Sleep quality after initial chemotherapy for breast cancer

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Abstract:
Goals of work: The goal of this study is to characterize sleep quality and quantity prior to and in the first three nights after initial chemotherapy for breast cancer.
Materials and methods: This study makes use of secondary analysis of data from two separate randomized clinical trials (RCT) of behavioral interventions to improve fatigue and sleep. Patients came from two comprehensive cancer centers, three clinical cancer centers, and 10 community clinics in five states. Participants were women with stage I—IIIA breast cancer treated with anthracycline and/or cyclophosphamide-based regimens.
Main results: Baseline data from each RCT were used in the analysis. Sixty-five percent of women self-reported poor sleep in the month preceding chemotherapy using the Pittsburgh Sleep Quality Index (PSQI) score >5. Three nights of actigraphy data indicated a wide range of sleep experience with an average of 10 awakenings and time (minutes) awake after sleep onset (WASO-M) averaging 61 min per night. The first night's sleep was the worst. There was no statistically significant relationship between self-reported poor sleep and sleep measures obtained by actigraphy. Women with poor sleep at baseline (global PSQI >5) had significantly lower ($p<0.001$) physical (PCS) and mental (MCS) health status. However, neither the PCS nor MCS was associated with any of the average actigraphy sleep parameters or night 1 parameters in the aggregated sample. Increasing age was also associated with poorer sleep.
Conclusions: A high percent of women with breast cancer begin chemotherapy with disturbed sleep and the initial nights after chemotherapy are characterized by sleep fragmentation that disrupts sleep maintenance. Interventions should focus on strategies to decrease the number and duration of night awakenings. Further research is needed to identify predictors of poor sleep during this time.
Keywords: Sleep, Chemotherapy, Breast cancer, Actigraphy, Neoplasm, Function

Article:

Introduction

Sleep–wake disturbances experienced by persons with cancer have received minimal attention from clinicians and researchers prior to the new millennium [1, 2]. Most estimates of the prevalence of various sleep–wake disturbances have been determined in cross-sectional surveys with mixed types of cancer, and range from 30% to 88% [3, 4]. Estimates in women with breast cancer have similar variability [5]. Although studies of sleep during treatment, post-treatment survivorship, and in women with metastatic disease have indicated problems such as difficulty falling asleep, frequent night-time awakenings, and increased daytime sleep, these studies are based on self-reports [6–10].

This report takes advantage of baseline data from two federally funded intervention trials to improve sleep and fatigue in order to characterize sleep quality and quantity prior to and in the first three nights after initial intravenous chemotherapy for breast cancer. The data sharing allows for analysis of both actigraphy and self-reported sleep data in 183 women receiving intravenous chemotherapy for breast cancer.

Review of literature

One specific area in which there is limited knowledge about sleep–wake patterns is during the initial period after receiving intravenous chemotherapy treatment for breast cancer. A review of the literature found only four studies on sleep–wake patterns during the first few nights after the initial intravenous chemotherapy treatment for breast cancer (Table 1) [7, 8, 11–13]. Each study provides a limited picture of sleep immediately following chemotherapy. There is evidence to suggest that although sleep efficiency may average above the recommended 85%, women experience problems with sleep maintenance, including increased number and duration of night awakenings; but data regarding total sleep time is conflicting. The number of night-time awakenings (average of eight to 10 per night) was above the normal adult experience of few and brief awakenings [14]. Time awake after sleep onset varied but was consistently more than the normal upper limit of 30 min/night. These data were all collected in small samples (n<75), reported limited sleep parameters, and did not consistently analyze for changes in the days following treatment.

The studies to date also did not consider whether sleep changes are associated with baseline sleep quality status, baseline mental or physical health status, or demographic or clinical variables. Such associations might lead clinicians to target those at high risk for sleep problems. In addition, understanding patterns of sleep disturbance might begin to inform the influence of sleep on fatigue which is known to peak 48- to 72-h post-chemotherapy. Inconsistent with general population studies, evidence that links age to sleep–wake disturbances in cancer is inconsistent and no studies used actigraphy [3]. There is no evidence to date that indicates that a specific stage of breast cancer influences sleep. Studies that examined associations between physical performance or functional status and sleep in cancer patients have yielded inconsistent results [4]. In a study using actigraphy in 24 patients receiving radiation therapy, there was a positive relationship between the Karnofsky performance status, sleep efficiency, and total sleep time [15]. No studies have specifically examined these relationships in women receiving initial chemotherapy for breast cancer.

