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Publication Date
2011

Peer reviewed|Thesis/dissertation

An Evaluation of Sleep and Pain Prior to and After Surgery for Breast Cancer

by

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DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Dedication and Acknowledgements

It is a pleasure to thank those who made this dissertation possible. This dissertation is dedicated to the women who tirelessly completed numerous assessments to provide the data for this research. I owe my deepest gratitude to my advisor, Dr. Christine Miaskowski, RN, PhD, FAAN, whose continuous supervision, dedication, expertise, and support enabled me to develop this research, as well as my program of research. It would have been next to impossible to write this dissertation without Dr. Miaskowski's help and guidance. I am grateful to my dissertation committee, Drs. Kathryn Lee, RN, PhD, FAAN, Brad Aouizerat, PhD and Laura Dunn, MD, who challenged me to thoroughly examine my area of research. In addition, I am most thankful for the love, support, and patience that my partner, family, and loved ones provided me throughout the doctoral program. My thanks must also go to Dr. Nancy Stotts, RN, EdD, FAAN for helping me to develop as an academician and professor throughout the doctoral program. I would also like to acknowledge the Gordon and Betty Moore Foundation and the American Cancer Society for funding my doctoral education and research.

An Evaluation of Sleep and Pain Prior to and After Surgery for Breast Cancer

Christina Van Onselen, RN, MS, PhD(c)

Abstract

Sleep disturbance is a common problem in women with breast cancer. However, only a limited amount of information is available on sleep disturbance and its correlates in these women. In this longitudinal study of neuropathic pain, lymphedema, and common symptoms in women who underwent surgery for breast cancer, 398 women with unilateral breast cancer were enrolled prior to surgery. Sleep disturbance and daytime sleepiness (DS) were assessed with the General Sleep Disturbance Scale (GSDS). Patients completed questionnaires prior to and for six months after surgery to assess clinical, demographic, and symptom characteristics. Prior to surgery, 28% of the patients had breast pain. Women with pain were younger, reported lower functional status, were more likely to be non-white, had not gone through menopause, and had a higher number of biopsies. Significantly higher percentage of women with breast pain (66.7%) had a mean total GSDS score above the cutoff for clinically meaningful sleep disturbance. No between group differences were found in any GSDS subscales or total GSDS scores or in fatigue and energy scores. Overall mean GSDS scores remained above the cutoff for clinically meaningful sleep disturbance over six months of the study. Higher severity scores for hot flashes, attentional fatigue, and physical fatigue predicted higher levels of sleep disturbance prior to surgery. Higher levels of depressive symptom scores predicted higher levels of sleep disturbance prior to surgery that declined slowly over six months. Higher levels of depressive symptoms, fatigue, and attentional fatigue predicted increased DS prior to surgery. Growth Mixture Modeling found three distinct subgroups of patients (i.e., High Sustained class (55.0%) had a high GSDS score prior to surgery that remained

high for six months; Low class (39.7%) had low GSDS score prior to surgery that persisted; Decreasing class (5.3%) had a high total GSDS score at baseline that decreased and then stabilized). Decreasing and High Sustained classes had higher physical fatigue, attentional fatigue, depressive symptoms, and trait anxiety compared to the Low class. High Sustained class had a higher proportion of women with hot flashes, lower energy scores and higher state anxiety scores than the Low class.

Table of Contents

Introduction

Sleep disturbance is a common problem in women with breast cancer, occurring in 20% to 70% (Bower, 2008; Fiorentino & Ancoli-Israel, 2006). Poor sleep is associated with decreased quality of life (Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002) and decreased emotional function (Janz et al., 2007) in these patients. Bower (2008) found that among breast cancer survivors with insomnia, 55% reported that their breast cancer brought about sleep disturbances. Most women diagnosed with breast cancer will undergo a surgical intervention ("Types of Treatment," 2010). Only four studies were found that evaluated sleep disturbance prior to surgery for breast cancer (Cimprich, 1999; Savard et al., 2009; Wright et al., 2009; Wright, Schnur, Montgomery, & Bovbjerg, 2010). Approximately, 70% (Savard, et al., 2009) to 80% (Cimprich, 1999) of women reported sleep disturbance prior to surgery for breast cancer. Despite its high prevalence, only a limited amount of information is available on sleep disturbance among women who undergo surgical intervention for breast cancer. In addition, limited research is available on associations between demographic, clinical, and symptom (i.e., pain, depression, fatigue) characteristics and sleep disturbance.

