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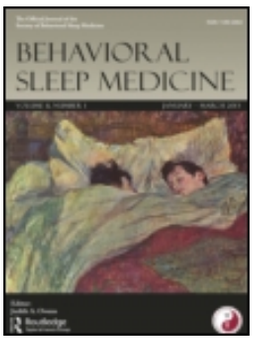

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This study examined the longitudinal relation between health-related quality of life (HR-QOL) and subjective and objective sleep quality in 166 women with newly diagnosed Stage-1 through Stage-3 breast cancer, who were scheduled to receive $\geq$ 4 cycles of adjuvant/neoadjuvant chemotherapy. HR-QOL was assessed with the Medical Outcomes Study 36-item Short Form, Physical Component Scale (PCS), and Mental Component Scale (MCS) scores; subjective sleep was assessed with the Pittsburgh Sleep Quality Index; and objective sleep was measured with actigraphy. Data were collected before starting chemotherapy and during the last week of Cycle 4 of chemotherapy. Patients reported poor HR-QOL and poor sleep quality before and during chemotherapy. Short sleep time and long naps were recorded at both time points. The MCS score was related to reports of poor sleep, but not to recorded sleep; worse PCS scores were associated with reports of poor sleep and less recorded naptime, suggesting sleep plays an important role in cancer patients' HR-QOL.

As cancer treatment has improved, survival has stopped being the sole endpoint of treatment, with improved quality of life becoming a vital outcome for cancer survivors. Due to its broad coverage of individual's feelings, beliefs, and perceptions, there is a lack of consensus on the exact definition of *quality of life* (Siddiqui, Kachnic, & Movsas, 2006; Soni & Cella, 2002). However, *health-related quality of life* (HR-QOL) is defined as a combination of health status, functional status, and quality of life (Guyatt, Feeny, & Patrick, 1993). Although there are different types of measurements for quality of life in cancer patients (Berger, Sankaranarayanan, & Watanabe-Galloway, 2007; Soni & Cella, 2002), the Medical Outcomes Study 36-item Short Form (SF–36; Ware & Kosinski, 2002) is one that is frequently used. The SF–36 measures HR-QOL, and a Physical Component Scale (PCS) score and a Mental Component Scale (MCS) score are usually generated and reported from the SF–36 (Ware, Kosinski, & Gandek, 2002).

Increasingly, cancer patients and their health care providers are becoming concerned with maintaining HR-QOL, as it frequently decreases after diagnosis or treatment (Pockaj et al., 2009; Trentham-Dietz et al., 2008). In addition, HR-QOL has been found to be a predictor of survival in patients with head and neck, lung, or colorectal cancers (Efficace et al., 2006; Karvonen-Gutierrez et al., 2008; Maione et al., 2009). Therefore, identifying which factors specifically contribute to poorer HR-QOL in cancer patients and exploring possible ways to improve HR-QOL have become very important therapeutic goals (Siddiqui et al., 2006; Soni & Cella, 2002).

Studies show that poor HR-QOL is associated with multiple factors in cancer patients, including sleep disturbances, fatigue, pain, anxiety, and depression (Frick, Tyroller, & Panzer, 2007; Redeker, Lev, & Ruggiero, 2000; Visser & Smets, 1998). However, only a handful of studies have examined the relationship between sleep disturbances and HR-QOL, and

sleep in those studies was often examined only as part of a symptom cluster (Dodd, Cho, Cooper, & Miaskowski, 2010; Miaskowski et al., 2006; Pud et al., 2008). A 2007 review of methodological approaches to the study of sleep disturbances and HR-QOL in cancer patients concluded that, although the changes of HR-QOL and sleep over time have been studied, the relationship between HR-QOL and sleep remained unclear (Berger et al., 2007). Limitations of most studies include a single-item subjective measurement of sleep and cross-sectional, rather than longitudinal, data collection (Berger et al., 2007), and a single-item measure of sleep is not effective in identifying sleep problems in cancer patients (Gooneratne et al., 2007). A few studies investigating sleep and HR-QOL in cancer patients have been published since the aforementioned review (Dodd et al., 2010; Eyigor, Eyigor, & Uslu, 2010; Lis, Gupta, & Grutsch, 2008; Pud et al., 2008; Sandadi et al., 2011), but most used questionnaires to measure sleep quality and, thus, were still limited by the subjective nature of the measurements, not focusing on HR-QOL–sleep relationship, and cross-sectional designs. Therefore, longitudinal studies examining the specific relationship between HR-QOL and sleep disturbances, especially between HR-QOL and comprehensively and objectively measured sleep, are needed in cancer patients.