Therefore, the purposes of this report were to:

1. Characterize sleep quality and quantity prior to and in the first three nights after initial intravenous chemotherapy for breast cancer;

2. Examine sleep measures in relation to pre-chemotherapy reports of being a good or poor sleeper and self-reported physical and mental well-being; and

3. Evaluate whether sleep measures are associated with specific demographic (age, education) and clinical (stage of disease) variables.

Table 1 Demographic and clinical characteristics of women with breast cancer

Characteristic	Study 1 n=101	Study 2 n=82	Combined n=183
Age (mean (SD))	50.48 (9.26)	50.96 (9.54)	50.70 (9.36)
Non-Hispanic (No. (%))	95 (96.0%)	77 (93.9%)	172 (95.0%)
White (No. (%))	92 (91.1%)	77 (93.9%)	169 (92.3%)
Married/partnered (No. (%))	80 (79.2%)	59 (72.0%)	139 (76.0%)
Education (No. (%))			
High school or less	20 (19.8%)	18 (22.0%)	38 (21.0%)
Some college or tech. school	36 (36.4%)	22 (26.8%)	58 (32.0%)
College graduate	43 (43.4%)	42 (51.2%)	85 (47.0%)
Clinical stage (No. (%))*			
1	21 (20.8%)	30 (36.6%)	51 (28.0%)
2	55 (54.5%)	41 (50.0%)	96 (52.7%)
3	24 (23.8%)	11 (13.4%)	35 (19.2%)

*p<0.05 (Chi square=6.74)

Materials and methods

This study was a secondary analysis of data from two separate data sets. The analysis reported here was conducted on the baseline data. Both studies were approved by appropriate institutional review boards and each

participant signed an informed consent. Additional IRB approval was obtained to share de-identified data for purposes of this analysis.

Design, setting, and sample of study 1

Study 1 was a randomized clinical trial (RCT) designed to test the effect of an intervention to manage fatigue and insomnia during cancer therapy on fatigue, insomnia, and functional status. Individuals were included in the clinical trial if they were adults, 18 and over, initiating chemotherapy (CTX) with or without radiotherapy and any prior treatment, other than surgery, had been completed at least 1 month prior. The sample of the RCT consisted of 222 individuals treated for breast, lung, colorectal, advanced prostate, gynecologic or testicular cancer, or lymphoma. For this analysis, only the breast cancer subset (n=125) was included. Exclusions were made for treatment with stem cell transplantation or biotherapy, chronic fatigue syndrome, diagnosed sleep disorder of narcolepsy or sleep apnea, overt evidence of a psychiatric disorder, or initiation of treatment for anemia or depression during the past 3 weeks.

Baseline questionnaires were completed prior to the initiation of chemotherapy and the delivery of the experimental intervention focused on energy and sleep enhancement (n=64) or the control intervention consisting of information about a healthy diet (n=61). Baseline actigraph data were collected for three nights beginning on the first day of chemotherapy.

Design, setting, and sample of study 2

Study 2 was a randomized clinical trial of an intervention to manage fatigue by improving sleep during adjuvant breast cancer CTX. The primary aim was to test the effect of the sleep intervention on fatigue. Individuals were included in the clinical trial if they were initiating anthracycline-based CTX. The sample of the RCT consisted of 219 women. Eligible individuals included adults age 19 and older who received an initial diagnosis of stages I—IIIA breast cancer, had undergone surgery, and were scheduled to receive adjuvant anthracycline-based chemotherapy. They were required to have a Karnofsky score of 60 or higher. Exclusion criteria included co-morbid conditions such as 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 requiring rotating or permanent night shifts.

Baseline questionnaires were completed prior to the first chemotherapy. Baseline actigraphy data and daily diaries were collected for two days prior to the first chemotherapy and continued for 7 days after the first chemotherapy treatment on all participants in study 2. The data used in the present analysis included actigraph data recorded for the first 3 days of the initial chemotherapy cycle. Participants in the experimental arm were coached 2 days prior to the first treatment to develop an individual sleep promotion plan (ISPP©). The control arm received equal time and attention with information about healthy eating. Because actigraphy data were collected after the initiation of intervention, only control subjects were included in this analysis.

