A Longitudinal Study of Measures of Objective and Subjective Sleep Disturbance in Patients with Breast Cancer Before, During, and After Radiation Therapy

Anand Dhruva, MD, **Steven M. Paul, PhD**, **Bruce A. Cooper, PhD**, **Kathryn Lee, RN, PhD**, **Claudia West, RN, MS**, **Bradley E. Aouizerat, PhD**, **Laura B. Dunn, MD**, **Patrick S. Swift, MD**, **William Wara, MD**, and **Christine Miaskowski, RN, PhD**
Schools of Medicine (A.D., L.B.D., W.W.) and Nursing (S.M.P., B.A.C., K.L., C.W., B.E.A., C.M.), University of California, San Francisco; and Alta Bates Comprehensive Cancer Center (P.S.S.), Berkley, California, USA

Abstract

Context—Sleep disturbance is a significant problem in oncology patients.

Objectives—To examine how actigraphy and self-report ratings of sleep disturbance changed over the course of and following radiation therapy (RT); investigate whether specific patient, disease, and symptom characteristics predicted the initial levels and/or the characteristics of the trajectories of sleep disturbance; and to compare predictors of subjective and objective sleep disturbance.

Methods—Patients (*n*=73) completed self-report questionnaires that assessed sleep disturbance, fatigue, depressive symptoms, anxiety, and pain prior to the initiation of RT through four months after the completion of RT. Wrist actigraphy was used as the objective measure of sleep disturbance. Hierarchical linear modeling (HLM) was used for data analyses.

Results—Mean wake after sleep onset (WASO) was 11.9% and mean total score on the General Sleep Disturbance Scale (GSDS) was 45. More than 85% of the patients had an abnormally high number of nighttime awakenings. Substantial interindividual variability was found for both objective and subjective measures of sleep disturbance. Body mass index predicted baseline levels of objective sleep disturbance. Comorbidity, evening fatigue, and depressive symptoms predicted baseline levels of subjective sleep disturbance, and depressive symptoms predicted the trajectory of subjective sleep disturbance.

Conclusion—Different variables predicted sleep disturbance using subjective and objective measures. The slightly elevated WASO found may be an underestimation of the degree of sleep disturbance when it is evaluated in the context of the high number of nighttime awakenings and patient's perception of poor sleep quality and quantity.

Address correspondence to: Christine Miaskowski, RN, PhD, FAAN Department of Physiological Nursing University of California 2 Koret Way – Box 0610 San Francisco, CA 94143-0610, USA chris.miaskowski@nursing.ucsf.edu.

Introduction

Sleep-wake disturbances occur in approximately 60% of patients with breast cancer and can persist after the completion of treatment (1-3). Although several cross-sectional studies found that sleep disturbance is associated with increased levels of fatigue, anxiety, and depression (4-8), as well as decreases in quality of life (9, 10), longitudinal data on sleep disturbance in breast cancer patients during and after cancer treatment are limited.

Assessment of sleep disturbance can include both objective (e.g., polysomnography, actigraphy) and subjective measures. Whereas polysomnography is considered the gold standard for the objective measurement of sleep disturbance, it correlates well with actigraphy (11). However, sleep quality questionnaires do not always correlate with objective measures, such as actigraphy (11). Therefore, both types of measures are recommended to evaluate various dimensions of sleep disturbance (12).

Only one cross-sectional (13) and one longitudinal study (14) were found that evaluated self-reported sleep disturbance in women with breast cancer during radiation therapy (RT). In a cross-sectional study of women with breast cancer receiving RT (13), 300 women were screened for insomnia using a brief questionnaire and those with insomnia were interviewed to obtain more details about it. Nineteen percent of these women met the diagnostic criteria for an insomnia syndrome and 51% experienced insomnia symptoms. Radiation therapy was implicated as contributing to sleep disturbance in 33 of 76 patients. In a longitudinal study of patients with breast (n=33) and prostate (n=23) cancer during RT (14), sleep was measured using the self-report Medical Outcomes Study – Sleep Scale at multiple time points prior to, during, and after RT. Hierarchical linear and nonlinear modeling (HLM) was used to analyze the data. In this study that focused on coping, women with breast cancer who were high in avoidance coping reported greater sleep dysfunction. Finally, only three studies (4, 15, 16) were found that used both subjective and objective measures to evaluate sleep disturbance in patients with breast cancer. However, these three studies evaluated sleep disturbance in patients undergoing chemotherapy for breast cancer. To our knowledge, no studies have used both types of measures to evaluate sleep disturbance in women with breast cancer during and following RT.

Therefore, given the paucity of data and the fact that a large percentage of patients with breast cancer will receive RT, the purposes of this longitudinal study, in a sample of breast cancer patients who underwent RT, were to examine how actigraphy (objective sleep disturbance) and self-report ratings of sleep disturbance (subjective sleep disturbance) changed from the time of the simulation visit to four months after the completion of RT; to investigate, for the objective and subjective measures, whether specific patient, disease, and symptom characteristics predicted the initial levels and/or the characteristics of the trajectories of sleep disturbance; and to compare predictors of subjective and objective sleep disturbance.

Methods

Patients and Settings

These analyses, drawn from a larger, descriptive, longitudinal study of symptoms in patients and their family caregivers (FCs), analyzed data from 73 women with breast cancer. Patients were eligible to participate if they: were adults (18 years of age or older); were able to read, write, and understand English; had a Karnofsky Performance Status (KPS) score (17) of 60 or greater; and were scheduled to receive adjuvant RT. Patients were excluded if they had metastatic disease, more than one cancer diagnosis, or had a diagnosed sleep disorder (for example, sleep apnea, narcolepsy, restless leg syndrome). They were recruited from RT departments located in a comprehensive cancer center and a community-based oncology program. The study was approved by the Human Subjects Committee at the University of California, San Francisco and at the second study site.