To our knowledge, only one study with a small sample of lung cancer patients ($n = 29$) used actigraphy and the SF–36 to examine the relationship of quality of life to sleep in cancer patients. No significant correlations were identified, except for a negative association between the PCS score of the SF–36 and sleep-log-documented sleep time (Le Guen et al., 2007). Prior findings from our laboratory showed that HR-QOL was associated with sleep quality, fatigue, and depressive symptoms before chemotherapy (Ancoli-Israel et al., 2006). In this study, we examined the longitudinal relationship between HR-QOL (as measured by the SF–36) and subjectively (questionnaire) and objectively (actigraph) measured sleep quality in breast cancer patients before the start of the first cycle of chemotherapy (baseline) and at the end of the last week of Cycle 4 (C4LW) treatment.

METHOD

Participants

Participants were from two completed studies of women with breast cancer undergoing chemotherapy. The first study focused on fatigue, sleep, and circadian rhythms (Study 1); the second study focused on chemotherapy-related cognitive impairments (Study 2). Both studies had similar protocols, and were conducted among women with newly diagnosed Stage-1 through Stage-3 breast cancer scheduled to receive at least four cycles of adjuvant or neoadjuvant anthracycline-based chemotherapy. Ninety-four women from Study 1 and 72 women from Study 2 met inclusion criterion (inclusion criteria are discussed later; see Figure 1 for the screening and enrollment processes). Study 1 data were collected between 2000 and 2005; and, as recommended at that time, women in Study 1 all received 3-week chemotherapy cycles. Study-2 data were collected between 2005 and 2010, at which point the recommended treatment regimen had changed to a 2-week cycle; therefore, 38 (63%) women in Study 2 received a 2-week cycle regimen of chemotherapy and 22 (37%) women received a 3-week cycle regimen of chemotherapy. The different lengths of treatment cycles were tested and controlled as confounders. There were no significant differences between the two samples for

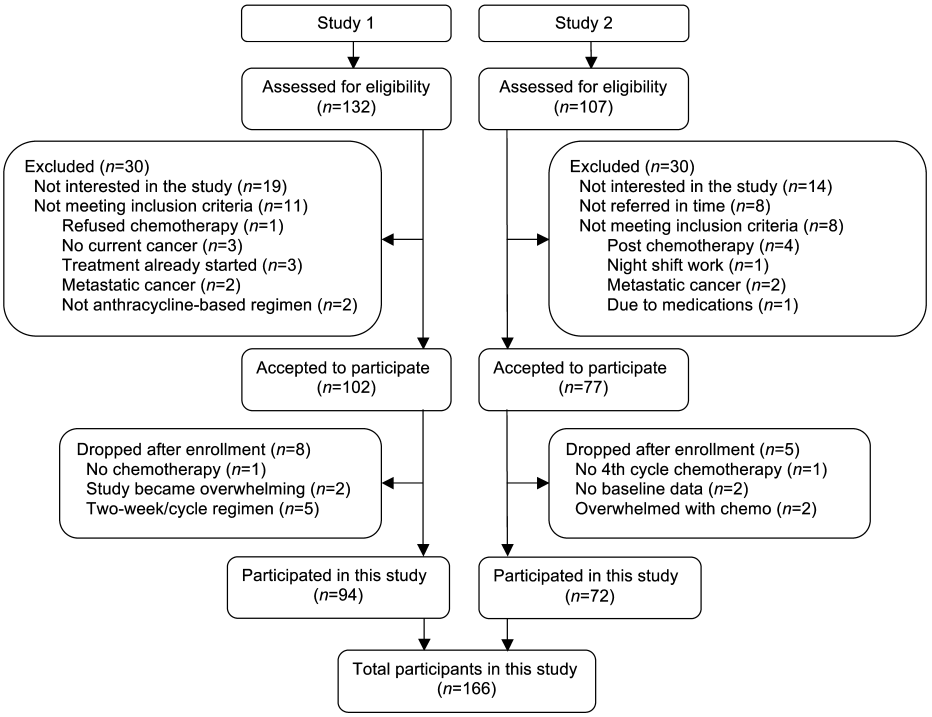

FIGURE 1 Screening and enrollment flowchart (Consolidated Standards of Reporting Trials [CONSORT] diagram showing the flow of participants).

age, race, body mass index (BMI), education level, marital status, annual household income, menopausal status, use of other medications, cancer stage, surgery type, chemotherapy regimen, HR-QOL, or subjective and objective sleep quality. Therefore, the two samples were merged, and a total of 166 women were included in this analysis. Detailed demographic and disease characteristics of the women are listed in Table 1.

Pregnant women, those undergoing bone marrow transplants, those with metastatic breast cancer, those with confounding underlying medical illnesses, those with significant preexisting anemia, or those with other physical or psychological impairments were excluded from both studies. The University of California Committee on Protection of Human Subjects and the University of California, San Diego Rebecca and John Moores Cancer Center's Protocol Review and Monitoring Committee approved both studies, and an informed consent was obtained from each woman at the beginning of her participation in the study.

