifying naps between the two devices was high (87%), and both devices were highly sensitive in detecting reported naps.[49] Given that women with breast cancer undergoing chemotherapy tend to be less physically active during the daytime, 10 minutes of inactivity was used to define naps in this study.

This study had some limitations. Data before surgery were not collected, thus it is not clear if the fatigue and poor sleep already existed before surgery. It is also possible that these symptoms were present at the time of diagnosis of breast cancer. There were no follow-up data after the end of chemotherapy; therefore, a longer-term relationship between sleep and fatigue cannot be confirmed by this study. Although a 10-minute actigraphic nap definition was used in this study, total nap time might still have been overestimated, as patients might have been awake but very still during some periods defined as naps. The generalizability of the results is also limited due the relatively highly educated population with higher household income, and due to the lack of data on other potential confounders, such as depression and anxiety. Although the using of medications was collected in this study, information on whether a medication was taken as a treatment for hot flashes was not recorded. Data were collected only in women with breast cancer; therefore the conclusions cannot be extended to men or to patients with other types of cancer. The study also however had some strengths, specifically the inclusion of objective measures of sleep and the longitudinal collection of data over four cycles (12 weeks) of chemotherapy.

In conclusion, in women with breast cancer, fatigue became worse, while reports of sleep quality remained poor during chemotherapy compared to pre-chemotherapy. Patients also slept more both during the night and day during the treatment administration week of each cycle. Fatigue was associated with disrupted subjective sleep quality and objective daytime sleepiness during chemotherapy. The significant relationship between fatigue and sleep disturbances in cancer patients suggests that they both may share some common underlying etiology and warrant further basic and clinical studies. Intervention studies examining if treating one specific symptom (e.g., sleep disturbances) could improve the other (e.g., fatigue) are also needed. Based on these findings, clinicians need to pay additional attention to those symptoms as they likely contribute to poor quality of life.

ACKNOWLEDGMENTS

This study was supported by NCI CA112035, UL1RR031980, NIH M01 RR00827, the UCSD Stein Institute for Research on Aging and the Department of Veterans Affairs Center of Excellence for Stress and Mental Health (CESAMH).

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Dimsdale has received research support from Sepracor unrelated to this manuscript. Dr. Ancoli-Israel serves on the advisory board or acts as a consultant for Ferring Pharmaceuticals Inc., GlaxoSmithKline, Merck, NeuroVigil, Inc., Pfizer, Phillip-Respironics, Sanofi-Aventis, Sepracor, Inc., and Schering-Plough. Dr. Parker received compensation for a speaking engagement for the Association of American Cancer Institute Meeting. The other authors have indicated no financial conflicts of interest.

REFERENCES

1. Mock V, Atkinson A, Barsevick A, et al. NCCN Practice Guidelines for Cancer-Related Fatigue. Oncology (Williston Park) 2000;14:151-61.
2. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. Oncologist 2007;12 Suppl 1:4-10:4-10.
3. Bardwell WA, Ancoli-Israel S. Breast cancer and fatigue. Sleep Med Clin 2008;3:61-71.
4. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol 2000;18:743-53.
5. Berger AM, Abernethy AP, Atkinson A, et al. Cancer-related fatigue. http://www nccn org/professionals/physician_gls/pdf/fatigue pdf 2011
6. National Institutes of Health State-of-the-Science Panel. National Institute of Health State-of-the-Science Conference Statement: Symptom management in cancer: Pain, depression and Fatigue, July 15-17, 2002. J Natl Cancer Inst 2003;95:1110-7.
7. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol 2001;19:895-908.
8. Lee KA. Sleep in midlife women. J Obstet Gynecol Neonatal Nurs 2009;38:331-2.
9. Ancoli-Israel S, Moore P, Jones V. The relationship between fatigue and sleep in cancer patients: A review. Eur J Cancer Care 2001;10:245-55.
10. Berger AM, Parker KP, Young-McCaughan S, et al. Sleep wake disturbances in people with cancer and their caregivers: state of the science. Oncol Nurs Forum 2005;32:E98-126.
11. Fiorentino L, Ancoli-Israel S. Insomnia and its treatment in women with breast cancer. Sleep Med Rev 2006;10:419-29.
12. Liu L, Ancoli-Israel S. Sleep disturbances in cancer. Psychiatry Ann 2008;38:627-34.
13. Miaskowski C, Dodd M, Lee K. Symptom clusters: the new frontier in symptom management research. J Natl Cancer Inst Monogr 2004;2004:17-21.
14. Dodd MJ, Miaskowski C, Lee KA. Occurrence of symptom clusters. J Natl Cancer Inst Monogr 2004;2004:76-78.
15. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. Oncol Nurs Forum 2001;28:465-70.

