



Published in final edited form as:

J Pain Symptom Manage. 2007 April ; 33(4): 398–409.

Values of Sleep/Wake, Activity/Rest, Circadian Rhythms, and Fatigue Prior to Adjuvant Breast Cancer Chemotherapy

Ann M. Berger, PhD, RN, AOCN, FAAN, Lynne A. Farr, PhD, Brett R. Kuhn, PhD, CBSM, Patricia Fischer, BSN, RN, CCRC, and Sangeeta Agrawal, MS

University of Nebraska Medical Center, Omaha, NE

Abstract

Fatigue is the most prevalent and distressing symptom experienced by patients receiving adjuvant chemotherapy for early stage breast cancer. Higher fatigue levels have been related to sleep maintenance problems and low daytime activity in patients who have received chemotherapy, but knowledge is sparse describing these relationships prior to chemotherapy. The Piper Integrated Fatigue Model[©] guided this study, which describes sleep/wake, activity/rest, circadian rhythms and fatigue, and how they inter-relate in women with Stage I, II or IIIA breast cancer during the 48 hours prior to the first adjuvant chemotherapy treatment. The present report describes these variables in 130 females, mean age = 51.4 years; the majority were married and employed. Subjective sleep was measured by the Pittsburgh Sleep Quality Index (PSQI) and fatigue was measured by the Piper Fatigue Scale (PFS). Wrist actigraphy was used to objectively measure sleep/wake, activity/rest, and circadian rhythms. Mean PSQI score was 6.73 ± 3.4 , indicating poor sleep. Objective sleep/wake results were within limits of normal (WNL) established for healthy individuals, except for the number and length of night awakenings. Objective activity/rest results were WNL except for low mean daytime activity. Circadian rhythm mesor was $132.3(24.6)$ and amplitude was $97.2(22.8)$. Mean PFS score was 2.56 ± 2.0 , with 72% reporting mild fatigue. There were significant relationships between subjective and objective sleep, but no consistent patterns. Higher total and subscale fatigue scores were correlated with most components of poorer subjective sleep quality ($r = 0.25$ to 0.42 , $P = < 0.005$).

Keywords

Sleep/wake; activity/rest; circadian rhythm; fatigue; actigraph; breast cancer; chemotherapy

Introduction

Cancer-related fatigue (CRF) associated with antineoplastic therapy can have a profound impact on an individual's life, with significant physical, emotional, social, and economic consequences that may persist for months or years after completing treatment (1). CRF has been defined by the National Comprehensive Cancer Network (p. FT-1) as "a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (2). Among the

Address reprint requests to: Ann M. Berger, PhD, RN, 985330 Nebraska Medical Center, Omaha, NE 68198-5330, E-mail: aberger@unmc.edu

Authors wish to disclose the absence of financial support and off-label or investigational use of drugs or devices for this study. This study was funded by the National Institute of Nursing Research (#5R01NR007762-05).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

many factors that have been found to be associated with CRF are the presence and severity of anxiety, pain, lower sleep quality, physical inactivity, and poor performance status (1). Models of CRF have linked disturbed sleep/wake patterns with fatigue (3) and models of impaired sleep have proposed that fatigue is an expected outcome of either restricted total sleep time or fragmented sleep during the night (4).

Previous studies in breast cancer patients provide limited information about the relationship between CRF and sleep prior to chemotherapy. Determining results from a large sample may provide information that will allow comparison across studies of CRF and sleep, and to clarify the effects of interventions designed to reduce CRF and improve sleep. Several randomized controlled trials, including one described in this article, are currently underway that test interventions to modify CRF by promoting quality sleep and increasing activity (5). Knowledge of the relationship between CRF and sleep is enhanced when studies include both subjective and objective measures.

Actigraphy involves the use of a portable device to record movement over time in the format of activity counts. The size of a man's wristwatch, the device is most commonly placed on the non-dominant wrist to objectively measure sleep/wake, activity/rest, and circadian activity rhythms (6). Fairly consistent terms have been reported in the literature to represent night sleep/wake variables (6), but there has been less consistency in reporting day activity/rest variables and circadian activity rhythms (7,8). Terms suggested by teams that participated in either a National Cancer Institute (NCI) sponsored State of the Science Conference on Sleep/Wake Disturbances in People with Cancer and their Caregivers (8) or an expert panel that developed consensus recommendations for a standard set of research assessments in insomnia (9) are reported in this paper. Twenty studies were found that reported results of the use of actigraphy to measure sleep/wake, activity/rest, and/or circadian rhythms in adult cancer patients. Almost all studies included samples of breast (10–17) or colo-rectal cancer patients (18–24); other samples included adults with early and advanced lung cancer (25–27); bone metastasis (28); childhood brain tumor cancer survivors (29), or a variety of cancers (30). Only two of the 20 studies focused on sleep/wake, activity/rest, circadian rhythms, and fatigue prior to the first adjuvant breast cancer chemotherapy treatment (10,15). This type of chemotherapy treatment is given after the main tumor has been removed and any remaining cancer is in small amounts (microscopic metastases).

Ancoli-Israel et al. (10) reported patterns for 72-hrs prior to chemotherapy and found that women ($n=73$) reported moderate fatigue and disturbed sleep that was verified by actigraphy results. Total sleep time while in bed at night was 6.0 hrs and 76% of the time spent in bed at night was spent asleep, both of which are below normal (8). Time awake after sleep onset (WASO) was 1.8 hr/night. This was much longer than the 30 minutes (min) considered normal. These data provided subjective and objective evidence of sleep disturbances in women prior to chemotherapy.