Measures

HR-QOL. HR-QOL was assessed with the SF–36 health survey. The SF–36 health status survey is a generic, 36-item, health status instrument, with eight subscales measuring eight domains of health: physical functioning, role limitations because of physical problems,

TABLE 1
Demographic, Disease, and Treatment Characteristics of the Participants

Variable	*Value*
Age (years)	
M (*SD*)	51.3 (9.6)
Range	31–80
BMI (kg/m^2)	
M (*SD*)	28.2 (7.0)
Range	17.4–61.9
Race: *n* (%)	
Caucasian	133 (80.1)
Non-Caucasian	33 (19.9)
Education: *n* (%)	
Some or completed high school	29 (17.5)
Some college	53 (31.9)
Completed college and above	84 (50.6)
Marital status: *n* (%)	
Never married	13 (7.8)
Divorced/separated/widowed	38 (22.9)
Married	115 (69.3)
Household annual income: *n* (%)	
$\leq$ \$30,000	25 (15.1)
$>$ \$30,000	119 (71.7)
Refused to answer	22 (13.2)
Menopausal status: *n* (%)	
Baseline	
Pre-menopause	65 (41.7)
Peri-menopause	16 (10.3)
Post-menopause	52 (33.3)
Hysterectomy	23 (14.7)
Not available	10
Cycle 4, Week 3	
Pre-menopause	7 (4.9)
Peri-menopause	28 (19.6)
Post-menopause	85 (59.4)
Hysterectomy	23 (16.1)
Not available	23
Cancer stage: *n* (%)	
Stage 1	40 (27.8)
Stage 2	66 (45.8)
Stage 3	38 (26.4)
Not available	22
Surgery type: *n* (%)	
Lumpectomy	60 (41.7)
Mastectomy	65 (45.1)
Double mastectomy	8 (5.6)
No surgery before chemotherapy	11 (7.6)
Not available	22

(*continued*)

TABLE 1
(*Continued*)

Variable	*Value*
Chemotherapy regimen: *n* (%)	
AC	38 (26.4)
AC + Docetaxel	34 (23.6)
AC + Paclitaxel	45 (31.2)
AC + Fluorouracil	4 (2.8)
Other	23 (16.0)
Not available	22
Chemotherapy cycle length: *n* (%)	
3-week	116 (75.3)
2-week	38 (24.7)
Not available	12

Note. $N = 166$. BMI = body mass index; AC = doxorubicin + cyclophosphamide; ECF = epirubicin + cytoxan + fluorouracil.

bodily pain, general health perceptions, vitality, social functioning, role limitations because of emotional problems, and mental health (Ware et al., 2002). The SF–36 has no questions related to sleep or fatigue. The SF–36 is a commonly used measurement of HR-QOL (Coons, Keininger, & Hays, 2000). Each subscale is scored on a range from 0 to 100, with lower scores indicating worse HR-QOL. Norm-based PCS and MCS scores are calculated from these eight subscales. Three subscales contribute primarily to the PCS (physical functioning, bodily pain, and role limitations because of physical problems), two subscales contribute primarily to the MCS (mental health and role limitations because of emotional problems), and the remaining three subscales contribute substantially to both summary scales (vitality, social functioning, and general health perceptions). Both PCS and MCS have a mean of 50 and a standard deviation of 10 in the 1998 general U.S. population, with a score <50 indicating that the HR-QOL is below the average (Ware & Kosinski, 2002).

Subjective sleep quality. Subjective sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989; Buysse et al., 1991). The PSQI is a 19-item questionnaire that 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 can range from 0 to 21, with high scores reflecting poor sleep quality. A total score >5 is considered poor sleep, and a cutoff score of 8 was suggested to indicate poor sleep in clinical populations (Beck, Schwartz, Towsley, Dudley, & Barsevick, 2004; Carpenter & Andrykowski, 1998).

Objective sleep quality. Objective sleep quality was measured with the Actillume (Ambulatory Monitoring, Inc., Ardsley, NY) or Actiwatch-Light (Actiwatch-L; Philips Respironics Mini Mitter, Bend, OR) actigraphs. The Actillume actigraph is a small device approximately $1 \times 3 \times 6$ cm in size, and it contains a piezoelectric linear accelerometer (sensitive to 0.003 *g* force