Measures

In both studies, subjective and objective measures of sleep/ wake were obtained. Questionnaires were used to obtain information about self-reported physical and mental functioning. Objective data were obtained by wrist actigraphy (Ambulatory Monitoring, Ardsley, NY, USA). Demographic information was obtained from the participant and clinical data were abstracted from the medical record.

Subjective sleep/wake

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item self-report questionnaire that measures subjective sleep quality during the past month [16, 17]. In this study the PSQI was used to describe quality of sleep prior to beginning chemotherapy. Responses to the items are grouped into seven components measuring sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication use, and daytime dysfunction. The components are weighted equally on a 0-3 scale, with a global PSQI score ranging from 0 to 21. Higher scores indicate more severe complaints and poorer sleep quality. Previous reports of internal consistency ranked from 0.77 to 0.83 [17]. In the present sample, Cronbach's alpha for the global PSQI was

0.73. Evidence for construct validity has also been demonstrated. A global score above 5 demonstrated sensitivity of 89.6% and specificity of 86.5% in differentiating good from poor sleepers who were in good health otherwise. This cut-off has been widely applied in sleep research. A cut-off score of 8 was found to discriminate good and poor sleep quality in 102 breast cancer survivors whose mean time since diagnosis was approximately 2.5 years [6].

Objective sleep/wake

Octagonal motionlogger actigraph devices (Ambulatory Monitoring, Ardsley, NY, USA) were used to quantify and record rest/activity cycles. Actigraphy offers a non-invasive method of objectively quantifying actual body movement over time [18]. The device resembles a wrist watch and was worn by each participant continuously on the non-dominant wrist. The actigraph was worn in their usual environment, whether at home, place of employment, or both. A diary was used to validate time in bed and time awake.

Actigraphy provides an index of sleep/wake and activity/ rest in natural settings, and it is a valid addition to diary information about sleep [19]. Actigraphy is sensitive and precise compared to self-report [20, 21]. Actigraphy provides continuous direct measurement of movement and indirect measurement of sleep. In healthy adults, scores are obtained using algorithms that correlate at greater than 90% with polysomnography, the gold standard for cortical activity measures of wake and sleep stages [22]. Sleep latency, or time to fall asleep, has not been found to be accurate using actigraphy [23] and therefore has not been included in this report.

We analyzed actigraphy data for up to 72 h beginning the morning of the day of the first chemotherapy treatment using a consistent approach. Days of the week varied among participants based on the day that chemotherapy was received. A systematic protocol was used to mark day and night for the analysis. Action 4 analysis program (Copyright (c) 1988–2001; Ambulatory Monitoring) was used to analyze data in 1-min epochs. Six sleep/wake parameters were selected for analysis including: total time in bed, total sleep time, number of awakenings, and minutes and percent of time awake after sleep onset (WASO-M and WASO-P). The sixth parameter, sleep percent (%), time asleep after sleep onset, is the preferred parameter to use to report sleep efficiency when using actigraphy because the value does not include the less reliable parameter of latency [24].

Physical and mental health status

The Medical Outcomes Study Health Survey (MOS-SF 12) was used in study 1 and the MOS-SF 36v2 was used in study 2. The SF-36 is a multi-purpose, short-form health survey with 36 questions that yields psychometrically based physical and mental health summary measures. Factor analytic studies have confirmed physical and mental health factors account for 80–85% of the reliable variance [25]. Published reliability statistics have exceeded the minimum standard of 0.70 recommended for measures used in group comparisons in more than 25 studies [26]; most have exceeded 0.80 [27, 28]. Reliability estimates for physical and mental summary scores usually exceed 0.90 [25]. In 1996, Version 2 was introduced, improving on the original dichotomous scaling by using five-level response scaling and increasing the sensitivity of the scale [27]. The MOSSF-12 was derived from items in the SF-36 [29]. Both scales compute component *t*-scores of physical health status (Physical Component Score—PCS) and mental health status (Mental Component Score—MCS) which are normed on a 0 to 100 scale. In a comparative study in a rheumatoid arthritis sample, correlations between the two versions were 0.94 for the PCS and 0.71 for the MCS [30]. Data also support equivalence of the two tools in patients with coronary artery disease [31]. Ware reported that the SF-12 achieved multiple *R* squares of 0.911 and 0.918 in prediction of the SF-36 PCS and the SF-36 MCS scores, respectively [29]. Thus these calculated, normed *t*-scores were deemed equivalent for this analysis.

