Contribution of Cancer Symptoms, Dysfunctional Sleep Related Thoughts, and Sleep Inhibitory Behaviors to the Insomnia Process in Breast Cancer Survivors: A Daily Process Analysis

Meredith E. Rumble, PhD[1]; Francis J. Keefe, PhD[2]; Jack D. Edinger, PhD[2,3]; Glenn Affleck, PhD[4]; P. Kelly Marcom, MD[2]; Heather S. Shaw, MD[5]

[1]University of Wisconsin, Madison, WI; [2]Duke University Medical Center, Durham, NC; [3]VA Medical Center, Durham, NC; [4]University of Connecticut Health Center, Farmington, CT; [5]University of North Carolina, Chapel Hill, NC

Study Objectives: Using a comprehensive cognitive-behavioral model of insomnia and a daily process approach, this study was conducted to examine the contribution of cancer symptoms and dysfunctional sleep related thoughts and behaviors to the process of insomnia in breast cancer survivors.

Design: Within-group longitudinal research design.

Setting: An academic medical center.

Participants: 41 women with breast cancer who had completed their primary cancer treatment and met Research Diagnostic Criteria for primary insomnia or insomnia comorbid with breast cancer.

Interventions: NA

Measurements and Results: For 28 days, participants completed morning diaries assessing sleep, nighttime pain and hot flashes, and dysfunctional sleep related thoughts and behaviors during the day and night, and evening diaries assessing daytime pain, fatigue, hot flashes, and mood. All diaries were collected using an automated telephone-based system. Results revealed that poorer sleep was related to nighttime pain and hot flashes in breast cancer patients. Time-lagged effects were also found. The current study identified higher levels of dysfunctional sleep related thoughts and sleep inhibitory behaviors during the day and night as antecedents of insomnia, and higher levels of pain, fatigue, and hot flashes and lower levels of positive mood and dysfunctional sleep related thoughts as consequences of insomnia in this population.

Conclusions: The current study found support for a comprehensive cognitive-behavioral model of insomnia, which has several theoretical, practice, and research implications.

Keywords: Insomnia, breast cancer, pain, fatigue, hot flashes, mood, CBT

Citation: Rumble ME; Keefe FJ; Edinger JD; Affleck G; Marcom PK; Shaw HS. Contribution of cancer symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors to the insomnia process in breast cancer survivors: a daily process analysis. *SLEEP* 2010;33(11):1501-1509.

INSOMNIA IS A PREVALENT AND DISTRESSING ISSUE FOR BREAST CANCER PATIENTS.[1-6] HOWEVER, THE PROCESS OF INSOMNIA IN THIS POPULATION HAS been largely understudied. Knowledge of this process would not only aid in further understanding insomnia in the context of breast cancer, but it would also foster the development of insomnia interventions for this population so that this prevalent and distressing issue could be better managed.

One model commonly used to understand the process of insomnia is a cognitive-behavioral model, which asserts that both dysfunctional sleep related thoughts (e.g., worries about the consequences of insomnia) and behaviors (e.g., napping, extending the opportunity to sleep, staying in bed awake) perpetuate insomnia long after precipitating factors may dissipate.[7,8] A large body of research shows support for this model in the context of primary insomnia (i.e., insomnia without any comorbid condition)[9-13] and demonstrates the efficacy and effectiveness of cognitive-behavioral therapy for insomnia (CBT) for primary insomnia.[14] In addition, a few studies have shown support for aspects of this model in the context of insomnia comorbid with breast cancer[3,15-19] as well as demonstrated the efficacy of CBT for this population.[20-22]

Although a cognitive-behavioral model of insomnia shows promise in understanding the process of insomnia in breast cancer patients, cancer-related factors that could potentially contribute to sleep difficulties must be considered. Breast cancer symptoms, such as pain, fatigue, hot flashes, and mood disturbance, are of particular interest as these symptoms have been shown to be associated with poorer sleep in this population.[2,3,19,23-27] Therefore, the current study sought to examine the contribution of pain, fatigue, hot flashes, mood disturbance, dysfunctional sleep related thoughts, and sleep inhibitory behaviors to the process of insomnia in breast cancer patients.

Process-related questions are challenging to answer with traditional statistical techniques, which typically treat data in a cross-sectional and aggregated fashion. Fortunately, there is a methodological approach, which has been used in other areas (e.g., pain and mood) to examine process-related questions.[28,29] This approach is called a daily process approach, which includes repeated prospective measurement of variables that are considered to change in meaningful ways on a daily basis.[30] Using sophisticated multilevel modeling techniques, this approach provides the unique opportunity to examine relationships as they occur over time.[30-33] For example, one can examine whether higher levels of pain during the day are related to poorer

Submitted for publication September, 2009
Submitted in final revised form June, 2010
Accepted for publication July, 2010
Address correspondence to: Meredith E. Rumble, PhD, Department of Psychiatry, University of Wisconsin, 6001 Research Park Boulevard, Madison, WI 53719; Tel: (608) 263-6100; Fax: (608) 236-4521; E-mail: rumble@wisc.edu

sleep that night and/or if poorer sleep that night is related to higher levels of pain the next day.

Therefore, using a daily process approach, the current study addressed three main questions in a population of breast cancer patients with insomnia. First, to examine nighttime associations, what is the day-to-day relationship between sleep and nighttime pain and hot flashes? Second, to examine the antecedents of poorer sleep, what is the day-to-day relationship between daytime symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors and that night's sleep? Third, to examine the consequences of poorer sleep, what is the day-to-day relationship between sleep and the next day's symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors?

METHODS

Design and Procedure

The current study used a within-group longitudinal research design. All study procedures were reviewed and approved by the Duke University Medical Center Institutional Review Board. Prospective participants were provided a full explanation of the study. Consenting participants then completed screening procedures, including structured diagnostic interviews for sleep and psychiatric disorders and a measure of insomnia severity. All screening procedures were conducted by an advanced doctoral student in clinical psychology with supervision from a licensed clinical psychologist with 25 years of experience with sleep disordered patients.