In another study, Berger et al. (15) found that women ($n=24$) reported mild fatigue (2.1 ± 2.0 on a 0–10 scale) and actigraphs showed some sleep variables were already disturbed 48-hrs prior to chemotherapy. Total rest time in a 24-hour period, defined as total time in bed (min) plus napping during the day (min) minus sleep latency and WASO (min), was 8.2 hrs. Sleep efficiency was 86%. Both were within normal limits (WNL) for healthy people (8). However, mean WASO was 1.2 hrs/night (mean total time in bed was 9.0 hrs.) and mean number of awakenings during the sleep period was 9.8 ± 6.3 (higher than the normal 2 to 6 times/night). These objective results indicate major sleep maintenance problems prior to adjuvant chemotherapy.

A better understanding of sleep/wake, activity/rest, and circadian rhythms and their relationship to other factors such as fatigue will be enhanced by examining a large sample of women with breast cancer prior to chemotherapy. Therefore, the purpose of this paper is to provide a description of the values of sleep/wake, activity/rest, circadian activity rhythms, and fatigue; and how they inter-relate in women with Stage I, II or IIIA breast cancer during the 48 hours prior to the first adjuvant chemotherapy treatment.

Methods

The present study is an analysis of baseline data from our Fatigue and Breast Cancer Study (FBC), which has enrolled 219 women with stage I, II, or IIIA breast cancer who received surgery and then adjuvant anthracycline-based chemotherapy. Participants in the experimental arm of the study are coached to develop and adhere to an “Individual Sleep Promotion Plan”© (ISPP). Participants assigned to the control arm receive equal time and attention and information about healthy eating topics. Details of the pilot study are found elsewhere (14–15). The Piper Integrated Fatigue Model© was the conceptual framework selected for the study (3). This model proposes that 14 biochemical, physiologic, and psychosocial patterns are the factors most likely to influence fatigue. Sleep/wake and activity/rest patterns were selected from the model to determine their relationship to fatigue prior to chemotherapy.

Eligibility criteria included adults ages 19 years and older diagnosed with stage I–IIIA breast cancer for the first time. Patients had undergone surgery and were scheduled to receive anthracycline-based adjuvant chemotherapy. Karnofsky score was equal to or higher than 60, and they were able to complete the research instruments. Exclusion criteria included co-morbid diagnosis of chronic fatigue syndrome, unstable congestive heart failure, chronic obstructive pulmonary disease, insulin-dependent diabetes, neuromuscular disease, sleep apnea, abnormal thyroid function, chronic steroid therapy, or working a job with rotating or permanent night shifts. The setting for this study was a mid-sized Midwestern city in the United States. Participants received chemotherapy at several local outpatient medical oncology clinics. Both subjective and objective measures of sleep/wake and activity/rest were obtained; circadian rhythms were only determined by objective measurement. As a subjective phenomenon, fatigue can only be ascertained by self-report, and was assessed in four subscales to determine mild, moderate, and severe fatigue experiences.

Subjective Sleep/Wake

The Pittsburgh Sleep Quality Index (PSQI) takes less than 10 minutes to complete and was administered on Day -2 prior to chemotherapy. This paper-and-pencil questionnaire measures subjective sleep quality during the previous month (31). Responses to the 19 items are grouped into seven components measuring sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medication use, and daytime dysfunction. These components are weighted equally on a 0–3 scale, with a global PSQI score ranging from 0–21. Higher scores indicate more severe complaints and a greater decrease in sleep quality. In women with breast cancer, Cronbach’s alpha for the global PSQI was 0.80 and was 0.82 in this study. Evidence for construct validity has also been demonstrated. A global PSQI score above 5 has been found to have a sensitivity of 89.6% and a specificity of 86.5% in differentiating good from poor sleepers. A cutoff score of 8 was found to discriminate poor sleep quality in cancer patients (32).

Objective Sleep/Wake, Activity/Rest and Circadian Rhythms

Octagonal Motionlogger™ Actigraphs (Ambulatory Monitoring, Inc, Ardsley, NY) were worn continuously for 48-hrs during usual daily activities. One-minute epochs were used to measure sleep/wake, activity/rest, and circadian rhythms. Six sleep/wake and five activity/rest variables

were selected that were identified by either an NCI-sponsored conference (8) or an expert panel that recommended a standard set of research assessment in insomnia (9). Four circadian rhythm variables were chosen: mesor (24-hr rhythm-adjusted mean activity movements); amplitude (measure of the extent of rhythmic change or range of activity and rest values over 24-hrs); acrophase (time of the peak in the 24-hr cycle); and goodness of fit (measure of robustness and consistency of the rhythm) (33). Days of the week of monitoring varied based on the day of the week of chemotherapy. The unit contains a piezoelectric linear accelerometer, a microprocessor, and 2 MB memory. Actigraphy offers a useful, noninvasive method of objectively quantifying actual movement over time. It is an important index of sleep/wake and activity/rest in natural settings, such as home or military fields of operation, and it is a valuable and valid addition to diary information (6,7). The sensitivity of the accelerometer has been optimized to collect high quality sleep/wake data from the wrist actigraph (34–36).