One hundred and thirty-four patients with breast cancer were approached and 73 consented to participate in this longitudinal study (54.5% response rate). The major reasons for refusal were being too overwhelmed with their cancer experience or too busy. No differences were found in any of the demographic or disease characteristics between patients who did and did not choose to participate in this study.

Study Measures

Objective data on wake after sleep onset (WASO; percentage of time awake between sleep onset and sleep offset, calculated as % of total sleep time [TST] that is spent awake and in bed) were obtained by continuous noninvasive monitoring of activity over 48 hours using wrist actigraphy, which has been validated with EEG measures of sleep and awakenings in men and women with both healthy and disturbed sleep patterns (18-20). It provides continuous motion data using a battery-operated, wristwatch-size microprocessor that senses motion with a piezoelectric beam and detects movement in all three axes. The accompanying Action 4® software (Ambulatory Monitoring, Inc., Ardsley, NY) allows analysis of activity and non-activity as well as automatic scoring of sleep and wake in one minute intervals.

Subjective sleep disturbance was assessed using the General Sleep Disturbance Scale (GSDS) (21). The GSDS consists of 21 items that evaluate various aspects of sleep disturbance. Each item is rated on a numeric rating scale (NRS) that ranges from 0 (never) to 7 (every day).The GSDS total score is the sum of the seven subscale scores (i.e., quality of sleep, quantity of sleep, sleep onset latency, midsleep awakenings, early awakenings, medications for sleep, excessive daytime sleepiness) that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). Each mean subscale score can range from 0 to 7. Higher total and subscale scores indicate higher levels of sleep disturbance. Subscales scores of three or greater and a GSDS total score 43.0 or more indicate a clinically significant level of sleep disturbance. The GSDS has well-established validity and reliability in shift workers, pregnant women, and patients with cancer and HIV (21-24). In the current study, the Cronbach's alpha for the GSDS total score was 0.81.

Additional study instruments included a demographic questionnaire, the KPS scale (17), the Lee Fatigue Scale (LFS) (25), the Center for Epidemiological Studies-Depression Scale (CES-D) (26), the Spielberg State-Trait Anxiety Inventories (STAI-S and STAI-T) (27), and a descriptive NRS for worst pain intensity from the Brief Pain Inventory (28).

The demographic questionnaire provided information on age, marital status, years of education, living arrangements, ethnicity, and employment status. In addition, patients completed a checklist of comorbidities.

Fatigue severity was measured using the 13-item LFS. Each item is rated using a 0 to 10 NRS and a total score is calculated as the mean of the 13 items that can range from 0 to 10, with higher scores indicating higher levels of fatigue severity. Respondents were asked to rate each item based on how they felt "right now," within 30 minutes of awakening (i.e., morning fatigue), and prior to going to bed (i.e., evening fatigue) for two consecutive days and nights. The LFS has been used with healthy individuals as well as in patients with cancer and HIV (22, 24, 29). It was chosen for the current study because it is relatively short and easy to administer and has established cutoff scores for clinically significant levels of fatigue (i.e., 3.2 or greater for morning fatigue, 5.6 or greater for evening fatigue). The LFS has well-established validity and reliability (25, 30). In the current study, the Cronbach's alphas for the LFS for evening and morning ratings were 0.95 and 0.96, respectively.

The CES-D comprises 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60, with scores of 16 or greater indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well-established concurrent and construct validity (26, 31, 32). In the current study, the Cronbach's alpha for the CES-D was 0.83.

The STAI-T and STAI-S inventories consist of 20 items each that are rated from one to four. The scores for each scale are summed and can range from 20 to 80. A higher score indicates greater anxiety. The cutoff scores for clinically significant levels of trait and state anxiety are 31.8 or greater and 32.2 or greater, respectively. The STAI-T measures an individual's predisposition to anxiety determined by his/her personality and estimates how a person generally feels. The STAI-S measures an individual's transitory emotional response to a stressful situation. It evaluates the emotional responses of worry, nervousness, tension, and feelings of apprehension related to how a person feels "right now" in a stressful situation. The STAI-S and STAI-T inventories have well-established criterion and construct validity and internal consistency reliability coefficients (27, 33, 34). In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.86 and 0.91, respectively.

Worst pain was evaluated using a descriptive NRS that ranged from 0 (no pain) to 10 (excruciating pain). A descriptive NRS is a valid and reliable measure of pain intensity (35). Because the majority of the patients in this study did not have pain, for the subsequent longitudinal analyses, pain was recoded as present or absent.

Study Procedures

At the time of the simulation visit, which occurred approximately one week prior to the start of RT, patients were approached by a research nurse to discuss participation in the study. During the simulation visit, the patient's treatment plan is formulated, measurements are taken, and the patient's skin is marked in order to insure that the patient is positioned correctly and in the same way for each RT treatment. After patients gave written informed consent, they completed the baseline study questionnaires, their height and weight were obtained, and blood was drawn for hemoglobin. Medical records were reviewed for disease and treatment information.

Patients wore the wrist actigraph on their nondominant wrist to monitor sleep and activity continuously for two consecutive days. Wrist actigraphy data were collected on weekdays to avoid confounding data with weekend sleep patterns. Data were collected for only 48 hours to reduce respondent burden, maximize the number of eligible patients, and minimize the amount of missing data.

The epoch length for the wrist actigraph was set at 30 seconds. Patients were asked to use the event marker on the wrist actigraph to indicate "lights out" and "lights on" time. Patients

reported no difficulties wearing the wrist actigraph. Because the actual time is important in the calculation of the amount of sleep obtained in the amount of time designated for sleep, having an additional source of information about nap times, bed times, and wake times is important. This information was recorded by patients in a two-day diary. Upon awakening, the patients used the diary to indicate the number of awakenings during the night. Patients returned the questionnaires and actigraphs to the research nurse at the completion of each of the assessments (i.e., baseline, weekly during RT, end of RT, monthly for two months, and every other month for two months for a total of 16 assessments over six months). Patients completed the GSDS at the time of the simulation visit (baseline) and monthly thereafter for a total of seven assessments.