After completing the screening procedures, eligible participants underwent a 28-day diary phase in which they completed a morning diary before 12:00 and an evening diary after 18:00 using an automated telephone-based data collection system (VoiceGuide, Katalina Technologies, Sydney, Australia), which provided a time and date stamp for each entry. Participants were compensated $0.15 for each diary completed at the appropriate date and time, and $1.65 for a full week of diaries completed on time for a possible total of $15.00 for all diaries. In addition, participants were called weekly (4 phone calls total) during the diary phase and given feedback about diary completion as well as an opportunity to ask any questions. Participants also recorded their medication use daily during the diary phase using a paper medication log. These logs were then mailed back at the end of the diary phase.

Participants

Five hundred seven breast cancer patients (stages I-IIIa) who had completed their primary cancer treatment (i.e., surgery, chemotherapy, and/or radiation) at Duke University Medical Center were sent recruitment letters for the current study. Of these potential participants, a number either did not respond to the recruitment letter (n = 193), had no sleep difficulties (n = 164), or lacked interest in participating (n = 64). Of the remaining potential participants (n = 86), 44 patients with insomnia were enrolled in the current study. The other 42 patients were excluded and not enrolled in the study as they: (a) had another uncontrolled medical condition (e.g., arthritis, thyroid disease) compromising sleep (n = 9); (b) met Diagnostic and Statistical Manual of Mental Disorders, fourth edition, (DSM-IV) criteria for a current mood, anxiety, alcohol or substance abuse, or psychotic disorder on the basis of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[34] (n = 11); (c) met criteria for another current sleep disorder (e.g., sleep apnea, restless leg syndrome) as assessed by the Duke Structured Interview for Sleep Disorders (DSISD)[35] (n = 16); or (d) had other significant issues impacting their sleep (e.g., caregiving) or their ability to participate (e.g., cognitive difficulties) (n = 6). These exclusion criteria were included so that the study sample had only sleep difficulties related to insomnia and cancer and was able to complete the study.

The 44 participants enrolled in the study met research diagnostic criteria (RDC)[36] for primary insomnia or insomnia comorbid with cancer as assessed by the DSISD.[35] Of the 44 patients enrolled, 2 patients completed less than 50% of the diaries and 1 patient withdrew shortly after enrollment, so these 3 participants consequently were not included in the final sample of the current study. The mean age for the final sample (N = 41) was 57 years (SD = 8.22), and the sample was mostly Caucasian (97.6%). Approximately 75.6% had received at least a college degree, 75.6% were married, and 58.5% were working.

In terms of breast cancer diagnosis, participants had been diagnosed with breast cancer for an average of 5.85 years (SD = 3.65); 34.15% had stage I breast cancer, 53.66% had stage II breast cancer, and 12.20% had stage IIIa breast cancer. In addition, 2 participants had a second primary breast cancer (stage 0 and II). All patients had completed their primary treatment (i.e., surgery, chemotherapy, and/or radiation). In terms of past primary treatment, 46.34% received lumpectomy, 53.66% received mastectomy, 68.29% received chemotherapy, and 70.73% received radiation. In terms of hormone therapy (e.g., tamoxifen), 90.24% received past hormone therapy, and 68.29% of the sample was receiving hormone therapy at the time of the current study. A little over half the sample (56.10%) was pre- or peri-menopausal prior to breast cancer treatment, and 100% of the sample was either peri- or post-menopausal after breast cancer treatment completion.[37]

In terms of insomnia diagnosis, 29 participants met criteria for primary insomnia, and 12 met criteria for insomnia comorbid with breast cancer. The average insomnia duration was 7.74 years (SD = 8.06), and 30 participants reported sleep difficulties starting after their breast cancer diagnosis, whereas 11 reported aggravation of pre-existing sleep difficulties with their breast cancer diagnosis. In addition, the sample scored an average of 11.88 (SD = 3.58) on the Insomnia Severity Index (ISI). An optimal clinical cutoff score of 8 has been recommended for cancer patients,[38] and 90.24% of the sample scored at or above this clinic cutoff. A small portion of the sample (n = 4) scored below this cut-off as there were no frequency or severity inclusion/exclusion criteria for this study.

Daily Measures

Morning daily diaries

Participants completed diaries every morning before 12:00 during the diary phase using an automated telephone-based data collection system. The morning diaries assessed sleep, pain, and hot flashes the previous night, and dysfunctional sleep related thoughts and sleep inhibitory behaviors the previous day and night.

Sleep diaries are a valid index of insomnia in that they provide the best indication of patient perception of sleep difficulties

and are more accurate than a one-time retrospective sleep estimate.[39] As recommended by Buysse et al.,[40] sleep was assessed daily by having participants log estimates of the time they went to bed (e.g., 22:30), the time they attempted to fall asleep (e.g., 23:00), how long it took them to fall asleep (e.g., 90 min), the number and duration of nocturnal awakenings (e.g., 2 awakenings lasting 20 and 60 min each), the time of their last awakening (e.g., 05:30), the time they got out of the bed (e.g., 07:00), and their overall sleep quality on a scale ranging from 0 (very poor) to 9 (excellent). From these data, only 2 sleep variables were extracted as a proxy for insomnia with the aim of limiting the number of statistical analyses. Sleep efficiency [(total sleep time)/(time in bed) * 100] was selected as it captures both sleep duration and time in bed, and sleep quality was selected as it captures the participant's overall impression of sleep.