Advantages of actigraphy include that it provides 24-hrs continuous, direct measurement of movement and indirect measurement of sleep. Actigraphy is sensitive and precise compared to self-report. It is user-friendly to wear, small, portable, light-weight, and comfortable. Scores can be quickly obtained using algorithms that correlate with polysomnography in normal adults at greater than 90%, the gold standard for cortical activity measures of wake and sleep stages (6).

Fatigue

The Piper Fatigue Scale (PFS) (37) measures subjective cancer-related-fatigue (CRF). The scale takes 2 to 5 minutes to fill out and was completed on Day -2 prior to chemotherapy. The PFS total score contains 22 items divided into four subscales of subjective fatigue: behavioral/severity (six items), sensory (five items), cognitive/mood (six items), and affective meaning (five items). Each item is anchored by two descriptors (e.g., strong versus weak), and participants circle a number from 0–10 that best describes their fatigue experience on that day. Total and subscale mean scores were obtained by summing the individual items of each subscale or total score and dividing by the number of items in the subscale or total score. Internal consistency of the total scale and the subscales range from alphas of 0.92–0.98 across numerous and diverse studies and was 0.95 and 0.92–0.95 in this study. Content and concurrent validity estimates have been reported in cancer patients. Ranges of scores have been divided into mild (0–3.99), moderate (4.0–6.99) and severe (7.0–10.0) to report results of this study.

Procedures

The study was approved by the local Scientific Review Committee for proposals involving cancer patients and the Institutional Review Board. All eligible patients were invited to participate in the study. Research nurses met the participants at their home or mutually agreeable place. The research nurse followed the study protocol to obtain informed consent, perform randomization stratified by site, sleep status history (good versus poor sleeper per item #6 on PSQI), number of chemotherapy treatments planned (four or more than four), and deliver the appropriate intervention.

Each participant received a full orientation to the study. Instructions were given for completing questionnaires and continuously wearing the actigraph beginning at the time they got out of bed on Day -2 prior to chemotherapy until they rose from bed on Day +7 after chemotherapy. Data from Days -2 and -1 (48-hrs prior to chemotherapy) will be reported here. Since chemotherapy treatments were given during the week, the 48-hrs of data collection could have occurred on any two-day periods except Thursday-Friday and Friday-Saturday. The actigraph event marker and the daily diary responses were used to discriminate wake from sleep times when setting the intervals prior to the analysis.

Plans for analysis of the questionnaires included computing the means, standard deviations and ranges. Spearman rank correlations were performed between variables. SPSS version 13 and SAS version 9.1 programs (38,39) were used for data management. All actigraphy data files were handled using the Action 4© software version 1.13 user's guide to obtain sleep/wake, activity/rest, and circadian rhythm variables results (40). Because of the limited time available for the participant and research nurse to meet prior to chemotherapy, it was determined that actigraphy day data met criteria for inclusion if the research nurse met the participant and started data collection by 1:00 p.m. on the first day. Data were included in the analysis if they contained at least one 24-hrs day/night cycle out of the desired 48-hrs of data collection. Out of 128 women with night actigraphy data, 11 (8.6%) had data from one night and 117 (91.4%) had data from two nights. Of the 130 subjects with day actigraphy data, 37 (28.5%) had data from one day and 93 (71.5%) had data from two days. About two-thirds of the women put the actigraph on at or before 9:00 am on the first day.

Actigraphy files in zero-crossing-mode (ZCM) were analyzed using the Cole-Kripke algorithm in Action 4© by two of the authors (AB & PF), who had established inter-rater reliability agreement greater than 80% on more than 50 files of both good and poor sleepers. The file was first scanned for missing data and if more than four hours of day data or two hours of night data were missing from each interval, that day or night was not used in the analysis. Time limits were set for the 48-hr period and automatic sleep scoring was performed. 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, sleep channel data, and cascading movement counts. The Action 4© user's guide assisted in analyzing data and generating sleep/wake, activity/rest, and circadian rhythms (40). Cosinor analysis fitted a cosine curve to the wrist activity data using a least-squares cosinor regression model to determine circadian rhythms (33).

This report includes 130 participants enrolled into the study from April, 2003 to November, 2005. During that 31-month period, 432 patients were screened, 175 consented, and 26 withdrew after consenting. Of the remaining 149 participants, 130 had adequate data for analysis. Table 1 displays the sample's demographic characteristics.

Results

Subjective sleep ratings as measured by the PSQI total and components are displayed in Table 2. The mean total score prior to chemotherapy (6.61 ± 3.42) was higher than the upper limit for normal sleep but lower than the proposed cut-off for cancer patients (32). Among the components, the sleep disturbance subscale had the highest score, with all participants reporting sleep maintenance insomnia once or twice a week. Fifty-seven percent of participants' total score was higher than 5 and 26% of participants' total score was higher than 8, reflecting subjectively poor sleep during the month prior to treatment.

Objective sleep/wake, activity/rest, and circadian rhythms values obtained by actigraphy are shown in Table 3. Sleep/wake variables include: sleep-onset latency (min), wake after sleep onset (WASO; min), number of awakenings (number), total sleep time (at night after sleep onset; min/hrs), and sleep efficiency (after sleep onset). Percent wake night is also included and is preferred over traditional sleep laboratory measures of sleep efficiency because sleep efficiency includes sleep latency, or time to fall asleep after the lights are out, which is less reliable when using actigraphy (41). Mean sleep/wake variables were WNL for all values except number of awakenings and WASO minutes.