Data Analysis

Descriptive statistics and frequency distributions were generated on the sample characteristics, baseline symptom severity scores, and sleep disturbance subscale scores using SPSS™ Version 18.0 (IBM Corporation, Armonk, NY). AU: PLS CHECK THAT VERSION 18 SHOULD BE ATTRIBUTED TO IBM. Body mass index (BMI) was calculated as the weight (kilograms) divided by the height (meters) squared.

Actigraphy files, programmed in zero-crossing mode with 30 second intervals, were analyzed using the Cole-Kripke algorithm in the Action 4® software (Ambulatory Monitoring, Inc., Ardsley, NY) by two of the researchers (KL and CW). The file was first scanned for missing data. The file was reviewed and intervals were individually set for each day and night period using, in order of priority, as decision guides: the event marker, diary data, channel data, and cascading movement data. Because no differences were found in WASO between the two days of data collection, mean values were calculated and used in the subsequent analyses.

HLM, based on full maximum likelihood estimation, was done using the software developed by Raudenbush and colleagues (36). The repeated measures of sleep disturbance were conceptualized as being nested within individuals. Compared with other methods of analyzing change, HLM has two major advantages. First, HLM can accommodate unbalanced designs, which allows for the analysis of data when the number and the spacing of the assessments vary across respondents. Although every patient was to be assessed on a pre-specified schedule, the actual number of assessments was not the same for all of the patients because some patients had longer periods of RT and some had scheduling conflicts. Second, HLM has the ability to model individual change, which helps to identify more complex patterns of change that are often overlooked by other methods (36, 37).

With HLM, the repeated measures of the outcome variables (i.e., subjective and objective sleep disturbance) are nested within individuals and the analysis of change in sleep disturbance scores has two levels: within persons (Level 1) and between persons (Level 2). At Level 1, the outcome is conceptualized as varying within individuals and is a function of person-specific change parameters plus error. At Level 2, these person-specific change parameters are multivariate outcomes that vary across individuals. These Level 2 outcomes can be modeled as a function of demographic or clinical characteristics that vary between individuals, plus an error associated with the individual. Combining Level 1 with Level 2 results in a mixed model with fixed and random effects (36, 38, 39).

Separate HLM analyses were done to evaluate changes over time in measures of objective (i.e., WASO as percent of time awake after sleep onset) and subjective (i.e., total GSDS score) sleep disturbance. Each HLM analysis proceeded in two stages. First, intra-individual variability in sleep disturbance over time was examined. In this study, time in weeks refers to the length of time from the simulation visit to four months after the completion of RT

(i.e., six months with a total of 16 assessments for WASO and seven assessments for GSDS). Three Level 1 models, which represented that the patients' sleep disturbance levels (a) did not change over time (i.e., no time effect), (b) changed at a constant rate (i.e., linear time effect), and (c) changed at a rate that accelerates or decelerates over time (i.e., quadratic effect), were compared. At this point, the Level 2 model was constrained to be unconditional (i.e., no predictors) and likelihood ratio tests were used to determine the best model. These analyses answered the first research question and identified the change parameters that best described individual changes in objective and subjective measures of sleep disturbance over time.

The second stage of the HLM analysis, which answered the second research question, examined interindividual differences in the trajectories of objective and subjective sleep disturbance by modeling the individual change parameters (i.e., intercept, linear, and quadratic slopes) as a function of proposed predictors at Level 2. Table 1 presents a list of the proposed predictors that was developed based on a review of the literature of sleep disturbance in women with breast cancer (4-8, 11, 12, 40-42). To improve estimation efficiency and construct models that were parsimonious, separate exploratory Level 2 analyses were done for objective and subjective sleep disturbance in which each potential predictor was assessed to see if it would result in a better fitting model if it alone was added as a Level 2 predictor. Predictors with a *t*-value of < 2.0, which indicates a lack of a significant effect, were dropped from subsequent model testing. All of the potentially significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Only predictors that maintained a significant contribution in conjunction with other variables were retained in the final models. A *P*-value of <0.05 indicates statistical significance.

Results

Patient Characteristics and Symptom Severity Scores

Table 2 displays the demographic, disease, and treatment characteristics of the 73 patients. This sample of patients, with a mean age of 55 years, was well-educated, had a KPS score of 87.7, an average BMI of 27.4, and an average of five comorbidities (58% of the sample had more than five comorbidities). The most common comorbid conditions were allergies (58.6%), back problems (54.8%), headaches (44.4%), and hypertension (27.8%). Fifty-six percent had localized disease (stage 1) while 44% had locally advanced (stage 2 or 3) disease. Seventy-four percent of the patients had breast conserving surgery. Almost 50% had a lymph node dissection and 55% had received chemotherapy prior to RT. The mean baseline symptom severity scores for the 73 patients are listed in Table 2.

Subscale Scores for Objective and Subjective Sleep Disturbance

Scores for the various actigraphy parameters and the subscale scores for the GSDS at baseline are listed in Table 3. The mean scores for the various actigraphy parameters were compared to healthy adult values (12) and the percentage of patients outside the normal range are reported in Table 3. For the GSDS, the percentage of patients who scored three or more on each of the subscales or 43 or more for the total score are listed in Table 3.

For actigraphy, 87% of the sample had an excessive number of awakenings, 46% had an abnormal WASO, and 58% had a TST below healthy adult values (i.e., 420-540 minutes per night). For the GSDS, 51% reported poor quality of sleep, 97% reported poor quantity of sleep, and 77% were above the cutoff score for the number of mid-sleep awakenings. Fifty-four percent of the patients were above the cutoff score for total GSDS score.