One item assessed the level of pain the previous night on a scale from 0 (no pain) to 9 (pain as bad as you can imagine). This item ("How much pain did you have last night?") was adapted from the Brief Pain Inventory (BPI), which is a measure that is commonly used with cancer patients to assess pain.[41] Items from this measure have demonstrated excellent test-retest reliability (r ranging from 0.78 to 0.93).[42] The validity of the BPI has also been supported by studies that have shown a significant relationship between higher pain ratings and increased analgesic and narcotic use.[42]

One item assessed the severity of hot flashes the previous night on a scale from 0 (not at all severe) to 9 (extremely severe). This item ("How severe were your hot flashes last night?") was selected from a questionnaire developed by Carpenter et al.[24,43] The hot flash severity item has demonstrated validity in that this item has been shown to be significantly related to items on the Hot Flash Daily Interference scale, which measures the overall impact of hot flashes on quality of life (r ranging from 0.57 to 0.78), and these significant relationships were maintained when hot flash severity and daily interference items were assessed 6 months later in this same sample (r ranging from 0.48 to 0.76).[43]

The Glasgow Sleep Effort Scale (GSES) assessed dysfunctional sleep related thoughts.[44] This scale was developed to assess sleep effort and can be used as a proxy for concerns about sleep. For the current study, this scale was adapted to reflect on thoughts the previous day and night versus over the past week with items such as "I got anxious about sleeping before I went to bed last night." and "I worried about not sleeping when I was in bed last night and could not sleep." Participants indicated how much they agree with each statement by indicating not at all, to some extent, or very much. Evidence supports the reliability of this scale (Cronbach $\alpha = 0.77$).[44] Kohn and Espie[45] also found that this scale best discriminated individuals with insomnia from those without sleep complaints compared to other similar scales. This scale has also demonstrated excellent sensitivity and specificity, in that a cut-off score of 2 correctly identified 92.1% of individuals with insomnia and 87.3% of individuals without sleep complaints.[44]

Nine items from the Sleep Hygiene Practice Scale (SHPS) were used to assess sleep inhibitory behaviors.[11] These 9 items (e.g., "I took a nap yesterday." and "I set aside time to relax before bedtime last night.") were selected based on the most frequently endorsed items from a pilot study conducted in our lab that investigated sleep inhibitory behaviors in breast cancer patients with insomnia.[19] Six of these 9 items assessed sleep inhibitory behaviors (i.e., napping, using sleep medication, drinking caffeinated beverages within 4 h of bedtime, exercising strenuously within 2 h of bedtime, sleep disturbance by noise, and sleep disturbance by a bed partner), and 3 items assessed sleep promoting behaviors (i.e., setting aside time to relax before bedtime, exercising in the afternoon or early evening, and having a comfortable nighttime temperature in the bedroom). Participants indicated whether they engaged in each activity or had each experience (i.e., "yes" or "no"). To score this measure, the sleep promoting behaviors were reverse scored, and then all items were summed. The SHPS has demonstrated good test-retest reliability ($r = 0.74$).[46] This measure also has demonstrated good evidence of validity in that insomnia sufferers who report higher levels of sleep inhibitory behaviors show significantly poorer sleep quality, and that this measure discriminates patients meeting criteria for insomnia from those who do not.[11,45,46]

Evening daily diaries

Participants completed diaries every evening after 18:00 during the diary phase using an automated telephone-based data collection system. The evening diary assessed pain, fatigue, hot flashes, and mood during that day. The same items used in the morning diary to assess pain and hot flashes during the night were used in the evening diary to assess pain and hot flashes during the day ("How much pain did you have today?" and "How severe were your hot flashes today?).

One item assessed the level of fatigue during the day on a scale from 0 (no fatigue) to 9 (fatigue as bad as you can imagine). This item ("How fatigued have you been today?") was adapted from the Brief Fatigue Inventory (BFI), which is a measure that is commonly used with cancer patients to assess fatigue.[47] Items from this measure have demonstrated criterion validity in that they have correlated highly with other well-validated fatigue measures (r ranging from 0.59 to 0.68).[48]

A mood rating scale assessed mood disturbance.[49] This scale consists of 5 negative affect items (e.g., "How depressed/blue have you felt today?") and 4 positive affect items (e.g., "How happy have you felt today?"). On a scale ranging from 0 (not at all) to 6 (extremely much), participants rated the degree to which they experienced each mood. Negative and positive affect items were averaged into 2 scales, negative mood and positive mood, respectively. Higher scores on either scale indicate higher levels of that particular mood. This measure has demonstrated excellent reliability in a sample of patients with sickle cell disease (Cronbach $\alpha = 0.88$ for positive mood and 0.89 for negative mood).[50] In addition, this measure was developed for daily use and has been used in daily diary studies with various populations, including patients with breast cancer as well as college students.[49,51]

Medication use

Using paper medication logs, participants were asked to report the type and dose of the medications they took the previous day each morning during the diary phase. Participants then mailed back these paper logs at the end of the diary phase. Each participant's medication use was quantified using the Medication Quantification Scale, Version 3 (MQS-III).[52] The MQS was developed within persistent pain populations and quantifies medication use by employing a common scale based on a mixture of assigned detriment weights for various pharmacological classifications of

Table 1—Means, standard deviations, and ranges of aggregated daily diary variables and medication use

Variable	Mean	Standard Deviation	Range
Total sleep time (in minutes)	399.50	45.42	270.7–496.9
Sleep efficiency (%)	81.93	7.04	62.9–92.9
Sleep quality	5.09	1.04	3.0–8.2
Nighttime pain	1.55	1.28	0.0–5.1
Nighttime hot flashes	1.95	1.72	0.0–6.1
Daytime pain	1.57	1.18	0.0–4.4
Daytime fatigue	3.33	1.27	1.1–5.5
Daytime hot flashes	2.01	1.71	0.0–6.1
Daytime negative mood	0.78	0.64	0.0–2.8
Daytime positive mood	3.78	0.73	2.6–5.0
Daytime/nighttime dysfunctional sleep related thoughts	1.49	1.21	0.1–4.7
Daytime/nighttime sleep inhibitory behaviors	1.89	0.74	0.4–3.3
Medication use	7.56	7.23	0–25

medications and dosage levels. The scores for each medication are then summed to yield the total MQS score for each participant with higher scores indicating higher levels of medication use.