Objective activity/rest variables obtained during the day include: daytime activity (count/min), total sleep time (min), total wake time (min), sleep percent day, and wake percent day. Mean

values for daytime activity counts/min (188.4 ± 5.9) were at the low end of the normal range (185–245 counts/min) indicating low activity during the two days prior to chemotherapy (42). Total sleep time and day sleep percent were WNL.

Circadian rhythms obtained by actigraphy include: mesor, amplitude, acrophase, and goodness of fit (GOF). These values are based on 48 or fewer hours of recording and may not be as accurate as 72 hour recordings. The mean mesor was $132.25(24.5)$, or 93% of the value of 138.20 ± 8.38 , and the amplitude was $97.18(22.8)$, or 86.5% of the value of 112.35 ± 4.93 , established by Farr and Boen using mid-life women scheduled for elective surgery (11,43). Acrophase and GOF values were WNL at 12:59 and 0.62 ± 11 .

Perceived fatigue ratings prior to chemotherapy are shown in Table 4. Total and subscale PFS scores were in the mild range with a mean of 2.56 ± 2.0 (0 to 10 scale). While 72% of the participants reported mild fatigue, 27 % reported moderate fatigue, and 1% reported severe fatigue. The cognitive/mood subscale (3.30 ± 2.4) was the fatigue subscale reported as most affected prior to chemotherapy.

Significant correlations between subjective and objective sleep/wake, activity/rest, circadian rhythms, and fatigue are displayed in Table 5. Regarding fatigue and subjective sleep, higher fatigue total scores were correlated with poorer sleep total scores ($r = 0.36, P < 0.0001$). Higher total and subscales fatigue scores were correlated with all components of poorer sleep except sleep duration and habitual sleep efficiency (Table 6). Higher fatigue scores were most strongly correlated with the daytime dysfunction PSQI component ($P < 0.001$).

When examining fatigue and objective measures of sleep/wake, activity/rest and circadian rhythms, only acrophase was significantly related with higher total and behavioral/severity, cognitive/mood, and affective meaning subscales scores. This means that those who got up and going later in the morning reported higher fatigue.

Tests of the associations between subjective and objective measures of sleep/wake found that the subjective PSQI total scores were not correlated with any of the objective sleep/wake variables. A few significant correlations were found between subjective PSQI sleep components and objective sleep/wake variables, including shorter perceived sleep duration and higher reported sleep disturbances with higher number of WASO minutes. Self-identified use of sleeping medications was related to higher sleep efficiency. In contrast, PSQI total scores reflecting poorer sleep were related to all of the objective activity/rest variables representing lower daytime activity and time awake ($P < 0.001$ to $P < 0.01$). In addition, higher total PSQI scores and the components of sleep quality, sleep latency, and habitual sleep efficiency were correlated with lower mesor ($P < 0.001$ to $P < 0.01$). Longer subjective sleep latency was the only component associated with lower amplitude ($P < 0.05$).

Discussion

The current study was undertaken to further establish values for sleep/wake, activity/rest, circadian rhythms, and fatigue and how they inter-relate in women with Stage I, II or IIIA breast cancer prior to the first adjuvant chemotherapy treatment. Findings provide an indication of expected values for comparison to other samples of women in studies examining these variables and their inter-relationships. These values also provide an important benchmark for interpreting any results of intervention studies to reduce CRF. Findings support the linkages posited in models between disturbed sleep/wake patterns and fatigue (3,4).

Results confirm the sleep maintenance problems and mild fatigue experienced by women with breast cancer even before receiving chemotherapy. Low daytime activity may be independent or dependent of the prior nights' sleep. Recognition that amplitude was almost 15% more

dampened than in the healthy population of mid-life women scheduled for elective surgery studied by Farr and Boen (11,43) generates hypotheses about the inter-relationships between activity rhythm variables and fatigue. Disrupted sleep, low daytime activity, and/or a dampened range of activity over 24-hr periods is likely to contribute to perceptions of mild fatigue prior to chemotherapy and moderate to severe fatigue after chemotherapy. While it has been difficult to untangle the mechanisms influencing CRF, these findings show it to be related to sleep/wake and activity/rest at this point in the treatment and not to be solely a result of chemotherapy.

It should be noted that these values obtained prior to chemotherapy do not represent a true baseline because they do not reflect patterns of sleep/wake, activity/rest or circadian rhythms of otherwise healthy middle-aged women. Nor do they represent a profile that should be the goal for interventions designed to improve sleep, reduce fatigue, and promote entrainment of circadian rhythms. They reflect the pathophysiological insult, emotional stress, and decision-making burden experienced by women at this point in the disease and treatment trajectory. However, it should be noted that more disturbed sleep per actigraphy may not be as highly correlated with polysomnography (36).

These findings support Ancoli-Israel et al.'s suggestion that sleep is already disturbed and fatigue is already present prior to chemotherapy (10). We are currently testing the ISPP© intervention designed to reduce fatigue by increasing day activity and improving sleep and circadian rhythms during and following chemotherapy. Patients may benefit from this intervention during chemotherapy, but are likely to require earlier introduction to the intervention in the cancer trajectory for maximum symptom management based on our initial findings from this study. We currently do not know whether disrupted sleep/wake, activity/rest, circadian rhythms, and higher fatigue are related to the effects of the cancer, the stress of diagnosis, recent surgery, mood disturbances, and/or the anticipation of chemotherapy and its impact on quality of life.