Objective Measure of Sleep Disturbance

Individual and Mean Change in the Objective Measure of Sleep Disturbance—

Fig. 1a displays the individual WASO trajectories for the 73 patients. The first HLM analyses examined how WASO changed from the time of the simulation visit to four months after the completion of RT. Linear, quadratic, and cubic trends were tested. The estimates of the linear change model for WASO are presented in Table 4 (unconditional model). Because the model had no covariates (i.e., unconditional), the intercept represents the estimated percentage of WASO (i.e., 11.861%) at the time of the simulation visit. The estimated linear rate of change in WASO, for each additional week, was 0.008 and not significant (P=0.81). Fig. 2a displays the trajectory for WASO from the time of the simulation visit to four months after the completion of RT. WASO increased very slightly over the course of RT (i.e., weeks 0 to 9), but this trend was not statistically significant. The variance in individual change parameters estimated by the models (i.e., variance components, Table 4) suggested that substantial interindividual differences existed in the trajectories of WASO (see Fig. 1a). These results suggested that further examination of interindividual differences in the individual change parameters was warranted.

Interindividual Differences in the Objective Measure of Sleep Disturbance—

The second stage of the HLM analyses tested the hypothesis that the pattern of change over time in WASO varied based on specific person, disease, treatment, and/or symptom variables that were found to influence sleep disturbance among patients who underwent RT for breast cancer. As shown in the final model in Table 4, the *slope* of the line for WASO is flat and the one variable that predicted interindividual differences in the *intercept* for WASO was BMI. No variables predicted interindividual differences in the *slope parameters* for WASO. To illustrate the effects of BMI on patients' trajectories of WASO, Fig. 2b displays the adjusted change curves for WASO that were estimated based on differences in BMI (i.e., lower and higher BMI calculated based on one standard deviation (SD) above and below the mean BMI score).

Subjective Measure of Sleep Disturbance

Individual and Mean Change in Subjective Measure of Sleep Disturbance—

Fig. 1b displays the individual GSDS total score trajectories of the 73 patients. The estimates of the linear change model for GSDS total scores are presented in Table 4 (unconditional model). Because the model had no covariates (i.e., unconditional), the intercept represents the estimated GSDS total score (i.e., 45.615) at the time of the simulation visit. The estimated linear rate of change in GSDS total score, for each additional week, was −0.177 (P<0.05). Fig. 3a displays the trajectory for subjective sleep disturbance from the time of the simulation visit to four months after the completion of RT. GSDS total score decreased slightly over the course of RT (i.e., weeks 0 to 9). Although the results indicate a *sample-wide* decrease in GSDS total score, they do not imply that all patients exhibited the same trajectory. The variance in individual change parameters estimated by the models (i.e., variance components, Table 4) suggested that substantial interindividual differences existed in the trajectories of subjective sleep disturbance (see Fig. 1b).

Interindividual Differences in the Subjective Measure of Sleep Disturbance—

As shown in the final model in Table 4, the three variables that predicted interindividual differences in the *intercept* for GSDS total score were the number of comorbidities, baseline level of evening fatigue, and baseline level of depressive symptoms. The variable that predicted interindividual differences in the *slope parameters* for GSDS total score was baseline level of depressive symptoms.

To illustrate the effects of the three different predictors on patients' trajectories of GSDS total score, Figs. 3b to 3d display the adjusted change curves for GSDS total score that were estimated based on differences in number of comorbidities (i.e., five or more comorbidities, yes or no), baseline level of evening fatigue (i.e., low evening fatigue/high evening fatigue calculated based on one SD above and below the mean evening fatigue score), and baseline level of depressive symptoms (i.e., low CES-D/high CES-D calculated based on one SD above and below the mean CES-D score).

It should be noted that the mean WASO and GSDS scores for the various groups depicted in all of the figures are *estimated or predicted means* based on the HLM analyses.

Discussion

This longitudinal study of breast cancer patients is the first to evaluate both objective and subjective measures of sleep disturbance during and after RT. The percentages of this sample with abnormal WASO and total GSDS scores at the initiation of RT were approximately 50%. This percentage is consistent with previous reports of sleep disturbance among cancer patients in general when occurrence rates are based on self-report measures (1, 43). However, the rate is much higher than the 19% of patients who met the criteria for insomnia syndrome, using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and International Classification of Sleep Disorders (ICSD) criteria, in an earlier cross-sectional study of women with breast cancer receiving RT (13). The fact that the self-report of sleep disturbance in this study is similar to earlier studies that used self-report measures, lends validity to the present findings. Reasons for these differences may relate to the instruments and methods used to classify sleep disturbance.

The HLM analysis of WASO that adjusted for covariates (Table 4, final model) demonstrated that at the initiation of RT, patients were awake after sleep onset for approximately 11% of their TST, which is above the cutoff for healthy adults (less than 10%) (12). This WASO is similar to that reported by Beck and colleagues (16) (11.5%) and Berger and colleagues (4) (13.9%), but less than that reported by Ancoli-Israel and colleagues (15) (24%) among women with breast cancer receiving chemotherapy. Furthermore, no improvements in WASO occurred over the six months of the study as evidenced by the flat predicted curve for WASO. This finding suggests that sleep disturbance persists in these women long after RT ends.

Higher BMI was associated with more objective sleep disturbance at the initiation of RT. Of note, 30% of the women had a BMI of more than 30, which is the cutoff score for obesity (44). Although two cross-sectional studies of risk factors for sleep disturbance did not find an association between BMI and sleep disturbance (6, 45), sleep apnea syndrome is associated with obesity (46). Whereas participants were excluded from this study if they had a diagnosed sleep disorder, such as sleep apnea, it is possible that some of the patients had undiagnosed sleep apnea. This finding warrants investigation in future studies.

In terms of subjective sleep disturbance, although the unadjusted GSDS score at baseline was 46, in the final model, after adjusting for covariates, the baseline GSDS total score was 41 (Table 4). The predicted trajectory for GSDS total scores had a small downward slope, which suggests only minimal improvement in subjective reports of sleep disturbance over the six months of the study. Consistent with findings from a cross-sectional study of a mixed patient population (47), a higher number of comorbidities was associated with higher GSDS scores at the initiation of RT. In this study, comorbidity was defined broadly and included conditions that ranged in severity from allergies and back problems to heart disease, stroke,

and liver disease. Additional research is warranted to determine the impact of specific comorbidities in addition to cancer on patients' perceptions of sleep disturbance.