Demographic and clinical information

Data were collected in each study at baseline using a study-specific questionnaire developed by each team. Data that were collected in a comparable manner in both studies included age, ethnic/racial background, marital status, education, and disease stage.

Data analysis

By combining the eligible participants, women with breast cancer from the two previously described studies, we identified 229 potential participants for the present study (n=125 from Study 1, n=104 from Study 2). We then systematically reviewed the samples to assure homogeneity before combining the samples for analysis. We examined actigraphy data for completeness and accuracy; 27 individuals were excluded due to having only one night of actigraphy data. We also evaluated the distribution of actigraphy sleep parameters; eight individuals were excluded due to extreme sleep parameter values. The first study included patients regardless of cancer stage. To assure equivalency, we dropped five advanced stage cancer participants from the Study 1 pool. Additionally, to equate chemotherapy regimens between the two studies, we decided to include only those receiving anthracycline and/ or cyclophosphamide-based regimens. We excluded six individuals from Study 1 who received alternative regimens. This resulted in a total sample of n=183 for the present study.

The two data sets were examined for equivalency across all major outcomes using the two one-sided test of equivalency [32, 33]. In this process, we constructed a confidence interval (CI) for the differences between two groups for key sleep parameters. We used team consensus to determine a CI around a delta (Δ) based on the concept of clinically important differences. We then computed a confidence interval for the actual Δ for the same measures, defined as ($\Delta \pm 1.64\sigma$) where σ is the pooled standard deviation of the two groups. Group differences and the confidence interval for each variable were examined to see if these differences fell within the confidence intervals proposed for each outcome. The results of these analyses were mixed and thus we proceeded conservatively, reporting both cohort data from each sample and aggregated data as appropriate.

Data were analyzed using SPSS V. 15 (SPSS, Chicago, IL, USA). Analyses included summary statistics, Pearson correlations, and comparisons using t-tests and analysis of variance (ANOVA). Repeated measures ANOVA was used to evaluate change in actigraphy patterns over time.

Results

Sample characteristics

The sample characteristics are summarized in Table 1. The sample included 183 women with breast cancer Stage I to III. There were no significant differences in age between the women in Study 1, age 28 to 75, and study 2, age 35 to 74. The women were predominantly Caucasian and almost 80% had at least some college education. Chi square analysis indicated that there were significant differences in clinical stage between the two samples (Chi square=6.74, p=0.03). Study 2 had more women with Stage I breast cancer and Study 1 had more women with Stage III.

Subjective and objective sleep

The first aim was to characterize sleep quality and quantity prior to and in the first three nights after initial intravenous chemotherapy for breast cancer. Sleep parameters during the last month were measured by the PSQI at baseline and are summarized in Tables 2 and 3 and described here. Using the standard cut-off of >5 on the global PSQI score, 65% of the women were classified as poor sleepers. Based on the overall sleep quality item of the PSQI (Item 6), about one fourth (25.7%) of the respondents reported "fairly bad" or "very bad" sleep quality at baseline. For total sleep time, 32.2% reported sleeping less than 6 h per night; 41.4% used sleeping medication during the past month; of which 21.5% were using sleeping medication three or more times per week. Almost half (44.9%) reported habitual sleep efficiency less than 85%. Almost two-thirds (63.3%) reported trouble waking up in the night. The most common sleep disturbances that occurred three or more times per week, based on PSQI individual items, were due to going to the bathroom, pain, and feeling too hot (see Table 3). Participants in Study 1 had higher PSQI component scores (except for sleep disturbances) than those in Study 2; the global PSQI score was significantly higher, 7.98 (Study 1) vs. 6.80 (Study 2) (p<0.05).

Sleep parameters measured by actigraphy for each night are summarized in Table 4. Due to different patterns within the two samples, we have reported summary data for each sample as well as the aggregated sample. All sleep parameters were worse on the first night following chemotherapy. Results from RM ANOVA for the aggregated sample indicated that there was a significant change in a positive direction over time for total sleep

time ($p< 0.01$) and number of awakenings ($p<0.05$). Analysis within each study sample revealed that this same pattern of improved total sleep time existed within the Study 2 sample; but the change over time within the Study 1 sample was non-significant. The number of awakenings in Study 2 was higher (11 vs. 10) on night 1 and then declined in a fairly linear fashion. In Study 1, the number of awakenings averaged slightly above 10 on both night 1 and 2 and then declined on the third night. The range and standard deviation of both variables were quite large indicating individual variation.