The current results can be compared to those in two prior studies. Ancoli-Israel et al. (10) and Berger et al. (15) both reported more WASO time than was found in this sample. The range of mean values reported in this study was 1.0 hr and was from 1.2 to 1.8 hrs spent awake at night in the prior studies. Total sleep time while in bed at night was 37 min longer in this sample (6.6 hrs) than in Ancoli-Israel et al.'s study (6.0 hrs). Ancoli-Israel's study did not provide information on participants' menopausal status for comparison, and that might explain the differences.

There are several possible explanations for why the total rest time was shorter in the present study than in Berger et al.'s study (15). Participants in the current larger sample had a total rest time of 6.5 hrs compared to 8.2 hrs in the smaller sample. The difference might be due to the number of participants who were employed at the time of year when data were collected. In the current study, 78% were employed and data were collected throughout the year. In the smaller study, 60% were employed and data were collected in fall and winter months. Other possibilities include differences in sample size and the duration of actigraph monitoring periods, which may reflect discrepancies in the number of week days versus weekend days collected.

The PFS was used in Berger et al.'s small sample and with this larger sample. In both studies, women reported mild fatigue (< 4.0) (15). Women reported moderate fatigue on the Multidimensional Fatigue Symptom Inventory-Short Form (MFI) in the study by Ancoli-Israel et al (10). A study comparing four cancer-related fatigue questionnaires, but not the PFS, recommended that the MFI undergo additional testing with cancer patients because of concerns regarding the construct validity of the instrument (44). Future comparisons that include both instruments would assist in understanding findings of this and other studies.

Lower daytime activity and increased nighttime restlessness have been found to be associated with higher fatigue during chemotherapy (12). This relationship appears to exist even prior to chemotherapy, although statistical significance was not reached. In both Berger et al.'s pilot intervention study (15) and in the current study, sleep efficiency higher than 85% and mild fatigue (<4.0) were reported. Ancoli-Israel et al.'s (10) descriptive study reported lower sleep efficiency (76%) and moderate fatigue prior to chemotherapy. These variables will be tested for their relationship at each treatment and at several selected times following the completion of chemotherapy.

In the present study, higher levels of fatigue were correlated with poorer subjective sleep in almost all components. Yet, no single objective sleep/wake variable was correlated with subjective sleep. All objective activity/rest variables, representing lower daytime activity and more day resting, were related to poorer subjective sleep. Lower mesor obtained by actigraphy was also associated with poorer perceived sleep. These results are consistent with previous findings that subjective and objective measures of sleep do not correlate, but rather complement each other (45). One possibility for these findings in this study is that the participant responses to the PSQI were in relation to sleep during the prior month, whereas the actigraphy recorded sleep during a specific 48 hrs of time. The point worth noting here is that associations between higher fatigue and poorer sleep are found prior to receiving chemotherapy.

There are advantages and disadvantages to the use of subjective and objective measures of sleep/wake, activity/rest, and circadian rhythm patterns in persons with cancer. Subjective instruments do not consistently correlate with objective measures; there may be missing data, responses require retrospective recall, and responses are difficult to control for time of day of completion of the instrument. Sleep diaries are not considered to be an accurate assessment, but rather subjective perceptions of sleep, and were only used in this study to determine bed-time and get-up times in order to create appropriate intervals for actigraphy analysis.

A limitation of objective data is that the actigraph may also have missing data related to malfunctioning, getting wet, failing to initialize or download correctly, and/or battery failure, which occurred only 1% of the time in this study. While the ideal study design would yield actigraphy data for a full 72-hrs prior to chemotherapy in order to study circadian rhythms, in addition to sleep/wake and activity/rest, it was not always feasible to recruit the participant to the study in time to collect 48-hrs of data. We recognize that this time limitation restricts our ability to perform accurate circadian rhythm analyses, including the ability to evaluate patterns of sleep/wake and activity/rest and their stability over time (7). There are known limitations with wrist actigraphy, including the reliability of the latency variable each night (35) and its inability to distinguish between immobile sleep and waking that may lead to an inflated total sleep time. Values for actigraphy data in healthy adult women are sparse in the literature and only sleep/wake values have been reported in a group of 20–40 year olds (45). Descriptions of procedures to set time limits and intervals, to handle missing data, and to establish inter-rater reliability (when appropriate) are sparse in the literature and have lead to inconsistent analysis of data files (46). Other instruments to measure activity may only be useful for collecting information about day activity. Polysomnography is only useful for sleep stage measures and is limited by higher cost than actigraphy and the artificial environment of a sleep laboratory.

In conclusion, these results for sleep/wake, activity/rest, circadian rhythms, and fatigue in a large sample of women prior to the first adjuvant breast cancer chemotherapy treatment provide values for comparison with future studies. Larger samples with 72 hours or more of data will be needed in future research to provide normative data values. The current study confirms that values obtained prior to chemotherapy are not a true baseline. Sleep maintenance problems, low daytime activity, and/or lower circadian rhythms likely contribute to the perceptions of mild fatigue prior to chemotherapy and moderate to severe fatigue after chemotherapy. To

maximize fatigue management, patients may benefit from an intervention introduced prior to cancer surgery that promotes night sleep, increases day activity, and entrains circadian rhythms.

Acknowledgements

The authors wish to acknowledge Kathryn Lee PhD, RN, CBSM, for her mentoring during this study.