Higher levels of evening fatigue at baseline were associated with higher GSDS scores at the initiation of RT. Although no studies were found that measured both morning and evening fatigue in patients with cancer, positive correlations were found between fatigue severity and sleep disturbance in several studies of oncology patients with a variety of cancer diagnoses (4, 15, 48). Of note, depressive symptoms was the only predictor of both the intercept and the linear trajectory of subjective sleep disturbance in this sample. Consistent with previous reports (6, 15, 48, 49), higher levels of depressive symptoms were associated with more sleep disturbance at baseline and a gradual improvement in subjective sleep disturbance over the six months of this study. The complex interplay between sleep disturbance, fatigue, and depression warrants additional investigation into whether these three symptoms represent a symptom cluster that shares a common biological mechanism (50).

It is interesting to note that different types of variables predicted subjective and objective sleep disturbance. Whereas subjective sleep disturbance was influenced by other subjective symptoms (i.e., depression, fatigue), only BMI predicted variability in WASO. These findings need to be confirmed and additional research is warranted on differential predictors of objective and subjective sleep disturbance that may suggest differences in the underlying mechanisms for these two components of sleep disturbance.

The mean WASO in this sample was 11% (with 46% of the sample having an abnormal WASO), which is above the normal range for healthy adults (less than 10%) (12). However, this parameter may be an underestimate of the severity of sleep disturbance in this sample. First, over 87% of the sample had an abnormally high number of awakenings per night, suggesting that patients were lying in bed awake and motionless for periods of time after each awakening, which would be scored as sleep during the analysis of the actigraphy data. Second, this mean number of awakenings corresponds to the GSDS subscale score that showed that 77% of the sample reported a significant number of mid-sleep awakenings on three or more nights per week. Taken together, these findings suggest that these women with breast cancer had a problem with sleep maintenance. In addition, given the fact that 51% of the sample reported poor sleep quality and 97% of the sample reported an insufficient amount of sleep on three or more days per week, future studies need to include both objective and subjective measures of sleep disturbance to provide a more comprehensive evaluation of this symptom. In addition, a comparison of findings from polysomnography and actigraphy may provide additional information on the magnitude and type of sleep disturbance in oncology patients.

An examination of the concordance between a number of the actigraphy parameters and the corresponding self-report measure suggests only minimal agreement when comparisons are done with the percentage of patients who scored above established cutoffs. For example, in terms of number of awakenings, 87% of the sample was above the healthy adult value of less than six per night using actigraphy and 77% of the sample scored above the cutoff of three or greater on the GSDS subscale of mid-sleep wakes. For sleep onset latency, the differences in the percentages of patients with abnormal objective and subjective values are larger (i.e., 26% versus 41%, respectively). Finally when the percentage of patients with abnormal TST (58%) was compared to the percentage of patients who reported an insufficient amount of sleep (97%), the difference between measures is large. Whereas the concordance between objective and subjective measures in healthy individuals tends to reflect an underestimation of self-reported sleep compared to actigraphy (51), the relatively low agreement between objective and self-report measures in this study is consistent with a previous report in oncology patients (12).

This study is limited by its small sample size, relatively well-educated patient population, and single cancer diagnosis and gender. However, few longitudinal studies of sleep disturbance in oncology patients are published and even fewer studies evaluated both objective and subjective measures of sleep disturbance in patients with a single cancer diagnosis. In addition, the HLM analyses optimized the evaluation of the study's longitudinal data. Vasomotor symptoms occur frequently in women undergoing treatment for breast cancer and may contribute to sleep disturbance (11). However, these symptoms were not measured in detail, which is another limitation of this study. The occurrence of sweats, which can accompany hot flashes, was measured as a single item in this study. Although this symptom is not equivalent to hot flashes, it may provide a general sense of the frequency of hot flashes in this sample. This symptom was reported by 28.2% of the patients prior to the initiation of RT. Given that a quarter of the patients experienced sweats, this symptom warrants investigation in future studies of sleep disturbance in patients with breast cancer.

In conclusion, findings from this study suggest that a significant number of women with breast cancer who are about to undergo RT experience problems with sleep maintenance that persists for six months. Women with a higher number of comorbidities and higher levels of evening fatigue and depressive symptoms, as well as women with a higher BMI, may be at greater risk for sleep disturbance. Additional research is needed to determine the specific predictors of sleep quality and number of awakenings in order to identify potential targets for interventions to improve sleep in these vulnerable patients.

Acknowledgments

References

1. Berger AM. Update on the state of the science: sleep-wake disturbances in adult patients with cancer. Oncol Nurs Forum. 2009; 36:E165–177. [PubMed: 19581220]

2. Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. J Clin Oncol. 1995; 13:2737–2744. [PubMed: 7595732]

3. Fortner BV, Stepanski EJ, Wang SC, Kasprowicz S, Durrence HH. Sleep and quality of life in breast cancer patients. J Pain Symptom Manage. 2002; 24:471–480. [PubMed: 12547047]

4. Berger AM, Farr LA, Kuhn BR, Fischer P, Agrawal S. Values of sleep/wake, activity/rest, circadian rhythms, and fatigue prior to adjuvant breast cancer chemotherapy. J Pain Symptom Manage. 2007; 33:398–409. [PubMed: 17397701]

5. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol. 2000; 18:743–753. [PubMed: 10673515]

6. Bardwell WA, Profant J, Casden DR, et al. The relative importance of specific risk factors for insomnia in women treated for early-stage breast cancer. Psychooncology. 2008; 17:9–18. [PubMed: 17428006]

7. Dirksen SR, Epstein DR, Hoyt MA. Insomnia, depression, and distress among outpatients with prostate cancer. Appl Nurs Res. 2009; 22:154–158. [PubMed: 19616162]