and above), a log-linear photometric transducer (sensitive from < 0.01 lux to > 100,000 lux), a microprocessor, 32K RAM memory, and associated circuitry. The Actiwatch-L is a watch-like device approximately $1 \times 2.5 \times 5$ cm in size. It also has a piezoelectric accelerometer (sensitive to < 0.01 *g* force), and its luminance sensor has a spectral sensitivity approximating that of the human eye (sensitive from 0.1–150,000 lux). The Actiwatch-L has a 64K on-board memory and associated circuitry. A 1-min epoch was used for both actigraphs. Once collected, data were downloaded onto a desktop computer and hand-edited with additional information from a sleep log completed by the participants' recording their time to bed, time up in the morning, naptime, and other information needed for editing the actigraphy data. The Action-4 software package for Actillume and Actiware 5 software for Actiwatch-L were used to score sleep and wake times. All women in Study 1 and 14 women in Study 2 wore the Actillume, and the other 58 women in Study 2 wore the Actiwatch-L. To establish equivalency between the two devices, a validation study in eight volunteers was conducted with both devices worn concurrently on the same wrist for 72 hr. The Actillume-derived summary activity count and the Actiwatch-L-derived activity count data, as well as the software-scored sleep/wake data based on the two types of activity counts, were highly correlated (both *r*s > .85) and, therefore, deemed equivalent for the purpose of this study. Actigraphy has been validated and shown to be reliable in recording sleep and wake in multiple studies (Ancoli-Israel et al., 2003; Lichstein et al., 2006).

Total sleep time (TST), total wake time (TWT) from time to bed to final awakening in the morning, and total naptime (NAPTIME) were calculated. Naps were defined as 10 min or more of consecutive actigraphic sleep during the hours between final up time and bedtime.

Procedure

Detailed procedural information for Study 1 can be found in Liu et al. (2005). Briefly, after consent forms were signed, medical records were abstracted for medical histories and current medications use. Study 2 followed similar procedures. Only data collected at baseline and during the C4LW are reported in this study.

Starting on the first day of each data collection time point, women wore an actigraph for 3 consecutive days (72 hr) and completed a daily sleep log, which was used for editing actigraphy data. For each woman, actigraphy was recording on the same day at each time point. The day chosen was based on the day of chemotherapy administration. Although the ideal recording time for an actigraph is generally 1 week, due to potential participant burden, the minimum of 3 days suggested by the American Academy of Sleep Medicine practice parameters for actigraphy was used (Ancoli-Israel et al., 2003).

Data Analysis

Descriptive statistics (means and standard deviations) were calculated for all outcomes at both time points. One-sample *t* tests were performed for PCS and MCS scores in comparison with U.S. norms. Pearson correlation analyses were performed for PCS and MCS scores and sleep parameters. A mixed-model analysis (Diggle, Liang, & Zeger, 1994) was used to test the significance of possible confounding factors, to examine changes in HR-QOL and sleep

(subjective and objective) over the course of chemotherapy, and to examine the longitudinal relationship between HR-QOL and sleep parameters. This modeling approach accounts for correlations in repeated measures within-subjects, and also allows for partially missing data. A random intercept was included in each mixed model to account for participant-specific effects.

To identify potential confounding factors, the following mixed models were developed: HR-QOL or sleep parameters were the response variables and demographic, disease, or treatment characteristics were the main effects. Variables with $p < .10$ were determined to be confounders, and were adjusted for in subsequent analyses. Changes in HR-QOL or sleep (subjective and objective) over time were separately examined with mixed models; chemotherapy week (time) was modeled as a fixed effect, and confounding factors were controlled in each model.

Finally, a set of mixed models was developed to explore the longitudinal relationship between HR-QOL (outcome) and sleep parameters (predictors). In those mixed models, total PSQI scores or objective sleep variables (TST, TWT, or NAPTIME) were the response variables, PCS or MCS scores were the main effects, and the sleep parameter was included as a random effect, thereby allowing for participant-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 (beta values) with standard errors and associated p values are presented.

All analyses were performed using version 9.2 of SAS (SAS Institute, 2008). All statistical tests with ps $< .05$ are reported as statistically significant.

RESULTS

As summarized in Table 1, the mean age of the 166 women was 51.3 years, 80% were Caucasian, 69% were married, 51% had at least completed a college education, 72% reported an annual income of > $30,000, 60% had a BMI $\geq$ 25, and 31% had a BMI >30. Twenty-five percent of the women received a 2-week cycle regimen of chemotherapy; 84% 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 or their therapy was indicated as an "other" regimen.

The following variables listed in Table 1 were tested as potential confounders in relation to HR-QOL and sleep: age, BMI, race, education, income, marital status, menopausal status, use of different medications, cancer stage, surgery type, adjuvant or neoadjuvant treatment, chemotherapy regimen, and cycle length of chemotherapy. According to the Stages of Reproductive Aging Workshop criteria (Soules et al., 2001), menopausal status was defined as pre-menopause, peri-menopause, and post-menopause; due to this particular study sample, one extra group, hysterectomy (surgical menopause), was also included as a type of menopausal status.

In addition to chemotherapy, patients used other medications to treat other symptoms (such as analgesics, antacids, antidepressants, antihypertensives, insulin, laxatives, diuretics, stimulants, and vitamins). Sedating medications, including antihistamines, minor tranquilizers, major tranquilizers, over-the-counter hypnotics, and sedative hypnotics, were categorized as sleeping medications. Medications identified as confounders are listed in Table 2.