References

1. Prue G, Rankin J, Allen J, Gracey J, Cramp F. Cancer-related fatigue: A critical appraisal. *Eur J Cancer* 2006;42:846–863. [PubMed: 16460928]
2. National Comprehensive Cancer NetworkNCCN clinical practice guidelines in oncology-v.1.2006. Retrieved July 10, 2006, from www.nccn.org
3. Piper BF, Lindsey AM, Dodd MJ. Fatigue mechanisms in cancer patients: developing nursing theory. *Oncol Nurs Forum* 1987;14:17–23. [PubMed: 3320981]
4. Lee, KA. Impaired sleep. In: Carrieri-Kohlman, V.; Lindsey, A.; West, C., editors. *Pathophysiological phenomena in nursing: Human responses to illness*. 3. St Louis: Saunders; 2003. p. 363-385.
5. National Institute of HealthCRISP data base, 2006. Retrieved July 10, 2006, from <http://crisp.cit.nih.gov/>
6. 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]
7. Littner M, Kushida CA, Anderson WM, et al. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. *Sleep* 2003;26(3):336–341.
8. Berger A, Parker K, 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–E126. [PubMed: 16270104]
9. Buysse DJ, Ancoli-Israel S, Edinger JD, et al. Recommendations for a standard research assessment of insomnia. *Sleep* 2006;29:1148–1166.
10. 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]
11. Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. *Oncol Nurs Forum* 1998;25:51–62. [PubMed: 9460773]
12. Berger AM, Farr L. The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. *Oncol Nurs Forum* 1999;26:1663–1671. [PubMed: 10573683]
13. Berger AM, Higginbotham P. Correlates of fatigue during and following adjuvant breast cancer chemotherapy: a pilot study. *Oncol Nurs Forum* 2000;27:1443–1448. [PubMed: 11058976]
14. Berger AM, VonEssen S, Kuhn BR, et al. Adherence, sleep, and fatigue outcomes after adjuvant breast cancer chemotherapy: results of a feasibility intervention study. *Oncol Nurs Forum* 2003;30:513–522. [PubMed: 12719750]
15. Berger AM, VonEssen S, Kuhn BR, et al. Feasibility of a sleep intervention during adjuvant breast cancer chemotherapy. *Oncol Nurs Forum* 2002;29:1431–1441. [PubMed: 12432414]
16. Kuo HH, Chiu MJ, Liao WC, Hwang SL. Quality of sleep and related factors during chemotherapy in patients with stage I/II breast cancer. *J Formos Med Assoc* 2006;105:64–69. [PubMed: 16440072]
17. Roscoe JA, Morrow GR, Hickok JT, et al. Temporal interrelationships among fatigue, circadian rhythm and depression in breast cancer patients undergoing chemotherapy treatment. *Support Care Cancer* 2002;10:329–336. [PubMed: 12029433]
18. Mormont MC, De Prins J, Levi F. [Study of circadian rhythms of activity by actometry: preliminary results in 30 patients with metastatic colorectal cancer]. *Pathol Biol (Paris)* 1996;44:165–171. [PubMed: 8761603]
19. Mormont MC, Langouet AM, Claustrat B, et al. Marker rhythms of circadian system function: a study of patients with metastatic colorectal cancer and good performance status. *Chronobiol Int* 2002;19:141–155. [PubMed: 11962672]
20. Mormont MC, Waterhouse J. Contribution of the rest-activity circadian rhythm to quality of life in cancer patients. *Chronobiol Int* 2002;19:313–323. [PubMed: 11962684]