Table 2 Baseline subjective measures: mean and SD of Pittsburgh Sleep Quality Index (PSQI) parameters at baseline

PSQI component	Study 1 (n=101) Mean (SD)	Study 2 (n=82) Mean (SD)	Combined (n=183) Mean (SD)
Subjective sleep quality*	1.24 (0.81)	0.98 (0.69)	1.13 (0.77)
Sleep latency	1.38 (1.01)	1.19 (1.01)	1.30 (1.01)
Duration	1.09 (0.93)	0.88 (0.80)	0.99 (0.87)
Habitual sleep efficiency	0.80 (1.01)	0.60 (0.85)	0.71 (0.95)
Sleep disturbances**	1.34 (0.54)	1.57 (0.55)	1.44 (0.55)
Use of sleep medication**	1.18 (1.32)	0.64 (1.08)	0.94 (1.24)
Daytime dysfunction	1.00 (0.61)	0.95 (0.67)	0.98 (0.63)
Global PSQI*	7.98 (4.12)	6.80 (3.64)	7.45 (3.94)

*$p<0.05$; **$p<0.01$ t-test of difference between cohorts

We also analyzed the actigraphy data averaged over two to three nights to describe the extent to which participants experienced sleep—wake changes that are indicative of poor sleep [34]. For the aggregated sample, 26.8% had sleep percent that was below 85% although total sleep time was greater than 8 h for 48.6% of participants. Almost half of the sample (47%) had 10 or more awakening per night.

Table 3 Number and percent of sleep disturbances at least three times per week from Pittsburgh Sleep Quality index (PSQI) at baseline

Sleep disturbance: how often did you have trouble sleeping because you	Number (n=183)	Percent
Wake up in the middle of the night or early morning	114	63.3
Have to get up to use the bathroom	88	49.2
Cannot get to sleep within 30 min	49	27.2
Have pain	45	25.0
Feel too hot	36	20.1
Cough or snore loudly	18	10.1
Feel too cold	7	3.9
Had bad dreams	4	2.2
Cannot breathe comfortably	2	1.1

Number and percent those responding who scored a "3" indicating a problem 3 or more nights per week

Objective sleep parameters and baseline (pre-chemotherapy) sleep and health status

The second aim was to examine differences in objective sleep parameters based on pre-chemotherapy self-reports of being a good or poor sleeper. We also examined associations of self-reported physical and mental well-being with sleep measures (see Table 5). The actigraphy sleep parameters, averaged over two or three nights, were compared with independent t-tests based on the baseline global PSQI score, categorized as good (<5) or poor (>5) [16]. Using this categorization, it is notable that 65% of participants were categorized as poor sleepers. Analysis using an alternative cut-off of 8 [6] reduced the percent of poor sleepers to 35%. Although each actigraphy parameter (except average number of awakenings) in the poor sleeper group did reflect poorer sleep, the differences were not statistically significant ($p>0.05$) with either cut-off score. We have reported data using the widely accepted cut-off of >5.0. There were also no differences in actigraphy parameters based on whether or not pain or hot flashes were disturbing sleep three or more times per week (per PSQI) prior to beginning chemotherapy.

Women with poor sleep at baseline (global PSQI >5) had significantly lower ($p<0.001$) physical (PCS) and mental (MCS) health status. The relationship between baseline health status as measured by the MOS-SF and the actigraphy sleep parameters were examined with Pearson correlations. Neither the PCS nor MCS were associated with any of the average actigraphy sleep parameters or night 1 parameters in the aggregated sample. The pattern of correlations varied between the study samples; all significant correlations were weak (<0.25).