TABLE 2
Uses of Medications for Other Symptoms

Medications	*n (%)*
Sleeping medications	
Baseline	
Yes	70 (42.7)
No	94 (57.3)
Not available	2
Cycle 4, Week 3	
Yes	59 (46.5)
No	68 (53.5)
Not available	39
Analgesics	
Baseline	
Yes	111 (68.1)
No	52 (31.9)
Not available	3
Cycle 4, Week 3	
Yes	46 (38.0)
No	75 (62.0)
Not available	45
Antacids	
Baseline	
Yes	42 (25.8)
No	121 (74.2)
Not available	3
Cycle 4, Week 3	
Yes	53 (43.8)
No	68 (56.2)
Not available	45
Antihypertensives	
Baseline	
Yes	18 (11.1)
No	144 (88.9)
Not available	4
Cycle 4, Week 3	
Yes	11 (8.3)
No	111 (91.7)
Not available	45
Laxatives	
Baseline	
Yes	31 (19.1)
No	131 (80.9)
Not available	4
Cycle 4, Week 3	
Yes	30 (24.8)
No	91 (75.2)
Not available	36

(*continued*)

TABLE 2
(*Continued*)

Medications	*n (%)*
Diuretics	
Baseline	
Yes	12 (7.4)
No	150 (92.6)
Not available	4
Cycle 4, Week 3	
Yes	8 (6.6)
No	113 (93.4)
Not available	36
Antidepressants	
Baseline	
Yes	32 (19.6)
No	131 (80.4)
Not available	3
Cycle 4, Week 3	
Yes	22 (18.2)
No	99 (81.8)
Not available	45
Insulin	
Baseline	
Yes	9 (5.6)
No	153 (94.4)
Not available	4
Cycle 4, Week 3	
Yes	6 (5.0)
No	115 (95.0)
Not available	45
Vitamins	
Baseline	
Yes	112 (68.7)
No	51 (31.3)
Not available	3
Cycle 4, Week 3	
Yes	71 (58.7)
No	50 (41.3)
Not available	45

Note. $N = 166$. Sleeping medications included antihistamines, minor tranquilizers, major tranquilizers, over-the-counter hypnotics, and sedative hypnotics.

At the $p < .10$ level, confounders for lower PCS scores were use of antacids ($p = .004$), annual household income < \$30,000 ($p = .01$), use of sleeping medications ($p = .02$), having not completed college ($p = .03$), use of insulin ($p = .05$), higher BMI ($p = .06$), 2-week cycle chemotherapy ($p = .07$), and pre- or peri-menopause status ($p = .09$); confounders for lower MCS scores were use of antidepressants ($p = .04$) and antihypertensives ($p = .04$), not

married ($p = .05$), younger age ($p = .07$), and use of antacids ($p = .09$); confounders for higher total PSQI scores were use of sleeping medications ($p = .006$), not married ($p = .03$), 2-week cycle chemotherapy ($p = .04$), use of laxatives ($p = .04$) and analgesics ($p = .07$), higher BMI ($p = .07$), and having not completed college ($p = .07$); confounders for shorter TSTs were higher BMI ($p = .004$), 2-week cycle chemotherapy ($p = .01$), non-Caucasian ($p = .03$), and use of antidepressants ($p = .07$); confounders for longer TWT were non-Caucasian ($p = .003$), 2-week cycle chemotherapy ($p = .01$), and higher BMI ($p = .02$); confounders for longer NAPTIME were use of diuretics ($p = .001$), antacids ($p = .07$) and antidepressants ($p = .07$), and higher cancer stage ($p = .09$). These confounding factors were adjusted accordingly in the mixed models.

HR-QOL

The mean PCS and MCS scores were both <50 at both time points, and one-sample *t* tests revealed that both scores were significantly below U.S. norms (Ware & Kosinski, 2002) at both time points (all *p*s $< .0001$); however, the changes of PCS and MCS scores from baseline to the C4LW chemotherapy did not reach statistical significance (PCS: 43.3 ± 9.8 vs. 41.2 ± 8.9; MCS: 46.5 ± 10.8 vs. 44.4 ± 12.4; both *p*s $> .05$) after controlling for confounders, suggesting that the women had poor HR-QOL before the start of chemotherapy, and HR-QOL continued to be poor during treatment.

Subjective Sleep Quality

Total and subscale scores of the PSQI before treatment and at the C4LW are listed in Table 3. Compared to baseline (65%), more women had a total PSQI score >5 (74%) at the C4LW, whereas the number of women with a score >8 remained relatively constant (39% baseline vs. 38% at the C4LW). From baseline to the C4LW, total PSQI scores and sleep efficiency and daytime dysfunction subscale scores rose significantly after controlling for confounders (all *p*s $< .05$); there were no significant changes in scores of the other five PSQI subscales. PSQI results suggest that women reported poor sleep quality before the start of treatment, and they reported even worse sleep quality after four cycles of chemotherapy.