Therefore, this dissertation consists of three papers that discuss findings from a longitudinal study of neuropathic pain, lymphedema, and common symptoms in patients who underwent surgery for breast cancer. The first paper reports on the findings related to breast pain, sleep disturbance, and fatigue prior to surgery for breast cancer. Approximately 28% of the sample reported breast pain prior to surgery for breast cancer. Women with breast pain were younger and reported lower Karnofsky Performance Status (KPS) scores than women without pain. Significantly more women with breast pain were

non-white (35.5%) and fewer had gone through menopause (53.8%). A significantly higher percentage of women with breast pain (66.7%) had a mean total General Sleep Disturbance Scale (GSDS) score greater than the cutoff for clinically meaningful sleep disturbance (≥43). After controlling for age, KPS, ethnicity, and menopausal status, no differences were found, between the two pain groups, in any of the GSDS subscale, as well as the total GSDS scores. In addition, after controlling for age, KPS, ethnicity, and menopausal status, no differences were found in fatigue and energy scores between the two pain groups. Women without breast pain reported significantly higher interference with sexual activity scores (2.96) compared to women with breast pain (1.62, p<0.04).

The second paper describes the trajectories of sleep disturbance and daytime sleepiness in women prior to and for six months after surgery for breast cancer. Based on findings from the Hierarchical Linear Modeling (HLM) analyses, the overall model demonstrated that mean GSDS scores remained above the cutoff for clinically meaningful sleep disturbance over the six months of the study. Higher severity of hot flashes, higher attentional fatigue, and higher physical fatigue predicted higher levels of sleep disturbance prior to surgery for breast cancer. Higher levels of depressive symptoms predicted higher levels of sleep disturbance prior to surgery that declined slowly throughout the six months of the study. Higher levels of depressive symptoms, fatigue, and attentional fatigue predicted increased daytime sleepiness (DS) prior to surgery for breast cancer.

The third paper evaluated for differences among three distinct subgroups of breast cancer patients prior to and for six months after surgery for breast cancer based on the results of an analysis using Growth Mixture Modeling (GMM). A three class solution

was found to fit the data best. The High Sustained class (55.0%) had a high GSDS score prior to surgery that remained high over the next six months. The Low class (39.7%) had a total GSDS score prior to surgery that was low and remained low for six months. The Decreasing class (5.3%) had a high total GSDS score at baseline that decreased and stabilized throughout the study. A higher percentage of women with hot flashes were in the High Sustained class compared to the Low class. A significantly higher proportion of women who underwent a mastectomy or breast reconstruction were in the Decreasing class compared to the High Sustained and Low classes. The Decreasing and High Sustained classes had higher fatigue, lower attentional fatigue, depressive symptoms, and trait anxiety compared to the Low class. The High Sustained class had lower energy scores and higher state anxiety scores than the Low class.

These findings suggest that sleep disturbance is problematic prior to and for up to six months after surgery for breast cancer. In addition, particular symptoms (i.e., depression, physical fatigue, attentional fatigue, anxiety, hot flashes) play a role in sleep disturbance and DS. Finally demographic and clinical characteristics, such as undergoing mastectomy and performance status, are associated with sleep disturbance.

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Differences in Sleep Disturbance and Fatigue Between Women With and Without

Breast Pain Prior to Breast Cancer Surgery

Christina Van Onselen, RN, MS, PhD(c)

Abstract

Objectives: To evaluate for differences in self-reported sleep disturbance, sleep interference, fatigue, and energy in women who did and did not have pain prior to surgery for breast cancer.

Methods: A total of 398 women who were diagnosed with unilateral breast cancer and about to undergo surgery for breast cancer completed the Patient Information Questionnaire, the Self-Administered Comorbidity Questionnaire, General Sleep Disturbance Scale (GSDS), Sleep Interference Scale (SIS), the Lee Fatigue Scale, and a pain measure prior to surgery. Differences between patients with and without pain were evaluated using independent sample t-tests and Chi Square analyses.

Results: Over 28% of patients had breast pain. Women with breast pain were significantly younger, reported lower Karnofsky Performance Status (KPS) scores, were more likely to be non-white, had not gone through menopause, and had a higher number of biopsies. A significantly higher percentage of women with breast pain (66.7%) had a total GSDS score greater than the cutoff for clinically meaningful sleep disturbance ($\geq$43). No differences were found in any subscale or total GSDS scores between the two pain groups. Women with breast pain reported significantly higher interference with sexual activity scores (2.96). No differences were found in fatigue and energy scores between the two pain groups.

Discussion: Over a quarter of women experience breast pain prior to surgery. Sleep disturbance, fatigue, and decreased levels of energy are significant problems for women prior to breast cancer surgery. Future studies need to evaluate the mechanisms that underlie sleep disturbance, fatigue, and decreased energy.