The MQS-III accounts for the following pharmacological classifications of medications: acetaminophen, anticonvulsants, antihypertensives, barbiturates, benzodiazepines, coclooxygenase-2 inhibitors, muscle relaxants, nonsteroidal anti-inflammatories, opioids, psychotropics, sedative hypnotics, and steroids.[52] In prior studies, the MQS has demonstrated excellent interrater reliability (r ranging from 0.95 to 0.99).[53,54] These studies have also demonstrated concurrent validity of this scale in that the higher scores on the MQS have been shown to significantly relate to higher levels of pain severity and interference.[53,54]

Baseline Measure

Insomnia Severity Index

The Insomnia Severity Index (ISI)[55] was given prior to the diary phase during the screening phase and assessed the perceived severity of insomnia over the course of the previous two weeks. The ISI consists of the following 7 items rated by participants on a 5-point scale from 0 to 4: the degree of difficulty falling asleep, staying asleep, and waking up too early as well as the degree of dissatisfaction with their sleep patterns, how noticeable their sleep difficulties are to others, and their distress/worry about their sleep difficulties. These items were then summed to make a score ranging from 0 to 28 with higher scores indicating greater insomnia severity. The ISI has recently demonstrated excellent reliability and validity in various cancer populations.[38] The ISI has also demonstrated excellent reliability and validity in the general population.[56]

RESULTS

Daily Diary and Medication Log Compliance

Of the 2296 diaries requested from the final sample (N = 41), 2128 (92.7%) entries were completed, and 2052 (89.4%) were completed on time. Forty participants (97.6%) also completed a medication log daily during the 28-day diary phase. These figures were only slightly lower when examining the compliance data from the 2408 diaries requested from all enrolled participants who started the diary phase (N = 43). That is, 2209 (91.7%) entries were completed, 2116 (87.9%) were completed on time, and 40 participants (93.0%) completed a 28-day medication log.

Descriptive Findings and Between-Person Relations

For the purposes of preliminary analysis, mean scores were calculated for each of the daily diary measures across the 28-day period for each participant. A mean score was also calculated for medication use using the MQS-III score. Table 1 presents the means, standard deviations, and ranges for these results. On average, participants slept approximately 6.5 h, had a sleep efficiency indicating that the slept about 82% of the time they spent in bed, and rated their sleep quality in the mid-range of this scale. These sleep characteristics are similar to median values from Espie et al.'s sample[21] of cancer survivors with insomnia. All values for pain, hot flashes, fatigue, negative mood, and positive mood were similar to other published diary study samples of breast cancer survivors.[24,51,58] On average during the day and night, participants endorsed low levels of dysfunctional sleep related thoughts and approximately 2 sleep inhibitory behaviors. As these scales have not been used in diary studies with cancer patients, we are uncertain if these values are similar to other published breast cancer survivor samples. Finally, although clinical categories are not available for the medication measure, the current sample's medication use is higher than a previously published sample of individuals with persistent pain and insomnia who had a score of 5.1 (SD = 6.4).[57]

For the purposes of preliminary analysis, the data were inspected for potentially important covariates (i.e., a number of demographic, medical, and insomnia variables). Demographic variables included age, level of education, marital status, and working status. Medical variables included the number of years since diagnosis, stage of breast cancer, lumpectomy, mastectomy, chemotherapy, radiation, past or current hormone therapy, current hormone therapy, current medication use, and change in menopausal status. Insomnia variables included insomnia diagnosis (primary insomnia or insomnia comorbid with breast cancer), insomnia duration, and insomnia symptom severity. Using correlational analyses, results revealed no significant relationships between any of the above potential covariates and both sets of aggregated diary variables (sleep as well as symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors). Race was not included in these variables, as the current sample was predominantly Caucasian. Thus, no covariates were identified for the remaining analyses.

Approach to Multilevel Analysis

The remaining analyses derive from a class of statistical procedures called random effects multilevel modeling.[30,32,33] These procedures partition the 2 sources of variance in our person-day dataset—differences between persons in the average levels of the daily variables and differences within persons in their daily reports over time. In the vernacular of multilevel

modeling, level 1 units refer to the discrete reports of sleep, pain, fatigue, hot flashes, negative mood, positive mood, dysfunctional sleep related thoughts, and sleep inhibitory behaviors. In the current study, multilevel analyses addressed the within-person relations between level 1 variables over time. More specifically, these analyses examined one set of same-day within-person relationships (i.e., the relationship between sleep and nighttime pain and hot flashes) and 2 sets of lagged within-person relationships (i.e., how daily symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors predict that night's sleep as well as how sleep predicts the next day's symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors) to address the study questions.

The SAS Proc Mixed procedure for multilevel data analysis furnished parameters in the form of unstandardized maximum likelihood estimates (SAS Institute, 1996). In these analyses, all predictors were person-centered, and intercepts and slopes were allowed to vary randomly; this enabled us to generalize the findings to the population of persons from which the sample was drawn, to the population of observations from which their daily reports were sampled, and to the population of within-person relations in which these samples are intended to represent.[30] The covariance matrix was unstructured, allowing different variances for the slope, intercept, and the slope-variance correlation. Due to the exploratory nature of this study, α was set at the 0.05 level for all analyses.

Table 2—Components of variance for daily diary measures

	Between-Person Variation		Within-Person Variation	
Daily Diary Measure	Variance Component	Percent of Total Variance	Variance Component	Percent of Total Variance
Sleep efficiency	43.39*	27.7	113.33*	72.3
Sleep quality	0.91*	20.7	3.49*	79.3
Nighttime pain	1.53*	49.8	1.54*	50.2
Nighttime hot flashes	2.83*	68.0	1.33*	32.0
Daytime pain	1.30*	48.9	1.36*	51.1
Daytime fatigue	1.49*	39.5	2.28*	60.5
Daytime hot flashes	2.81*	68.4	1.30*	31.6
Daytime negative mood	0.38*	37.3	0.64*	62.7
Daytime positive mood	0.38*	37.6	0.63*	62.4
Daytime/nighttime dysfunctional sleep related thoughts	1.30*	27.8	3.37*	72.2
Daytime/nighttime sleep inhibitory behaviors	0.50*	36.8	0.86*	63.2