TABLE 3
Pittsburgh Sleep Quality Index Total and Subscale Scores Before and After Chemotherapy

	*Total**		*Sleep Quality*		*Sleep Latency*		*Sleep Duration*		*Sleep Efficiency**		*Sleep Disturbance*		*Sleep Medication*		*Daytime Dysfunction***	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Baseline	7.3	3.7	1.2	0.8	1.0	1.0	0.8	0.8	0.9	1.1	1.5	0.6	1.0	1.3	0.8	0.6
C4LW	8.0	3.9	1.2	0.8	1.1	0.9	0.8	0.8	1.1	1.2	1.6	0.6	1.1	1.3	1.0	0.7

Note. For the Pittsburgh Sleep Quality Index, higher scores indicate poorer sleep quality. C4LW = last week of Cycle-4 chemotherapy.

*$p < .05$. **$p < .001$ (between 2 time points adjusted for body mass index, marital status, college degree, use of laxatives, analgesics and sleep medications, and a 2-week cycle of chemotherapy).

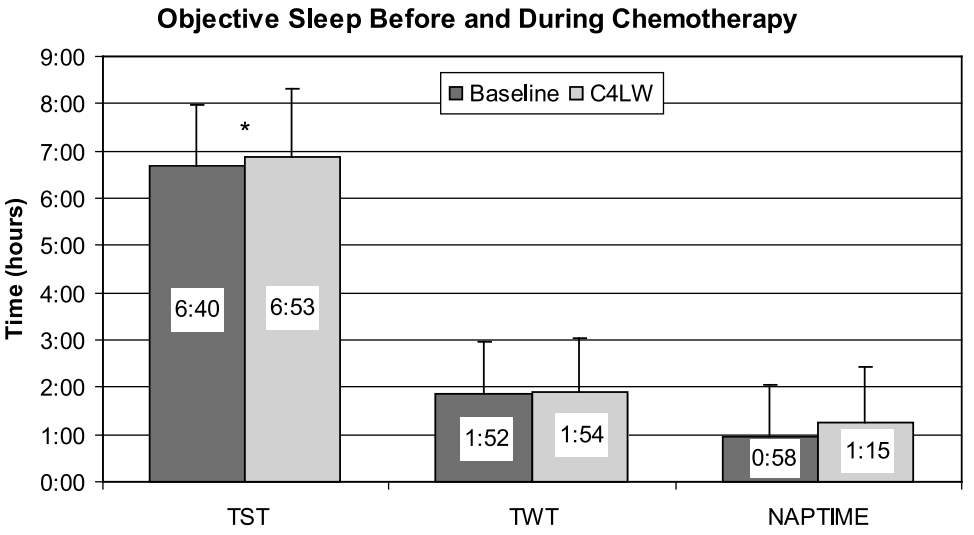

FIGURE 2 Objective sleep—total sleep time (TST), total wake time (TWT), and total naptime (NAPTIME)—before (baseline) and during the last week of Cycle-4 (C4LW) chemotherapy. *Note.* Compared to baseline, after four cycles of chemotherapy, nighttime TST (hour:minute) significantly increased (6:40 ± 1:18 vs. 6:53 ± 1:23; $p = .03$) after controlling for confounders (time, body mass index [BMI], race, chemotherapy cycle length, and use of antihypertensives), but remained < 7 hr at both time points. There were no significant changes in nighttime TWT (hour:minute: 1:52 ± 1:60 vs. 1:54 ± 1:80; $p = .50$) or daytime NAPTIME (hour:minute: 0:58 ± 1:40 vs. 1:15 ± 1:80, $p = .20$), but both remained relatively high after adjusting for confounders (TWT: adjusted for time, BMI, race, and chemotherapy cycle length; NAPTIME: adjusted for time, cancer stage, and use of antacids, antidepressants. and diuretics).

Objective Sleep Parameters

As seen in Figure 2, compared to baseline, women were sleepier at night and continued being sleepy during the day after the C4LW. Controlling for confounders, TST increased significantly from baseline to the C4LW ($p = .034$), although mean TST was < 7 hr at both time points. There were no significant changes in TWT or NAPTIME after controlling for confounders (both *p*s > .20), but women were awake for about 2 hr at night and napped for close to 1 hr at both time points. More women slept >7 hr per night (43% at baseline vs. 49% at the C4LW), and more were napping >1 hr per day at the C4LW (46%) compared to baseline (39%).

Associations Between HR-QOL and Sleep

As shown in Table 4, lower PCS and MCS scores at baseline and the C4LW were significantly associated with higher total PSQI scores and higher scores on most of the PSQI subscales. Lower PCS scores were also associated with longer naptimes at both time points (both *p*s < .05), whereas the MCS was not significantly correlated with any of the objective sleep parameters.