8. Van Onselen C, Dunn LB, Lee K, et al. Relationship between mood disturbance and sleep quality in oncology outpatients at the initiation of radiation therapy. Eur J Oncol Nurs. 2010; 14(5):373–379. [PubMed: 20080444]

9. Bower JE. Behavioral symptoms in patients with breast cancer and survivors. J Clin Oncol. 2008; 26:768–777. [PubMed: 18258985]

10. Vargas S, Wohlgemuth WK, Antoni MH, et al. Sleep dysfunction and psychosocial adaptation among women undergoing treatment for non-metastatic breast cancer. Psychooncology. 2010; 19:669–673. [PubMed: 19626593]

11. Vena C, Parker K, Cunningham M, Clark J, McMillan S. Sleep-wake disturbances in people with cancer part I: an overview of sleep, sleep regulation, and effects of disease and treatment. Oncol Nurs Forum. 2004; 31:735–746. [PubMed: 15252429]

12. 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. [PubMed: 16270104]

13. Savard J, Simard S, Blanchet J, Ivers H, Morin CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. Sleep. 2001; 24:583–590. [PubMed: 11480655]

14. Thomas KS, Bower J, Hoyt MA, Sepah S. Disrupted sleep in breast and prostate cancer patients undergoing radiation therapy: the role of coping processes. Psychooncology. 2010; 19:767–776. [PubMed: 19885853]

15. Ancoli-Israel S, Liu L, Marler MR, et al. Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. Support Care Cancer. 2006; 14:201–209. [PubMed: 16010529]

16. Beck SL, Berger AM, Barsevick AM, et al. Sleep quality after initial chemotherapy for breast cancer. Support Care Cancer. 2010; 18:679–689. [PubMed: 19521723]

17. Karnofsky, D. Performance scale. Plenum Press; New York: 1977.

18. Morgenthaler T, Alessi C, Friedman L, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep. 2007; 30:519–529. [PubMed: 17520797]

19. Ancoli-Israel S, Cole R, Alessi C, et al. The role of actigraphy in the study of sleep and circadian rhythms. Sleep. 2003; 26:342–392. [PubMed: 12749557]

20. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. Sleep. 2006; 29:1155–1173. [PubMed: 17040003]

21. Lee KA. Self-reported sleep disturbances in employed women. Sleep. 1992; 15:493–498. [PubMed: 1475563]

22. Lee KA, DeJoseph JF. Sleep disturbances, vitality, and fatigue among a select group of employed childbearing women. Birth. 1992; 19:208–213. [PubMed: 1472269]

23. Lee KA, Gay C, Portillo CJ, et al. Symptom experience in HIV-infected adults: a function of demographic and clinical characteristics. J Pain Symptom Manage. 2009; 38:882–893. [PubMed: 19811886]

24. 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; 17:320–332. [PubMed: 10355211]

25. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res. 1991; 36:291–298. [PubMed: 2062970]

26. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement. 1977; 1:385–401.

27. Spielberger, CG.; Gorsuch, RL.; Suchene, R.; Vagg, PR.; Jacobs, GA. Manual for the State-Anxiety (Form Y): self evaluation questionnaire. Consulting Psychologists Press; Palo Alto, CA: 1983.

28. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain. 1983; 17:197–210. [PubMed: 6646795]

29. Lee KA, Portillo CJ, Miramontes H. The fatigue experience for women with human immunodeficiency virus. J Obstet Gynecol Neonatal Nurs. 1999; 28:193–200.

30. Lee KA, Lentz MJ, Taylor DL, Mitchell ES, Woods NF. Fatigue as a response to environmental demands in women's lives. Image J Nurs Sch. 1994; 26:149–154. [PubMed: 8063323]

31. Carpenter JS, Andrykowski MA, Wilson J, et al. Psychometrics for two short forms of the Center for Epidemiologic Studies-Depression Scale. Issues Ment Health Nurs. 1998; 19:481–494. [PubMed: 9782864]

32. Sheehan TJ, Fifield J, Reisine S, Tennen H. The measurement structure of the Center for Epidemiologic Studies Depression Scale. J Pers Assess. 1995; 64:507–521. [PubMed: 7760258]

33. Bieling PJ, Antony MM, Swinson RP. The State-Trait Anxiety Inventory, Trait version: structure and content re-examined. Behav Res Ther. 1998; 36:777–788. [PubMed: 9682533]

34. Kennedy BL, Schwab JJ, Morris RL, Beldia G. Assessment of state and trait anxiety in subjects with anxiety and depressive disorders. Psychiatr Q. 2001; 72:263–276. [PubMed: 11467160]

35. Jensen MP. The validity and reliability of pain measures in adults with cancer. J Pain. 2003; 4:2–21. [PubMed: 14622723]

36. Raudenbush, S.; Bryk, A. Hierarchical linear models: Applications and data analysis methods. 2nd ed. Sage Publications; Thousand Oaks, CA: 2002.

37. Raudenbush SW. Comparing personal trajectories and drawing causal inferences from longitudinal data. Annu Rev Psychol. 2001; 52:501–525. [PubMed: 11148315]

38. Li LW. Longitudinal changes in the amount of informal care among publicly paid home care recipients. Gerontologist. 2005; 45:465–473. [PubMed: 16051909]

39. Li LW. From caregiving to bereavement: trajectories of depressive symptoms among wife and daughter caregivers. J Gerontol B Psychol Sci Soc Sci. 2005; 60:P190–198. [PubMed: 15980286]

40. Blazer DG, Hays JC, Foley DJ. Sleep complaints in older adults: a racial comparison. J Gerontol A Biol Sci Med Sci. 1995; 50:M280–284. [PubMed: 7671031]

41. Dorrepaal KL, Aaronson NK, van Dam FS. Pain experience and pain management among hospitalized cancer patients. A clinical study. Cancer. 1989; 63:593–598. [PubMed: 2463876]

42. Berger AM, Wielgus K, Hertzog M, Fischer P, Farr L. Patterns of circadian activity rhythms and their relationships with fatigue and anxiety/depression in women treated with breast cancer adjuvant chemotherapy. Support Care Cancer. 2009 [Epub ahead of print].

43. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol. 2001; 19:895–908. [PubMed: 11157043]

44. World Health Organization. Report of a WHO consultation. Vol. 894. World Health Organization; 2000. Obesity: preventing and managing the global epidemic; p. 1-253.Techinical Report Series

45. Sivertsen B, Krokstad S, Overland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. J Psychosom Res. 2009; 67:109–116. [PubMed: 19616137]

46. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. JAMA. 2004; 291:2013–2016. [PubMed: 15113821]

47. Taylor DJ, Mallory LJ, Lichstein KL, et al. Comorbidity of chronic insomnia with medical problems. Sleep. 2007; 30:213–218. [PubMed: 17326547]

48. Palesh OG, Roscoe JA, Mustian KM, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. J Clin Oncol. 2010; 28:292–298. [PubMed: 19933917]

49. Savard J, Simard S, Hervouet S, et al. Insomnia in men treated with radical prostatectomy for prostate cancer. Psychooncology. 2005; 14:147–156. [PubMed: 15386779]

50. Miaskowski C, Aouizerat BE. Is there a biological basis for the clustering of symptoms? Semin Oncol Nurs. 2007; 23:99–105. [PubMed: 17512436]

51. Carskadon MA, Dement WC, Mitler MM, et al. Self-reports versus sleep laboratory findings in 122 drug-free subjects with complaints of chronic insomnia. Am J Psychiatry. 1976; 133:1382–1388. [PubMed: 185919]
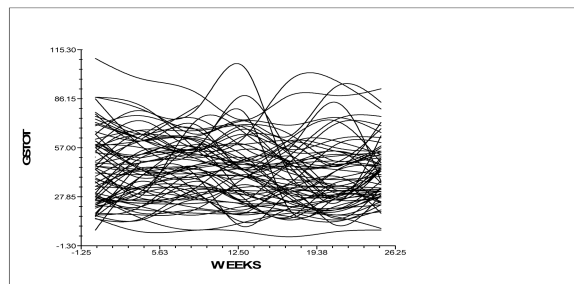
A.
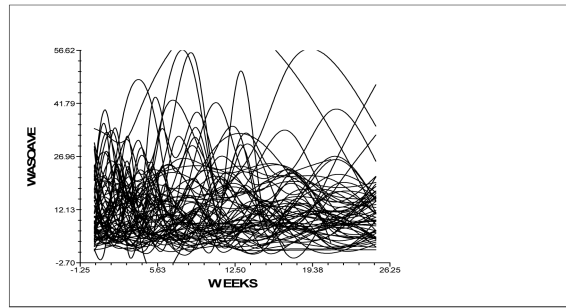
B.

Fig. 1.
Spaghetti plot of the 73 patients' individual trajectories for wake after sleep onset (WASO - A) and total scores on the General Sleep Disturbance Scale (GSDS - B) over the 25 weeks of the study.
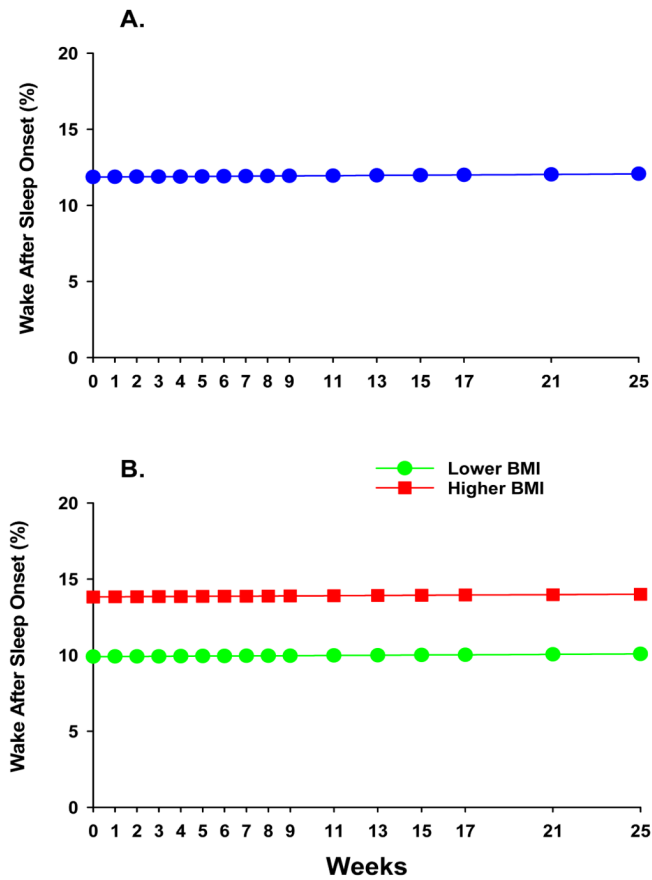
Fig. 2.
Trajectories of wake after sleep onset (WASO) over the 25 weeks of the study (A) and the influence of body mass index (BMI; B) on interindividual differences in the intercept for WASO (B).
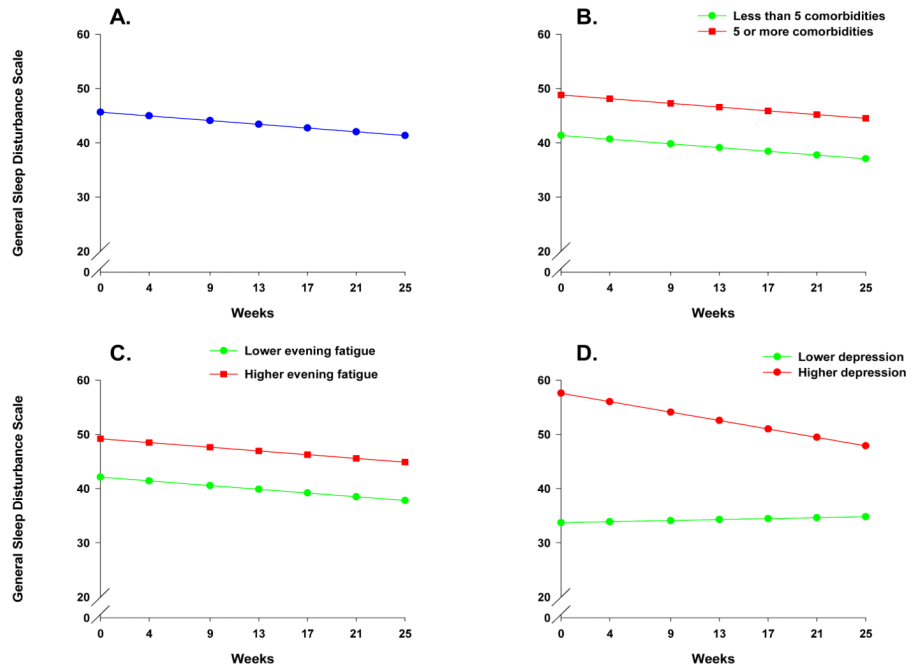
Fig. 3.
Trajectories of total scores on the General Sleep Disturbance Scale (GSDS) over the 25 weeks of the study (A); the influence of comorbidities (B) and evening fatigue (C) on interindividual differences in the intercept for total GSDS score and the influence of depressive symptoms (D) on the intercept and linear slope for total GSDS score.