Table 4 Mean and standard deviation of sleep parameters from actigraphy by night and averaged over time

Variable	Night 1	Night 2	Night 3	Average of at least two nights of data n=183	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Range
Total time in bed (min)				540.46 (76.86)	323–761
Total (n=163)	529.04 (97.07)	547.52 (96.06)	547.84 (108.39)		
Study 1 (n=84)	534.98 (94.01)	545.58 (87.35)	540.54 (103.45)		
Study 2 (n=79)*	522.73 (100.43)	549.57 (105.06)	555.61(113.56)		
Total sleep time (min)				470.88 (81.63)	256–656
Total (n=163)**	453.81 (102.51)	481.17 (100.87)	479.21 (109.74)		
Study 1 (n=84)	473.88 (100.47)	487.88 (91.05)	482.48 (100.83)		
Study 2 (n=79)**	432.47 (100.95)	474.03 (110.49)	475.75 (119.04)		
Number of awakenings				10.05 (5.16)	0–29
Total (n=163)*	10.62 (6.38)	10.43 (6.26)	9.43 (6.39)		
Study 1 (n=84)	10.20 (6.17)	10.40 (6.44)	9.31 (7.36)		
Study 2 (n=79)	11.06 (6.61)	10.46 (6.09)	9.56 (5.20)		
WASO-M (min)				60.87 (41.62)	0–219
Total (n=163)	64.89 (56.16)	57.43 (46.33)	60.09 (61.70)		
Study 1 (n=84)	54.00 (54.10)	51.68 (41.00)	53.43 (56.68)		
Study 2 (n=79)	76.47 (56.31)	63.54 (50.95)	67.18 (66.26)		
WASO-P (percent)				11.51 (8.03)	0–42
Total (n=163)	12.52 (10.10)	10.77 (9.24)	11.02 (10.41)		
Study 1 (n=84)	10.24 (10.87)	9.63 (7.56)	9.78 (9.53)		
Study 2 (n=79)	14.95 (10.74)	12.00 (10.65)	12.35 (13.07)		
Percent sleep				88.49 (8.03)	63–100
Total (n=163)	87.48 (11.03)	89.22 (9.24)	88.98 (11.42)		
Study 1 (n=84)	89.76 (10.87)	90.37 (7.55)	90.22 (9.53)		
Study 2 (n=79)	85.05 (10.74)	88.00 (10.65)	87.65 (13.07)		

Sample sizes decrease due to listwise deletion

*p<0.05; **p<0.01, time effect of RMANOVA

Table 5 Differences in average actigraphy sleep parameters and baseline health status based on Pittsburgh Sleep Quality Index (PSQI) Scores[a] (cut-off of 5) of being a good (n=62) or poor (n=115) sleeper at baseline

		No.	Mean	SD	Minimum	Maximum
Sleep parameter						
Average of total time in bed (min)	Good sleeper	62	541.32	75.44	336.67	761.00
	Poor sleeper	115	542.57	75.20	384.00	719.00
Average sleep time (min)	Good sleeper	62	475.22	78.53	286.67	610.33
	Poor sleeper	115	470.40	82.33	256.33	655.67
Average number of awakenings	Good sleeper	62	10.27	5.63	2.33	29.33
	Poor sleeper	115	10.10	4.95	0.00	26.33
Average WASO-M (min)	Good sleeper	62	58.07	40.89	6.00	170.67
	Poor sleeper	115	63.13	42.51	0.00	218.67
Average WASO-P (percent)	Good sleeper	62	10.84	7.55	1.29	28.00
	Poor sleeper	115	11.86	8.37	0.00	37.37
Average sleep percent	Good sleeper	62	89.16	7.55	72.00	98.71
	Poor sleeper	115	88.14	8.37	62.63	100.00
Health status						
Physical health status subscale MOS-SF**	Good sleeper	61	48.25	9.05	26.35	61.66
	Poor sleeper	114	42.36	9.74	23.47	65.86
Mental health status subscale of MOS-SF**	Good sleeper	61	52.14	8.53	27.98	67.06
	Poor sleeper	114	46.99	11.18	15.08	66.00

[a] PSQI, ≤5=good sleeper; >5=poor sleeper

**p<0.01: t-test of differences between groups

Table 6 Pearson correlations between age and actigraphy sleep parameters from night 1

Sleep measures	Entire cohort (n=183) Age	Cohort 1: (n=101) Age	Cohort 2: (n=82) Age
Number of awakenings	0.084	0.044	0.112
WASO-M	0.150*	0.182	0.155
WASO-P	0.190*	0.276**	0.171
Sleep time (min)	−0.267**	−0.350*	−0.218*
Total time (min)	−0.187*	−0.262*	−0.136
Sleep percent	−0.190*	−0.285**	−0.171

Correlations were examined for both night 1 (worst night) and the average of all nights. Significant results were similar and night 1 correlations are reported here

*Correlation is significant <0.05 level (two-tailed)

**Correlation is significant at <0.01 level (two-tailed)

Demographic and clinical correlates

The third aim was to examine associations between specific demographic (age, education) and clinical (stage of disease) variables with sleep measures. Pearson correlations were examined to determine whether there was an association between age and sleep parameters averaged across the three nights for the entire sample, and in the cohorts from each study (Table 6).