*P < 0.0001

Between- and Within-Person Variability in Daily Diary Measures

The total variance in daily measures across the diary period is composed of differences between persons in their average scores (i.e., the trait component of the daily diary measures) and differences within persons in the fluctuation of these scores (i.e., the state component of these measures). Table 2 lists the between- and within-person variance components, their significance, and the relative contribution of each component to the total variance of scores. Results revealed that there is sufficient between- and within-person variation to warrant further multilevel modeling analyses for all variables.[33]

Same-Day Within-Person Relations: Sleep with Nighttime Pain and Hot Flashes

For the first set of analyses, a series of regression equations examined the within-person relations of sleep with nighttime pain and hot flashes (e.g., how does less efficient sleep at night relate to that night's pain?). Each regression equation fit the error terms to a first-order autoregressive model, AR(1), to control for autocorrelation. To illustrate these models, the equation relating nightly sleep efficiency to nighttime pain was as follows:

$$(\text{nightly pain})_{it} = b_0 + b_1\,(\text{nightly sleep efficiency}_t) + e_t$$

Table 3—Unstandardized maximum likelihood estimates (b) for within-person relations between sleep and nighttime pain and hot flashes

	Nighttime Pain			Nighttime Hot Flashes		
Sleep Variable	b	t	P	b	t	P
Sleep Efficiency	-0.01	-3.77	0.0002	-0.02	-3.79	0.0002
Sleep Quality	-0.11	-3.44	0.0006	-0.17	-4.49	< 0.0001

Table 3 displays the results, which revealed that less efficient sleep and poorer sleep quality were significantly related to both increased nighttime pain and hot flashes.

Lagged Within-Person Relations: Daytime Symptoms, Dysfunctional Sleep Related Thoughts, and Sleep Inhibitory Behaviors Predicting That Night's Sleep

For the second set of analyses, a series of regression equations examined the within-person relations of daytime symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors predicting that night's sleep (e.g., how does pain experienced during the day relate to less efficient sleep that night?). Each regression equation also controlled for the previous night's sleep variable (i.e., sleep efficiency or sleep quality) to better assess temporality in these associations. That is, examining the change in tonight's sleep compared to the previous night's sleep that may be due to that day's symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors. To illustrate these models, the equation of that day's pain predicting that night's sleep efficiency was as follows:

$$(\text{that night's sleep efficiency})_{it} = b_0 + b_1\,(\text{that day's pain}_t) + b_2\,(\text{the previous night's sleep efficiency}_t) + e_t$$

Table 4 displays these results, which revealed that higher levels of dysfunctional sleep related thoughts and sleep inhibitory behaviors for the previous day and night were significantly related to less efficient sleep and poorer sleep quality that night.

Table 4—Unstandardized maximum likelihood estimates (b) for the within-person relations of daytime symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors predicting that night's sleep

	That Night's Sleep Efficiency[a]			That Night's Sleep Quality[b]		
Daytime Variables	**b**	**t**	**P**	**b**	**t**	**P**
Daytime pain	0.09	0.26	0.7922	-0.09	-1.52	0.1291
Daytime fatigue	0.24	0.91	0.3650	-0.03	-0.44	0.6591
Daytime hot flashes	-0.44	-1.29	0.1988	0.04	0.60	0.5484
Daytime negative mood	-0.47	- 0.79	0.4291	-0.03	-0.34	0.7326
Daytime positive mood	0.34	0.68	0.4974	0.05	0.54	0.5922
Daytime/nighttime dysfunctional sleep related thoughts	-4.17	-6.48	< 0.0001	-0.74	-8.64	< 0.0001
Daytime/nighttime sleep inhibitory behaviors	-1.68	-3.53	0.0004	-0.29	-3.50	0.0005

[a]controlling for the previous day's sleep efficiency; [b]controlling for the previous day's sleep quality

On the other hand, daytime symptoms were not found to significantly relate to a change in that night's sleep.

Lagged Within-Person Relations: Sleep Predicting the Next Day's Symptoms, Dysfunctional Sleep Related Thoughts, and Sleep Inhibitory Behaviors

For the third set of analyses, a series of regression equations examined the within-person relations of sleep predicting the next day's symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors (e.g., how does less efficient sleep at night relate to the next day's pain?). Each separate regression equation controlled for the previous day's daytime variable (pain, fatigue, hot flashes, negative mood, positive mood, sleep related thoughts, or sleep related behaviors) to better assess temporality in these associations. That is, examining the change in today's symptoms, thoughts, and behaviors compared to the previous day's symptoms, thoughts, and behaviors that may be due to the previous night's sleep. To illustrate these models, the equation of that night's sleep efficiency predicting the next day's pain was as follows:

$$(\text{the next day's pain})_{it} = b_0 + b_1(\text{that night's sleep efficiency}_t) + b_2(\text{the previous day's pain}_t) + e_t$$

Tables 5 and 6 display the results from this set of analyses. Results revealed that poorer sleep quality was significantly related to increased pain, fatigue, and hot flashes the next day. Results also revealed that less efficient sleep was significantly related to increased fatigue and hot flashes the next day. In terms of mood, results revealed that less efficient sleep was significantly related to lower levels of positive mood the next day. In terms of dysfunctional sleep related thoughts, results revealed that poorer sleep quality was significantly related to lower levels of dysfunctional sleep related thoughts the next day. Sleep did not significantly predict changes in sleep inhibitory behaviors the next day.

DISCUSSION

Using a daily process approach, the current study addressed three main questions. The first research question examined the relationship between sleep and nighttime pain and hot flashes. Results revealed that poorer sleep was significantly related to higher levels of nighttime pain and hot flashes. Past cross-sectional research has demonstrated a relationship of poorer sleep to pain and hot flashes in breast cancer patients.[2,3,24,27] What is novel about the findings of the present study is that they were obtained using a daily process approach. Taken together, these collective findings suggest that there is a clear relationship of poorer sleep to pain and hot flashes in breast cancer patients.