TABLE 4
Correlation Coefficients Between Health-Related Quality of Life and Subjective and Objective Sleep Measures

	PCS		*MCS*	
Sleep Parameters	*Baseline*	*C4LW*	*Baseline*	*C4LW*
PSQI total score	−0.263**	−0.347***	−0.400***	−0.426***
Sleep quality	−0.278**	−0.226**	−0.314***	−0.377***
Sleep latency	−0.078	−0.129	−0.251**	−0.211*
Sleep duration	−0.065	−0.105	−0.221**	−0.112
Sleep efficiency	−0.127	−0.113	−0.224**	−0.211*
Sleep disturbance	−0.310**	−0.445***	−0.116	−0.250**
Sleep medication	−0.115	−0.196*	−0.140	−0.220*
Daytime dysfunction	−0.179*	−0.401***	−0.506***	−0.476***
Actigraphy				
Total sleep time	0.131	−0.010	0.123	0.027
Nighttime total wake time	−0.100	−0.155	−0.052	−0.059
Total naptime	−0.173*	−0.216*	−0.027	−0.105

Note. PCS = Physical Component Scale of the Medical Outcomes Study 36-item Short Form (SF–36). Higher scores indicate better health-related quality of life (HR-QOL); MCS = Mental Component Scale of the SF–36. Higher scores indicate better HR-QOL; PSQI = Pittsburgh Sleep Quality Index. Higher scores indicate poorer sleep quality; C4LW = last week of Cycle-4 chemotherapy.

*$p < .05$. **$p < .01$. ***$p < .0001$.

Associations Between Changes of HR-QOL and Changes in Sleep

As shown in Table 5, mixed-model results revealed that changes in PCS scores were negatively associated with changes in total PSQI scores and NAPTIME. Changes in MCS scores were also negatively associated with changes in total PSQI scores. Specifically, every increase of 1 point of the total PSQI score was associated with a decrease of 0.5 points of the PCS score and a decrease of 1.1 points of the MCS score; every increase of 1 hr of naptime was associated with a decrease of 1.3 points of the total PCS score. There were no associations between changes in the PCS score and objective nighttime sleep (TST and TWT) or between the MCS score and objective sleep parameters (TST, TWT, and NAPTIME). When only those with <7 hr TST at baseline ($n = 90$) were examined, change in the PCS was negatively associated with change in TWT ($t = 2.20$, $p = .03$), indicating that women reported lower PCS scores if they slept <7 hr before chemotherapy and had more TWT at night.

DISCUSSION

The results of this study showed that HR-QOL was poor before chemotherapy (as previously reported by Ancoli-Israel et al., 2006) and did not worsen over time, whereas self-reported sleep quality was poor before (Ancoli-Israel et al., 2006) and got worse after chemotherapy, with

TABLE 5
Mixed Model Results With PCS or MCS as the Response Variable and Parameter of Subjective or Objective Sleep as the Main Effect

		Mixed Model Results		
SF–36	*Sleep Parameters*	*Adjusted β*	*Standard Error*	*p*
PCS score[a]	Total PSQI score	−0.498	0.164	**.0032**
	TST	0.377	0.496	.4500
	TWT	−0.823	0.545	.1300
	NAPTIME	−1.276	0.542	**.0210**
MCS score[b]	Total PSQI score	−1.06	0.188	**< .0001**
	TST	0.560	0.577	.3300
	TWT	−0.473	0.655	.4700
	NAPTIME	−0.578	0.621	.3500

Note. SF–36 = Medical Outcomes Study 36-item Short Form; PCS = Physical Component Scale of the SF–36. Higher scores indicate better health-related quality of life (HR-QOL); MCS = Mental Component Scale of the SF–36. Higher scores indicate better HR-QOL; PSQI = Pittsburgh Sleep Quality Index. Higher scores indicate poorer sleep quality; TST = nighttime total sleep time; TWT = nighttime total wake time; NAPTIME = daytime total naptime.

[a]Adjusted for time, body mass index, education level, household income, menopausal status, chemotherapy cycle length, and use of sleeping medications, antacids, and insulin. [b]Adjusted for time, age, marital status, and use of antacids, antidepressants, and antihypertensives.

more women scoring above the cutoff for good sleep. Objectively, the women were sleepier after chemotherapy, but continued to spend long periods awake at night and to nap during the day. In addition, the self-reported variables of HR-QOL and sleep quality were consistently related to each other at both time points, and both changed for the worse in synchrony over time. However, HR-QOL and recorded sleep changes were generally not related to each other, and did not change synchronously over time, except for PCS and NAPTIME.

In this study, in addition to subjective sleep data, objective measures of sleep were also collected. The PCS was negatively correlated with NAPTIME at both time points, indicating that more naptime was associated with worse physical HR-QOL. There was, however, no relation between other objective nighttime sleep parameters and HR-QOL, although TST was <7 hr and TWT was almost 2 hr at both time points. When we examined only those women with <7 hr of sleep at baseline, the changes in physical HR-QOL were negatively associated with changes in nighttime TWT, with those staying awake longer at night reporting worse physical HR-QOL. These results suggest that a significant relationship between low physical HR-QOL and poor objective sleep might exist in patients with shorter sleep time, but this hypothesis needs to be tested in larger samples.