Younger women's sleep was of higher quality based on several sleep measures. In the entire sample, younger women spent more total time (minutes) in bed, had more total sleep time, and a higher sleep percent (p=0.02 to 0.001). Younger age was also associated with more total sleep time in both cohorts (p=0.02–0.03). In the Study 1 cohort only, older women had higher WASO-P, percent time awake (p<0.001).

Educational level was divided into two groups: those with and without education beyond high school. Using t-tests, no associations were found between education and sleep measures except more average sleep time in those with education beyond high school. Using one-way analysis of variance procedures, there were no differences in sleep variables based on stage of disease in either cohort or the aggregated sample.

Discussion

This report makes an important contribution to understanding the sleep experience in women initiating intravenous chemotherapy for breast cancer. Sharing two similar datasets provides a relatively large and robust sample to examine sleep/wake parameter and correlates. The sample far exceeds prior research in which sample sizes were mostly 25 or less. The sample is relatively homogeneous clinically as all women have limited stage breast cancer and are receiving chemotherapy with commonly used approaches—anthracycline and/or cyclophosphamide. Although some women were prescribed dose-dense regimens or those containing taxanes, this variability in treatment did not affect the first cycle. The sample is diverse in age but limited to predominantly Caucasian and well-educated women. Generalizability to a more racially and ethnically diverse population is thus limited. The samples differed statistically only on the distribution of disease stage, a factor that has not yet been strongly associated with sleep/wake disturbances.

Plausible reasons for the differences in objective sleep parameters between samples 1 and 2 may relate to differences in pre-chemotherapy sedation, anti-emetic regimens, and use of sleeping medications. These variables were not measured in a detailed enough way in either study to allow comparisons and such detail will be important to include in future studies. Dexamethasone is commonly used in anti-emetic regimens and may have contributed to poorer sleep quality on the night after the chemotherapy was administered. Additionally, the incidence of uncontrolled nausea from the chemotherapy may have differed between the two samples. The PSQI showed that participants in study 1 made greater use of sleep medications prior to treatment; it is possible that this practice continued during cancer therapy.

The results of the PSQI indicate that a high proportion of women begin chemotherapy with a history of poor sleep. Yet, the aggregated sample mean of 7.45 on the global PSQI score was somewhat lower than the 8.8 previously reported by Berger [12]. Problems in maintaining sleep were predominant and the highest PSQI component score was for sleep disturbances. Common causes of sleep disturbance (that is going to the bathroom, pain, and being too hot) were similar to those reported by Fortner [35]. These results reinforce findings [36, 37] that most women experience disturbances in sleep/wake at the start of chemotherapy. The etiology of these sleep/wake disturbances may be due to the effects of cancer, stress, recent surgery, or mood disturbances such as anxiety-related anticipation of beginning chemotherapy [37]. This pattern also may be due to distress related to other symptoms or symptom clusters, such as the co-occurrence of pain, fatigue, or nausea.

Analysis of sleep using actigraphy confirmed a pattern of disrupted sleep. The number of night-time awakenings (average of 10) was higher than normal [14, 34] and similar on average to those reported by Berger [12]. Sleep percent and WASO-M (an hour on average) are similar to reports in smaller samples [12, 13]. In spite of disrupted sleep, average time in bed exceeded 8 h and quantity of total sleep time averaged 7 to 8 h. These findings parallel those of Berger [12]who reported over 8 h of total rest, defined as total bed plus daytime naps minus sleep latency and WASO-M, but are higher than the study conducted by Payne in a Clinical Research Center where 11 women had a little over 6 h of sleep [13].