The second research question examined potential antecedents of daily insomnia in breast cancer patients (What is the day-to-day relationship between daytime symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors and that night's sleep?). Analyses of these lagged effects revealed that dysfunctional sleep related thoughts and sleep inhibitory behaviors for the previous day and night consistently and significantly predicted less efficient sleep and poorer sleep quality that night. The finding that both dysfunctional sleep related thoughts and sleep inhibitory behaviors were antecedents of poor sleep fits well with a cognitive-behavioral model of insomnia, which asserts that insomnia is perpetuated by both maladaptive cognitions and behaviors.[7,8] These findings also correspond well with those of our pilot study, which found that breast cancer patients with insomnia had significantly higher levels of dysfunctional sleep related thoughts and a variety of sleep inhibitory behaviors than breast cancer patients without sleep complaints.[19]

Past cross-sectional research has demonstrated a relationship of sleep to pain, fatigue, hot flashes, and mood disturbance.[2,3,19,23-27] However, it is important to note that the results from the current study using a daily process approach found that these other potential antecedents (e.g., daytime pain, fatigue, hot flashes, positive mood, and negative mood) did not predict poorer sleep that night.

The third and final research question examined potential consequences of daily insomnia in breast cancer patients (What is the day-to-day relationship between sleep and the next day's symptoms, dysfunctional sleep related thoughts, and sleep inhibitory behaviors?). In terms of sleep predicting the next day's symptoms, results revealed that poorer sleep significantly predicted higher levels of pain, fatigue, and hot flashes, and lower levels of positive mood the next day. Prior cross-sectional studies have reported a relationship of sleep to pain, fatigue, hot flashes, and mood in breast cancer patients.[2,3,19,23,24,26,27] These cross-sectional studies, however, did not have the ability to examine the direction of relationships between sleep and these symptoms. However, the current study, which used lagged analyses, suggests that poorer sleep can lead to an array of symptom-related consequences.

This study also examined whether or not a poorer night's sleep predicted the next day's dysfunctional sleep related thoughts and behaviors. Surprisingly, this study only found that lower levels of sleep quality during the night predicted signifi-

cantly lower levels of dysfunctional sleep related thoughts the next day. This result does not fit well with a cognitive-behavioral model of insomnia, which asserts that both dysfunctional sleep related thoughts and sleep inhibitory behaviors perpetuate insomnia. One possible explanation for these findings relates to the way in which the data were collected for both dysfunctional sleep related thoughts and behaviors. The simplest approach would have been to collect measures of thoughts and behaviors at the end of the day when collecting other daytime measures (daytime pain, fatigue, hot flashes, negative mood, and positive mood). However, in the current study, the scales assessing thoughts and behaviors contained items assessing these factors during the day, at bedtime, and throughout the night. Given the nature of these measures, they were collected in the morning along with measures of sleep and nighttime pain and hot flashes. Thus, this methodological choice may account for the unexpected findings.

Table 5—Unstandardized maximum likelihood estimates (b) for the within-person relations of sleep predicting the next day's symptoms

Nighttime Variables	Next-Day Pain[a]	Next-Day Fatigue[b]	Next-Day Hot Flashes[c]	Next-Day Negative Mood[d]	Next-Day Positive Mood[e]
Sleep efficiency					
b	-0.003	-0.03	-0.01	-0.0008	0.006
t	-0.72	-4.85	-2.03	0.30	2.88
P	0.47	< 0.0001	0.04	0.77	0.004
Sleep quality					
b	-0.07	-0.17	-0.07	-0.02	0.03
t	-2.54	-4.21	-2.48	-0.86	1.34
P	0.01	< 0.0001	0.01	0.39	0.18

[a]controlling for the previous day's pain; [b]controlling for the previous day's fatigue; [c]controlling for the previous day's hot flashes; [d]controlling for the previous day's negative mood; [e]controlling for the previous day's positive mood

Table 6—Unstandardized maximum likelihood estimates (b) for the within-person relations of sleep predicting the next day's dysfunctional sleep related thoughts and sleep inhibitory behaviors

Dysfunctional Sleep Related Thoughts[a]						Sleep Inhibitory Behaviors[b]					
Sleep Efficiency			Sleep Quality			Sleep Efficiency			Sleep Quality		
b	t	P	b	t	P	b	t	P	b	t	P
0.01	1.31	0.19	0.11	2.45	0.01	-0.001	-0.48	0.63	0.01	0.55	0.58

[a]controlling for the previous day's dysfunctional sleep related thoughts; [b]controlling for the previous day's sleep inhibitory behaviors

This study has several strengths. First, the current study utilized a daily process approach and sophisticated multilevel modeling techniques to examine the day-to-day within-person relationships among sleep, cognitive-behavioral factors, and breast cancer-related symptoms. The knowledge of these relationships is important not only because it enables one to develop a more comprehensive model of insomnia in breast cancer patients, but also because it can inform the development of future insomnia interventions for breast cancer patients. Second, the present study used an automated telephone-based data collection system to collect diary data. This data collection system provided a time and date stamp for all entries so that diary compliance could be assessed. Finally, the current study employed standardized diagnostic interviews to determine if patients met eligibility/ineligibility criteria in terms of sleep and psychiatric disorders, which insures greater reliability of the study sample's characterization overall. Taken together, these strengths are noteworthy refinements over prior research.

This study also has several limitations. One limitation already noted is the possible methodological issue with how the data were collected for dysfunctional sleep related thoughts and behaviors. Future studies should develop more comprehensive measures for both thoughts and behaviors that could be administered both before bedtime and in the morning. Another limitation is the lack of racial diversity in the study sample. Thus, future studies need to replicate these findings with more racially diverse samples. Finally, although participants underwent structured diagnostic interviews for sleep and psychiatric disorders, participants did not undergo polysomnography or other medical assessments to further rule out other comorbidities. Future studies should incorporate these additional screening features to further insure the sample's characteristics.