21. Mormont MC, Waterhouse J, Bleuzen P, et al. Marked 24-h rest/activity rhythms are associated with better quality of life, better response, and longer survival in patients with metastatic colorectal cancer and good performance status. *Clin Cancer Res* 2000;6:3038–3045. [PubMed: 10955782]
22. Chevalier V, Mormont MC, Cure H, Chollet P. Assessment of circadian rhythms by actimetry in healthy subjects and patients with advanced colorectal cancer. *Oncol Rep* 2003;10:733–737. [PubMed: 12684651]
23. Rich T, Innominato PF, Boerner J, et al. Elevated serum cytokines correlated with altered behavior, serum cortisol rhythm, and dampened 24-hour rest-activity patterns in patients with metastatic colorectal cancer. *Clin Cancer Res* 2005;11:1757–1764. [PubMed: 15755997]
24. Minors D, Akerstedt T, Atkinson G, et al. The difference between activity when in bed and out of bed. I. Healthy subjects and selected patients. *Chronobiol Int* 1996;13:27–34. [PubMed: 8761934]
25. Lee K, Cho M, Miaskowski C, Dodd M. Impaired sleep and rhythms in persons with cancer. *Sleep Med Rev* 2004;8:199–212. [PubMed: 15144962]
26. Levin RD, Daehler MA, Grutsch JF, et al. Circadian function in patients with advanced non-small-cell lung cancer. *Br J Cancer* 2005;93(11):1202–1208. [PubMed: 16265345]
27. Rumble ME, Keefe FJ, Edinger JD, Porter LS, Garst JL. A pilot study investigating the utility of the cognitive-behavioral model of insomnia in early-stage lung cancer patients. *J Pain Symptom Manage* 2005;30:160–169. [PubMed: 16125031]
28. 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]
29. Van Someren EJ, Swart-Heikens J, Endert E, et al. Long-term effects of cranial irradiation for childhood malignancy on sleep in adulthood. *Eur J Endocrinol* 2004;150:503–510. [PubMed: 15080780]
30. Young-McCaughan S, Mays MZ, Arzola SM, et al. Research and commentary: change in exercise tolerance, activity and sleep patterns, and quality of life in patients with cancer participating in a structured exercise program. *Oncol Nurs Forum* 2003;30:441–454. [PubMed: 12719744]
31. Buysse DJ, Reynolds CF 3rd, 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. [PubMed: 2748771]
32. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. *J Psychosom Res* 1998;45:5–13. [PubMed: 9720850]
33. Lentz MJ. Time-series analysis-cosinor analysis: a special case. *West J Nurs Res* 1990;12(3):408–412. [PubMed: 2363294]
34. de Souza L, Benedito-Silva AA, Pires ML, et al. Further validation of actigraphy for sleep studies. *Sleep* 2003;26:81–85. [PubMed: 12627737]
35. Lichstein KL, Stone KC, Donaldson J, et al. Actigraphy validation with insomnia. *Sleep* 2006;29:232–239. [PubMed: 16494091]
36. Tryon WW. Issues of validity in actigraphic sleep assessment. *Sleep* 2004;27:158–165. [PubMed: 14998254]
37. Piper BF, Dibble SL, Dodd MJ, et al. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncol Nurs Forum* 1998;25:677–684. [PubMed: 9599351]
38. SPSS for Windows ver. 13.0. Chicago: SPSS Inc; 2004.
39. SAS Institute. Ver. 9.1. Cary, NC: SAS; 2004.
40. Ambulatory Monitoring, Inc. User's guide to Action 4, version 1.13. Ardsley, NY: Ambulatory Monitoring, Inc;
41. Blackwell T, Ancoli-Israel S, Gehrman PR, et al. Actigraphy scoring reliability in the study of osteoporotic fractures. *Sleep* 2005;28:1599–1605. [PubMed: 16408420]
42. Brown AC, Smolensky MH, D'Alonzo GE, Redman DP. Actigraphy: a means of assessing circadian patterns in human activity. *Chronobiol Int* 1990;7:125–133. [PubMed: 2242506]
43. Farr, L.; Boen, L. NASA Space Grant Consortium Symposium. Lincoln, NE: Nebraska Academy of Sciences; 1996. Comparison of rectal and axillary temperature rhythms with activity.

44. Meek PM, Nail LM, Barsevick A, et al. Psychometric testing of fatigue instruments for use with cancer patients. *Nurs Res* 2000;49:181–190. [PubMed: 10929689]
45. Tworoger SS, Davis S, Vitiello MV, Lentz MJ, McTiernan A. Factors associated with objective (actigraphic) and subjective sleep quality in young adult women. *J Psychosom Res* 2005;59:11–19. [PubMed: 16126091]
46. Berger AM, Wielgus KK, Young-McCaughan S, et al. Methodological challenges when using actigraphy in research. *Cancer as a model*. in review

Table 1
Demographic Characteristics of the Sample Prior to Chemotherapy (*n*=130)

Variable	Numbers	Percent	Range
Age	Mean= 51.40+ 9.68		34–83 years
Marital Status	Single =13	10	
	Married =91	70	
	Divorced =22	17	
	Widowed =4	3	
Employment Status	Managers, professionals =51	40	
	Technical, sales, office, production, laborers =50	38	
	Homemaker, retired, unemployed =29	22	
	Hours of work: Mean=31.7		0–65 hours
Education	Less than high school=5	4	
	High school graduate =23	18	
	Some college= 41	31.5	
	College graduate =41	31.5	
	Post college graduate=20	15	
Ethnicity	Asian = 1	0.8	
	African American = 6	4.7	
	Caucasian = 119	91.5	
	Hispanic = 4	3.0	
Cancer Stage	Stage I = 45	36	
	Stage II= 60	48	
	Stage IIIA= 20	16	
Type of Surgery	Lumpectomy = 60	46	
	Modified Mastectomy = 37	29	
	Modified Mastectomy with Reconstruction = 33	25	
Menopause Status	Stopped >12 months =63	51	
	Stopped 6–12 months ago =3	2	
	Irregular past 6 months =13	11	
	Regular past 6 months =45	36	

Note: Missing data when numbers do not add up to 130.

Table 2
Subjective Sleep^a Prior to First Chemotherapy (*n*=130)

Variable	Possible Range	Mean	SD	Mean score range 0–0.9 (<i>n</i> , %)	Mean score range 1.–1.9 (<i>n</i> , %)	Mean score range 2–2.9 (<i>n</i> , %)
Total score (<i>n</i> =127)	0–21	6.61 ^b	3.42			
Sleep quality	0–3	1.0	0.68	25 (19)	85 (65)	20(15)
Sleep latency	0–3	1.11	0.93	37 (28)	54 (42)	39 (30)
Sleep duration	0–3	0.76	0.81	59 (46)	44 (34)	26 (20)
Habitual sleep efficiency	0–3	0.59	0.89	79 (62)	28(22)	20(16)
Sleep disturbances	0–3	1.55	0.57	0 (0)	64(49)	66(51)
Use of sleeping medications	0–3	0.74	1.17	87(67)	13(10)	30(23)
Daytime dysfunction	0–3	0.88	0.57	28(22)	90(69)	12(9)
Total score (<i>n</i> =127)				Mean score <=5 55(43)	Mean score >5 72(57)	Mean score >8 33(26)

Note: Missing data when numbers do not add up to 130.

SD = standard deviation.