16. Roscoe JA, Kaufman ME, Matteson-Rusby SE, et al. Cancer-related fatigue and sleep disorders. Oncologist 2007;12 Suppl 1:35-42.
17. Savard J, Simard S, Hervouet S, Ivers H, Lacombe L, Fradet Y. Insomnia in men treated with radical prostatectomy for prostate cancer. Psychooncology 2004;30:474-84.
18. Curran SL, Beacham AO, Andrykowski MA. Ecological momentary assessment of fatigue following breast cancer treatment. J Behav Med 2004;27:425-44.
19. Berger AM, Higginbotham P. Correlates of fatigue during and following adjuvant breast cancer chemotherapy: a pilot study. Oncol Nurs Forum 2000;27:1443-8.
20. Miaskowski C, Lee KA. Pain, fatigue and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: a pilot study. J Pain Symptom Manage 1999;17:320-32.
21. Silva GE, Goodwin JL, Sherrill DL, et al. Relationship between reported and measured sleep times: the sleep heart health study (SHHS). J Clin Sleep Med 2007;3:622-30.
22. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? Epidemiology 2008;19:838-45.
23. Stein KD, Martin SC, Hann DM, Jacobsen PB. A multidimensional measure of fatigue for use with cancer patients. Cancer Pract 1998;6:143-52.
24. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. J Pain Symptom Manage 2004;27:14-23.
25. Buysse DJ, Reynolds CFI, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.
26. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res 1998;45:5-13.
27. Beck SL, Schwartz AL, Towsley G, Dudley W, Barsevick A. Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients. J Pain Symptom Manage 2004;27:140-148.
28. Ancoli-Israel S, Clopton P, Klauber MR, Fell R, Mason WJ. Use of wrist activity for monitoring sleep/wake in demented nursing home patients. Sleep 1997;20:24-27.
29. Jean-Louis G, Kripke DF, Cole RJ, Assmus JD, Langer RD. Sleep detection with an accelerometer actigraph: comparisons with polysomnography. Physiol Behav 2001;72:21-8.
30. Ancoli-Israel S, Cole R, Alessi CA, Chambers M, Moorcroft WH, Pollak C. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003;26:342-92.
31. Liu L, Marler M, Parker BA, et al. The relationship between fatigue and light exposure during chemotherapy. Support Care Cancer 2005;13:1010-7.
32. Diggle PJ, Liang KY, Zeger SL. Analysis of longitudinal data. Oxford: Clarendon Press, 1996.
33. Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW) Park City, Utah, July, 2001. Menopause 2001;8:402-7.
34. Dhand R, Sohal H. Good sleep, bad sleep! The role of daytime naps in healthy adults. Curr Opin Pulm Med 2006;12:379-82.
35. Zee PC, Ancoli-Israel S. Does effective management of sleep disorders reduce cancer-related fatigue? Drugs 2009;69:29-41.
36. Lee BN, Dantzer R, Langley KE, et al. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. Neuroimmunomodulation 2004;11:279-92.
37. Wood LJ, Nail LM, Gilster A, Winters KA, Elsea CR. Cancer chemotherapy-related symptoms: evidence to suggest a role for proinflammatory cytokines. Oncol Nurs Forum 2006;33:535-42.
38. Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. J Clin Oncol 2008;26:971-82.
39. Mock V, Hassey D, Meares CJ, et al. Effects of exercise on fatigue, physical functioning and emotional distress during radiation therapy for breast cancer. Oncol Nurs Forum 1997;24:991-1000.
40. Yang HL, Chen XP, Lee KC, Fang FF, Chao YF. The effects of warm-water footbath on relieving fatigue and insomnia of the gynecologic cancer patients on chemotherapy. Cancer Nurs 2010;33:454-60.
41. Demiralp M, Oflaz F, Komurcu S. Effects of relaxation training on sleep quality and fatigue in patients with breast cancer undergoing adjuvant chemotherapy. J Clin Nurs 2010;19:1073-83.
42. Berger AM, Kuhn BR, Farr LA, et al. Behavioral therapy intervention trial to improve sleep quality and cancer-related fatigue. Psychooncology 2009;18:634-46.
43. Barsevick A, Beck SL, Dudley WN, et al. Efficacy of an intervention for fatigue and sleep disturbance during cancer chemotherapy. J Pain Symptom Manage 2010;40:200-16.
44. Yoon IY, Kripke DF, Youngstedt SD, Elliott JA. Actigraphy suggests age-related differences in napping and nocturnal sleep. J Sleep Res 2003;12:87-93.
45. Yaffe K, Blackwell T, Barnes DE, Ancoli-Israel S, Stone KL. Preclinical cognitive decline and subsequent sleep disturbance in older women. Neurology 2007;69:237-42.
46. Goldman SE, Hall M, Boudreau R, et al. Association between nighttime sleep and napping in older adults. Sleep 2008;31:733-40.
47. Dautovich ND, McCrae CS, Rowe M. Subjective and objective napping and sleep in older adults: are evening naps ”bad” for nighttime sleep? Sleep 2008;56:1681-6.
48. Yuksel H, Sogut A, Yilmaz H, Yilmaz O, Dinc G. Sleep actigraphy evidence of improved sleep after treatment of allergic rhinitis. Ann Allergy Asthma Immunol 2009;103:290-4.
49. Lotjonen J, Korhonen I, Hirvonen K, Eskelinen S, Myllymaki M, Partinen M. Automatic sleep-wake and nap analysis with a new wrist worn online activity monitoring device vivago WristCare. Sleep 2003;26:86-90.