In conclusion, the current study found support for a comprehensive cognitive-behavioral model of insomnia for breast cancer patients using a daily process approach. This comprehensive model includes not only dysfunctional sleep related thoughts and behaviors, but also the cancer-related symptoms of fatigue, pain, hot flashes, and mood disturbance. More specifically, in terms of nighttime associations, higher levels of both pain and hot flashes were associated with higher levels of sleep difficulties. In addition, lagged associations identified higher levels of dysfunctional sleep related thoughts and behaviors as antecedents of insomnia and higher levels of pain, fatigue, hot flashes, and lower levels of positive mood as consequences of insomnia. Thus, given the antecedent findings, a comprehensive insomnia intervention for this population could use a traditional insomnia-focused CBT protocol as its foundation. Given the nighttime association findings, a comprehensive insomnia intervention also needs to incorporate new intervention components that address nighttime pain and hot flashes.

Future research could expand upon these findings by testing the efficacy of a more comprehensive insomnia intervention for this population in improving not only sleep, but also pain, fatigue, hot flashes, and positive mood. Future research also could expand upon these findings by examining how the relationships of interest differ among participants with distinctive characteristics (e.g., patients closer to time of diagnosis versus those further from diagnosis). Finally, future research could examine the process of insomnia with similar methods in other insomnia populations (e.g., insomnia comorbid with psychiatric illness, primary insomnia) as this study only examined the insomnia process in middle-aged breast cancer survivors.

ACKNOWLEDGMENTS

We would like to acknowledge the Duke Oncology midlevel providers, including David Coniglio, PA, Dana Fifield, NP, and Lynn Scallion, NP, who provided assistance in the recruitment process, and Mengshuang Guo, who provided assistance in the technical aspects of manuscript preparation. Additionally, we would like to acknowledge the breast cancer patients who took part in this research. This study was funded by a Division 38 (Health Psychology) Student Research Award awarded to Dr. Rumble.

The study was performed at Duke University Medical Center, Durham, NC.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Rumble has received research support from Sanofi-Aventis. Dr. Edinger has received research support from Phillips/Respironics and Helicor and has consulted for Phillips/Respironics and Kingsdown. Dr. Shaw has been involved in studies sponsored by Bionovo, GlaxoSmithKline, Genentech, Roche, and Sanofi-Aventis without direct personal compensation. Dr. Marcom has received research support from Novartis and Genentech, speaking engagement honoraria from Genentech, compensation for providing educational preceptorship to sales representatives from Novartis, and has consulted for AstraZenenca. Drs. Keefe and Affleck have indicated no financial conflicts of interest.

REFERENCES

1. Carpenter, J, Andrykowski M. Menopausal symptoms in breast cancer survivors. Oncol Nurs Forum 1999;26:1311-17.
2. Couzi R, Helzlsouer K, Fetting J. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. J Clin Oncol 1995;13:2737-44.
3. Fortner B, Stepanski E, Wang S, Kasprowicz S, Durrence H. Sleep and quality of life in breast cancer patients. J Pain Symptom Manage 2002;24:471-80.
4. Lindley C, Vasa S, Sawyer W, Winer E. Quality of life and preferences for treatment following systematic adjuvant therapy for early-stage breast cancer. J Clin Oncol 1998;16:1380-7.
5. Northouse L, Caffey M, Deichelbohrer L, et al. The quality of life of African American women with breast cancer. Res Nurs Health 1999;22:449-60.
6. Savard J, Simard S, Blanchet J, Ivers H, Morin C. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. Sleep 2001;24:583-90.
7. Edinger J, Hoelscher T, Marsh G, Lipper S, Ionescu-Pioggia M. A cognitive-behavioral therapy for sleep-maintenance insomnia for older adults. Psychol Aging 1992;7:282-9.
8. Morin C, Kowatch R, Barry T, Walton E. Cognitive-behavior therapy for late-life insomnia. J Consult Clin Psychol 1993;61:137-46.
9. Carney C, Edinger J. Identifying critical beliefs about sleep in primary insomnia. Sleep 2006;29:444-53.
10. Harvey A. Identifying safety behaviors in insomnia. J Nerv Ment Dis 2002;190:16-21.
11. Lacks P, Rotert M. Knowledge and practice of sleep hygiene techniques in insomniacs and good sleepers. Behav Res Ther 1986;24:365-8.
12. Morin C, Stone J, Trinkle D, Mercer J, Remsberg S. Dysfunctional beliefs and attitudes about sleep among older adults with and without sleep complaints. Psychol Aging 1993;8:463-7.
13. Wicklow A, Espie C. Intrusive thoughts and their relationship to actigraphic measurement of sleep: toward a cognitive model of insomnia. Behav Res Ther 2000;38:679-93.
14. Morin C, Bootzin R, Buysse D, Edinger J, Espie C, Lichstein K. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998-2004). Sleep 2006;26:1398-414.
15. Berger A. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. Oncol Nurs Forum 1998;25:51-62.
16. Broeckel J, Jacobsen P, Horton J, Balducci L, Lyman G. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J Clin Oncol 1998;16:1689-96.
17. Davidson J, MacLean A, Brundage M, Schulze K. Sleep disturbance in cancer patients. Soc Sci Med 2002;54:1309-21.
18. Graydon J, Bubela N, Irvine D, Vincent L. Fatigue-reducing strategies used by patients receiving treatment for cancer. Cancer Nurs 1995;18:23-28.
19. Rumble M, Edinger J, Keefe F, Porter L, Marcom P. A pilot study examining the utility of the cognitive-behavioral model of insomnia in early stage breast cancer patients. Sleep 2005;28(Suppl):A228.
20. Epstein D, Dirksen S. Randomized trial of a cognitive-behavioral intervention for insomnia in breast cancer survivors. Oncol Nurs Forum 2007;34:E51-E59.
21. Espie C, Fleming L, Cassidy J, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared with treatment as usual for persistent insomina in patients with cancer. Sleep 2008;26:4651-8.
22. Savard J, Simard S, Ivers H, Morin C. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, Part I: Sleep and psychological effects. J Clin Oncol 2005;23:6083-96.
23. Bower J, Ganz P, Desmond K, Rowland J, Meyerowitz B, Belin T. Fatigue in breast cancer survivors: Occurrence, correlates, and impact on quality of life. J Clin Oncol 2000;18:743-53.
24. Carpenter J, Johnson D, Wagner L, Andrykowski M. Hot flashes and related outcomes in breast cancer survivors and matched comparison women. Oncol Nurs Forum 2002;29:E16-E25.
25. Carpenter J, Elam J, Ridner S, Carney P, Cherry G, Cucullu H. Sleep, fatigue, and depressive symptoms in breast cancer survivors and matched healthy women experiencing hot flashes. Oncol Nurs Forum 2004;31:591-8.
26. Okuyama T, Akechi T, Kugaya A, et al. Factors correlated with fatigue in disease-free breast cancer patients: Application of the Cancer Fatigue Scale. Support Care Cancer 2000;8:215-22.
27. Savard J, Davidson J, Ivers H, et al. The association between nocturnal hot flashes and sleep in breast cancer survivors. J Pain Symptom Manage 2004;27:513-22.
28. Keefe F, Affleck G, France C, et al. Gender differences in pain, coping, and mood in individuals having osteoarthritic knee pain: A within-day analysis. Pain 2004;110:571-7.
29. Tennen H, Affleck G, Zautra A. Depression history and coping with chronic pain: A daily process analysis. Health Psychol 2006;25:370-9.
30. Affleck G, Zautra A, Tennen H, Armeli S. Multilevel daily process designs for consulting and clinical psychology: a preface for the perplexed. J Consult Clin Psychol 1999;67:746-54.
31. Bolger N, Davis A, Rafaeli E. Diary methods: Capturing life as it is lived. Annu Rev Psychol 2003;54:579-616.
32. Kreft I, de Leeuw J. Introducing multilevel modeling. London: Sage, 1998.
33. Singer J, Willett J. Applied longitudinal data analysis: Modeling change and event occurrence. New York: Oxford, 2003.
34. First M, Spitzer R, Gibbon M, Williams J. Structured clinical interview for DSM-IV Axis I Disorders-clinician version (SCID-CV). 4th ed. Washington, DC: American Psychiatric Association, 1998.
35. Carney C, Edinger J, Olsen M, Stechuchak K, Krystal A, Wyatt J. Interrater reliability for Insomnia diagnoses derived from the Duke Structured Interview for Sleep Disorders. Sleep 2008;31(Suppl):A250.
36. Edinger J, Bonnet M, Bootzin R, et al. Derivation of research diagnostic criteria for insomnia: Report of an American Academy of Sleep Medicine Work Group. Sleep 2004;27:1567-96.
37. Brambilla D, McKinlay S, Johannes C. Defining the perimenopause for application in epidemiologic investigations. Am J Epidemiol 1994;140:1091-95.
38. Savard M, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients. Psychooncology 2005;14:429-41.
39. Sateia M, Doghramji K, Hauri P, Morin C. Evaluation of chronic insomnia: An American Academy of Sleep Medicine Review. Sleep 2000;23:243-308.
40. Buysse D, Ancoli-Israel S, Edinger J, Lichstein K, Morin C. Recommendations for standard research assessment of insomnia. Sleep 2006;29:1155-73.
41. Cleeland C. Measurement of pain by subjective report. In Chapman C, Loeser J, eds. Issues in pain measurement. New York: Raven Press, 1989:391-403.