^a Subjective sleep measured by Pittsburgh Sleep Quality Index (31)

^b Good sleeper < or = 5; poor sleeper >5 (28); poor sleeper with cancer >8 (32).

Table 3
Actigraph for Sleep/Wake, Activity/Rest, and Circadian Rhythms Prior to Chemotherapy ($n=128-130$)

Variable	Mean	SD	Range
<i>Sleep/wake</i>			
Sleep-onset latency (min)	11.38	17.88	0-187
Wake after sleep onset (WASO) (min/hr)	62.49/1.04	66.01	0-427 min
Number of awakenings	9.70	5.47	0-27.5
Total sleep time (min/hr)	396.84/6.61	95.74	90.0-604.5
Sleep efficiency (percentage)	86.13	15.14	17.4-100
Percent Wake night	13.87	15.14	0-82.6
<i>Activity/rest</i>			
Mean daytime activity	188.37	35.89	57.1-250.1
Total sleep time (min/hr)	64.17/1.07	57.79	0-285
Total wake time (min/hr)	829.72/13.83	133.53	71.5-1081
Sleep percent day	7.49	7.57	0-52.1
Wake percent day	92.51	7.57	47.9-100
<i>Circadian rhythms</i>			
Mesor	132.25	24.56	52.2-187
Amplitude	97.18	22.80	26.4-145.7
Acrophase	12:59	-	-
Goodness of Fit	0.62	0.11	0.3-0.88

SD = standard deviation.

Table 4
 Fatigue^{a, b} and Distribution of Scores Prior to Chemotherapy (n=130)

Variable	Possible Range	Mean	SD	Range	Mild (0–3.99) ^c	Moderate (4.0–6.99) ^c	High (7.0–10.) ^c
Behavioral/severity	0–10	1.91	2.1	0–7.3	107	19	4
Sensory	0–10	2.58	2.3	0–9.6	91	33	5
Cognitive/mood	0–10	3.30	2.4	0–9.0	76	48	6
Affective meaning	0–10	2.56	2.1	0–7.8	91	37	2
Total score	0–10	2.56	2.0	0–8.0	93	35	2

^aFatigue measured by Piper Fatigue Scale (37).

^bDescriptors for each item ranging from 0–10 to indicate none to severe.

^cNote: number of participants whose scores were within the range for each level.

Table 5
 Significant Correlations between Fatigue, Subjective Sleep, and Actigraph Measures of Sleep/Wake, Activity/Rest, and Circadian Rhythm ($n=128-130$)

Variable	Fatigue (Total score/PFS)	Subjective Sleep (Total score/PSQI)	Sleep Quality	Sleep latency	Sleep duration	Habitual sleep efficiency	Sleep disturbances	Use of sleeping medication	Daytime dysfunction
Fatigue (Total Score/PFS)		0.36 ^b	0.31 ^c	0.25 ^c			0.28 ^c	0.25 ^c	0.42 ^b
<i>Actigraph Sleep/Wake</i> ^a									
Sleep-onset latency		0.16 ^e	0.18 ^d			0.15 ^e	0.24 ^c	0.25 ^c	
Total sleep time					-0.20 ^d		0.18 ^d		
Number of awakenings					0.15 ^e		-0.17 ^d		
Wake after sleep onset									
Sleep Efficiency								0.18 ^d	
<i>Actigraph Activity/Rest</i>									
Mean daytime activity		-0.22 ^c							
Wake time day	-0.15 ^e	-0.23 ^b		-0.21 ^c					
Wake percent		-0.21 ^c							
Sleep time day		0.21 ^c							
Sleep percent		0.21 ^c							
<i>Circadian rhythms</i>									
Mesor		-0.27 ^c							
Amplitude			-0.18 ^d						
Acrophase	0.20 ^d			-0.24 ^c				0.17 ^d	
Goodness of Fit				0.16 ^e	-0.24 ^c			0.16 ^e	

^a Objective sleep variables obtained from wrist actigraphy.

^b $P < 0.001$.

^c $P < 0.01$.

^d $P < 0.05$.

^e Trend $t = 0.051-0.10$.

Table 6

Correlations Between Subjective Sleep and Fatigue ($n=130$)

Variable	Fatigue ^d Total Score	Behavioral/Severity	Sensory	Cognitive/mood	Affective meaning
Total Score ^b	0.36 ^d	0.35 ^d	0.26 ^e	0.30 ^d	0.37 ^d
Subjective sleep quality ^c	0.31 ^d	0.25 ^e	0.31 ^e	0.31 ^d	0.28 ^d
Sleep latency ^c	0.24 ^e	0.24 ^e	NS	0.18 ^f	0.28 ^d
Sleep duration ^c	NS	NS	NS	NS	NS
Habitual sleep efficiency ^c	NS	NS	NS	NS	NS
Sleep disturbances ^c	0.28 ^e	0.29 ^e	0.20 ^f	0.24 ^e	0.25 ^e
Use of sleeping medication ^c	0.25 ^e	0.25 ^e	NS	0.22 ^e	0.27 ^e
Daytime dysfunction ^c	0.42 ^d	0.38 ^d	0.34 ^d	0.42 ^d	0.37 ^d

NS = not significant.

^a Fatigue measured by Piper Fatigue Scale (PFS).^b Sleep measured by Pittsburgh Sleep Quality Index (PSQI).^c Components of the PSQI.^d $P < 0.001$.^e $P < 0.01$.^f $P < 0.05$.