The study provided an opportunity to examine sleep parameters over three nights. There was a high degree of variance in most sleep parameters indicating a wide range of sleep experiences. Although there was a statistically significant change in selected sleep parameters over the three nights for the aggregated sample, the pattern varied between the two samples. Study 2 participants had worse sleep quality on the first night and thus a greater rate of improvement and a significant change over time. Similar patterns have not been described in previous research. The pattern also differs from Payne's report as the worst night of sleep in this sample was the first night after chemotherapy, while it was the second night in Payne's study [13]. Payne's subjects were not sleeping in their own home however [13]. The pattern reported in this study would be congruent with peaks in fatigue that occur 48- to 72-h post-treatment as poor sleep on nights 1 and 2 might contribute to increased fatigue [11, 38]. The degree of change in number of nighttime awakenings and WASO-M, though statistically significant, may not represent a clinically important change. The average night-time awakenings decreased to nine per night and WASO-M remained at 60 min, still indicating sleep disruption.

There were no differences in actigraphy patterns over time between good and poor sleepers as identified by the pre-chemotherapy global PSQI cut-off scores of 5 and 8. These findings were surprising although this relationship has not been examined in similar samples of women with breast cancer. This finding supports other research that indicates that the commonly accepted subjective indicator of poor sleep quality (PSQI scores >5 or 8) is measuring perceptions that complement, but are not consistently correlated with objective measures in either the general population [39] or in cancer patients [40]. It also might indicate that sleep disturbance after chemotherapy is similar regardless of self-reported sleep quality prior to treatment.

There were significant differences in mental and physical health status based on good/poor sleeper status; poor sleepers had lower health status at baseline. The etiology of this relationship is unclear: does lower health status causes poor sleep or vice versa? In this sample, poorer health status was not related to the sleep parameters measured by actigraphy. This finding is in contrast to the relationship between sleep and performance status found by Miaskowski and Lee [15] in patients receiving radiation therapy.

The associations found between the age and sleep measures were not surprising. There is solid evidence that sleep is more fragmented as we age, and that, in general sleep is of higher quality in younger women compared to older women [41-43]. The lack of association of educational level with sleep measures was not an unexpected finding as socioeconomic status has been found to have a more robust relationship with both subjective and objective sleep quality [44]. Women varied from stages I to III breast cancer. These stages represent localized disease so differences in sleep based on stage were not expected. A less extensive stage of breast cancer was associated with an increased risk for insomnia in a sample of 300 women who had been

treated with radiotherapy for non-metastatic breast cancer [5]. Savard suggested a likely explanation for this finding was pre-existing sleep difficulties that were aggravated by cancer.

Limitations

The study was limited in that not all variables in two distinct studies could be matched, thus reducing the number of co-variates that could be included. SF-12 and SF-36 scores were compared. Literature supports such an approach but the items were not identical and this difference in measures may be one reason for differences in patterns of correlations. Actigraphy does not provide the best measure of sleep latency and thus this parameter is limited to self-report on the PSQI. The study 2 sample wore the actigraphy pre-chemotherapy and may have acclimated to wearing it by the time measurements used in this analysis were obtained. Generalizability to diverse racial or ethnic groups is limited. We also were unable to analyze for influences of pre-medications as well as specific chemotherapy regimens or doses.

Implications

Treatment of sleep/wake disturbance must begin with assessment prior to and during the treatment process. Interventions need to focus on improving sleep maintenance by decreasing the number of awakenings and reducing the time awake after each disruption. Specific strategies may include management of other symptoms such as fatigue, pain, or nausea; minimizing stimuli after awakening to use the bathroom; relaxation techniques; cognitive-behavioral therapy, and short-term pharmacologic therapy. Clearly, sleep/wake disturbance in this population may be complex and tailored approaches are warranted, especially given the high variability in sleep experience.

Further research should try to better profile demographic and clinical risk factors to better characterize the predictors of sleep/wake disturbance during this period. Identifying patients at high risk for greater sleep/wake disturbances may allow for more targeted and effective interventions, thus allowing for better use of professional resources. Further study is needed to determine the cause of sleep disruption and to examine interventions to decrease the number and duration of sleep disturbances. More in-depth research of sleep latency is also needed. Research is also needed to evaluate interventions, such as the ones tested in Studies 1 and 2 in which nurse counselors provided a structured and multi-faceted cognitive-behavioral approach to enhancing sleep quality, as well as to better understand sleep patterns during the surgical recovery phase, throughout chemotherapy and through survivorship.

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