42. Daut R, Cleeland C, Flanery R. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain 1983;17:197-210.
43. Carpenter J. The hot flash related daily interference scale: A tool for assessing the impact of hot flashes on quality of life in breast cancer patients. J Pain Symptom Manage 2001;22:979-89.
44. Broomfield N, Espie C. Toward a valid, reliable measure of sleep effort. J Sleep Res 2005;14:401-7.
45. Kohn L, Espie C. Sensitivity and specificity of measures of the insomnia experience: A comparative study of psychophysiologic insomnia, insomnia associated with mental disorder and good sleepers. Sleep 2005;28:1-9.
46. Brown F, Buboltz W, Soper B. Relationship of sleep hygiene awareness, sleep hygiene practices, and sleep quality in university students. Behav Med 2002;28:33-8.
47. Mendoza T, Wang X, Cleeland C, et al. The rapid assessment of fatigue severity in cancer patients. Cancer 1999;85:1186-96.
48. Okuyama T, Wang X, Akechi T, et al. Validation study of the Japanese version of the Brief Fatigue Inventory. J Pain Symptom Manage 2003;25:106-17.
49. Thomas D, Diener E. Memory accuracy in the recall of emotions. J Pers Soc Psychol 1990;59:291-7.
50. Gil K, Carson J, Porter L, Scipio C, Bediako S, Orringer E. Daily mood and stress predict pain, health care use, and work activity in African American adults with sickle cell disease. Health Psychol 2004;23:267-74.
51. Porter L, Mishel M, Neelon V, Belyea M, Pisano E, Soo M. Cortisol levels and responses to mammography screening in breast cancer survivors: A pilot study. Psychosom Med 2003;65:842-8.
52. Harden R, Weinland S, Remble T, et al. Medication Quantification Scale Version III: Update in medication classes and revised detriment weights by survey of American Pain Society physicians. J Pain 2005;6:364-71.
53. Guck T, Fleischer T, Pohren E, Tanner L, Criscuolo C, Leibrock L. The Medication Quantification Scale: Measurement of medication usage at a multidisciplinary pain center. J Back Musculoskelet Rehabil 1999;13:33-8.
54. Steedman S, Middaugh S, Kee W, Carson D, Harden R, Miller M. Chronic-pain medications: Equivalence levels and method of quantifying usage. Clin J Pain 1992;8:204-14.
55. Morin C. Insomnia: Psychological assessment and management. New York: Guildford Press, 1993.
56. Bastien C, Vallières A, Morin C. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297-307.
57. Currie S, Wilson K, Pontefract A, deLaplante L. Cognitive-behavioral treatment of insomnia secondary to chronic pain. J Consult Clin Psychol 2000;68:407-16.
58. Curran S, Beacham A, Andrykowski M. Ecological momentary assessment of fatigue following breast cancer treatment. J Behav Med 2004;27:425-44.
59. Reich J, Zautra A, Davis M. Dimensions of affect relationships: models and their integrative implications. Rev Gen Psychol 2003;7:66-83.