In addition to the significant relationship between HR-QOL and subjective sleep quality, the unique finding of this study was that the worse physical HR-QOL was correlated with longer naps. To our knowledge, this is the first study to report a relationship between HR-QOL and naptime in breast cancer patients undergoing chemotherapy. Adequate napping (e.g., not >30 min per day) has been shown to have multiple health benefits, but frequent and longer napping may lead to adverse long-term health outcomes (Dhand & Sohal, 2006). In this study, almost

one-half of the women napped >1 hr at both study time points. Although TST increased during the C4LW compared to baseline, the mean TST was still <7 hr at the C4LW. This shorter TST and longer napping time may indicate poor daytime sleep habits and lower sleep quality. On the other hand, excessive napping might lead to reduced physical activity during the day. Thus, it is not surprising that the physical component of HR-QOL was associated with NAPTIME in this group of women. This phenomenon might also be explained by our previous findings, which showed that more fatigue was associated with longer naptime in women with breast cancer undergoing chemotherapy (Liu et al., 2012) because fatigue is one of the most important contributors to low HR-QOL (Bower et al., 2000; Curt, 2000).

Another interesting finding of this study was that the mental component of HR-QOL was not associated with objective sleep parameters. A possible explanation for this result is that actigraphy measures objective sleep quality, whereas mental HR-QOL is based on subjective feelings. In the same manner that actigraph-measured sleep is associated more with results from polysomnography than with subjectively reported sleep in sleep diaries (Ancoli-Israel et al., 2003), it is not surprising that these objective sleep parameters were not related to mental HR-QOL. As discussed earlier, subjectively measured sleep quality (PSQI) was significantly associated with subjectively reported mental HR-QOL.

As summarized by Berger et al. (2007), although quality of life in cancer patients has been extensively studied, the relationship between quality of life and sleep was not the primary aim of those studies, and the direct relationship between quality of life and sleep has rarely been explored. A few studies explored the relationship between quality of life and subjective sleep (Eyigor, Eyigor, & Uslu, 2010; Gooneratne et al., 2007; Lis, Gupta, & Grutsch, 2008; Sandadi et al., 2011) in patients with different types of cancer, and all found a relationship between lower quality of life and reports of poor sleep quality or sleep disturbance. The significant relationships between HR-QOL and total PSQI scores found in this study confirm these previously discussed findings.

A few studies have tested different intervention strategies to improve HR-QOL in cancer patients. In the Berger et al. (2007) review, 10 intervention studies were identified and several intervention strategies were studied, such as pharmacology, exercise, massage, and cognitive-behavioral therapy (CBT); however, findings were inconclusive, and almost all the intervention studies were conducted in cancer survivors after completion of cancer treatments. The significant associations between HR-QOL and subjective and objective sleep quality revealed in this study, together with the suggestive effects from those intervention studies in cancer survivors, suggest that HR-QOL may be improved in women with breast cancer by improving sleep quality and optimization of sleep and napping behaviors. This hypothesis needs to be tested in well-designed, controlled intervention studies.

Strengths of this study included objective, as well as subjective, measures of sleep and the longitudinal design. Along with its strengths, this study also had some limitations. Data were collected after surgery, but before chemotherapy, so it is unknown if the relationship between HR-QOL and sleep also exists after diagnosis of cancer, but before surgery. Data were obtained from women with breast cancer and from women with relatively higher education levels and higher household annual incomes, so conclusions cannot be extended to men, to patients with different socioeconomic statuses, or to women with different cancers. Although data generated by two types of actigraphs were highly correlated in our validation study (data not reported), two types of actigraphs from different manufacturers may still potentially affect the results.

Even with great effort to acquire diagnosis and treatment information for all participants, some data were still missing for a portion of women (mostly from Study 2).

In summary, this study revealed that HR-QOL was low and sleep quality was poor in breast cancer patients prior to chemotherapy, and that HR-QOL remained unchanged, but continued to be low after chemotherapy while sleep quality got worse. This decreased HR-QOL was significantly associated with both subjectively reported poor sleep quality and objectively measured naptime, and changes in one were associated with changes in the other. These data suggest that clinicians need to pay more attention to sleep in women with breast cancer undergoing treatment, as it is possible that improving sleep may also improve quality of life. Studies are needed to examine if improving sleep quality and maladaptive sleep behaviors using intervention strategies, such as Cognitive Behavioral Therapy for Insomnia (CBT–I), might also improve HR-QOL in cancer patients. Intervention studies with well-chosen comparisons are needed, and should be initiated early in the course of cancer treatments. Long-term follow-ups after the completion of treatment are especially warranted.

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