Table 1

Potential Predictors of Intercept (I) and Linear Coefficient (LC) for Subjective and Objective Sleep Disturbance

Potential Predictors	Subjective Sleep Disturbance		Objective Sleep Disturbance	
	I	LC	I	LC
Person				
Age				
Lives alone				
Marital status				
Education				
Ethnicity				
Employment status				
Children at home				
Body mass index			∎	
Disease and treatment				
KPS score	∎			
Comorbidities	∎			
Stage of disease				
Total dose of radiation				
Previous chemotherapy				
Previous hormone therapy				
Symptoms				
Baseline evening LFS score	∎			
Baseline CES-D score	∎	∎		
Presence of pain at baseline				
Baseline AFI score	∎	∎		
Baseline Trait Anxiety score	∎			

AFI = Attentional Functional Index; CES-D = Center for Epidemiologic Studies Depression Scale; KPS = Karnofsky Performance Status; LFS = Lee Fatigue Scale;

∎ = From exploratory analysis had a *t*-value of > 2.00

Table 2

Demographic, Disease, and Treatment Characteristics of the Patients (*n*=73)

Characteristic	Mean (Standard Deviation)
Age (years)	55.1 (11.0)
Education (years)	16.2 (2.7)
Karnofsky Performance Status score	87.7 (12.4)
Number of comorbidities	5.3 (2.6)
Weight (pounds)	165.2 (43.6)
Body mass index	27.4 (7.3)
Hemoglobin (g/dl)	12.7 (1.2)
Lives alone	41.0%
Marital status	
Married/partnered	28.8%
Divorced/separated	30.1%
Other	41.1%
Ethnicity	
Non-White	30.0%
White	70.0%
Employed	
Yes	45.0%
No	55.0%
Children at home	22.0%
Stage	
Localized	56.2%
Locally advanced	43.8%
Any chemotherapy received	55.0%
Lymph node dissection	49.0%
Total dose of RT (cGys)	5829 (438.3)
Mean Total Sleep Time (minutes) at baseline	418.6 (72.6)
Mean symptom severity scores at baseline	
GSDS score	44.7 (21.7)
LFS score for morning fatigue	2.9 (2.1)
LFS score for evening fatigue	4.9 (1.8)

Characteristic	Mean (Standard Deviation)
CES-D score	12.0 (9.2)
Trait Anxiety Inventory score	36.2 (11.3)
State Anxiety Inventory score	33.7 (12.9)
Patients with pain at baseline	49.3%
Patients reporting sweats frequently or constantly	28.2%

CES-D = Center for Epidemiologic Studies Depression Scale; GSDS = General Sleep Disturbance Scale; LFS = Lee Fatigue Scale; RT = radiation therapy

Table 3

Mean Values for Various Actigraphy Parameters and General Sleep Disturbance Subscale Scores

Actigraphy Parameters and GSDS Subscales	Mean (SD)	Percentage Outside Normal Range[a]	Normal Range/Cutoffs
Actigraphy			
Sleep onset latency (minutes)	14.7 (12.2)	25.6	<20 minutes
Percent wake after sleep onset (WASO)	11.0 (8.3)	46.2	<10%
Number of awakenings	15.1 (8.8)	87.2	<6
Wake duration (minutes)[b]	3.5 (2.6)		
Total sleep time (TST) minutes hours	419.8 (69.8) 7.0 (1.2)	57.7	>420 minutes
Sleep period time (minutes)	493.1 (71.1)		
Sleep efficiency (%)	85.5 (8.7)	26.9	>80%
General Sleep Disturbance Scale (GSDS)			
Quality of sleep	2.8 (2.1)	51.3	>3.0
Quantity of sleep	4.6 (1.3)	97.4	>3.0
Sleep onset latency	2.4 (2.5)	41.0	>3.0
Mid sleep wakes	4.5 (2.5)	76.9	>3.0
Early awakenings	2.9 (2.4)	51.3	>3.0
Excessive daytime sleepiness	2.3 (1.4)	30.8	>3.0
Medications for sleep	0.4 (0.7)	1.3	>3.0
Total score	45.4 (21.8)	53.9	43.0

[a]Percentage abnormal for actigraphy is based on deviations from healthy adult values. Percentage abnormal for GSDS is based on the cutoff of 3.0 for each subscale score and 43.0 for the total GSDS score.

[b]Mean time awake per awakening.

$^{c}P < 0.05.$