Introduction

The majority of the 261,000 women diagnosed with breast cancer in 2010[1] will undergo a surgical intervention[2, 3]. While some information is available on the prevalence and severity of anxiety and depression in women prior to breast cancer surgery[4, 5], studies of other common symptoms such as sleep disturbance[6-9], fatigue[7, 10, 11], and pain[12-14] are more limited.

Of note, findings from two recent reviews[15, 16] suggest that 20% to 70% of women with breast cancer experience sleep disturbance during and following cancer treatment. In addition, 55% of women reported that their cancer diagnosis brought about the sleep disturbance[15]. In studies that evaluated self-reported [7, 8] and objective levels[6, 9] of sleep disturbance prior to a surgical intervention for breast cancer, between 70%[8] and 88%[7] of the patients reported this symptom. In one study that used actigraphy to evaluate sleep disturbance prior to surgery[6], women's mean sleep efficiency (SE) index was 85% and lower SE scores were associated with higher postoperative pain severity (r = -0.44) and pain interference scores (r = -0.49, both p<0.05).

The occurrence and impact of fatigue during chemotherapy (CTX) and radiation therapy (RT) for breast cancer are well documented. In fact, findings from two reviews[15, 17] suggest that 25% to 99% of women experience fatigue during treatment for breast cancer. In addition, across these studies, 30% to 60% of patients complain of moderate to severe fatigue. Only three studies[7, 10, 11] evaluated fatigue prior to surgery for breast cancer. In one study[11], preoperative levels of fatigue were positively correlated with the expectancy of post-surgical fatigue severity (r= 0.19, p<0.05). In the other two studies, between 32.5%[10] and 77%[7] of women reported fatigue prior to surgery. No studies were

found that evaluated both the occurrence and severity of fatigue in women prior to surgery for breast cancer and its relationship to other symptoms.

Pain in the breast or arm prior to surgery was evaluated in only four studies[12-14,18]. In one of the earliest prospective studies[12], 10% of women (n=93) reported pain in the ipsilateral arm prior to surgery for breast cancer. In a follow-up, retrospective evaluation of this sample[13], 30% of women reported that they had breast pain prior to surgery. In a more recent study[14], 87.8% of the patients reported breast tenderness prior to surgery. Finally, work from our research group found that approximately 30% of women reported pain in their breast prior to surgery.

Given the large number of women who undergo surgery for breast cancer, little is known about the occurrence of clinically meaningful levels of sleep disturbance, fatigue, and breast pain in women *prior* to surgery. In addition, no data are available on the impact of preoperative breast pain on sleep disturbance and fatigue. Given the paucity of prospective studies on sleep disturbance, fatigue, and breast pain in women prior to surgery for breast cancer, the purposes of this study were to evaluate for differences in self-reported sleep disturbance and sleep interference, as well as self-reported fatigue and energy in women who did and did not have breast pain prior to surgery for breast cancer.

Materials and Methods

Patients and Settings

This descriptive, cross-sectional study evaluated for sleep disturbance, fatigue, and breast pain in a sample of women who were scheduled to undergo surgery for breast cancer. Patients were identified and their willingness to participate was determined by clinicians at each of the study sites (i.e., university-based comprehensive cancer center,

two public hospitals, three community-based oncology programs). Women who were willing to participate met with a research nurse to determine eligibility based on a number of inclusion and exclusion criteria. Women were eligible to participate if they: were >18 years of age; diagnosed with unilateral breast cancer; about to undergo surgery for breast cancer; were able to read, write, and understand English; and provided written informed consent. Women were excluded if they had distant metastasis at the time of diagnosis, had bilateral breast cancer, and/or were undergoing a bilateral mastectomy (including prophylactic mastectomy).

A total of 516 patients were approached and 410 enrolled in the study (response rate of 79.4%). The major reasons for refusal were: too busy, overwhelmed with the cancer diagnosis, or insufficient time available to do the baseline assessment prior to surgery.

Instruments

The Patient Information Questionnaire obtained demographic and clinical information about age, gender, educational level, ethnicity, marital status, employment status, financial status, Karnofsky Performance Status (KPS) score[19,20], and current and past medical history. In addition, patients' medical records were reviewed for disease and treatment information.

The Self-Administered Comorbidity Questionnaire (SCQ) was designed to ascertain comorbidity in clinical and health service research settings[21]. The questionnaire consists of 13 common medical conditions that were simplified into language that could be understood without any prior medical knowledge. The patient indicated if they had the condition using a dichotomous "yes/no" format. If they indicated that they had a

condition, they were asked if they received treatment for it (yes/no; proxy for disease severity) and did it limit their activities (yes/no; indication of functional limitations). Patients could add two additional conditions not listed on the instrument. For each condition, a patient could receive a maximum of 3 points. Because 13 defined medical conditions are listed, the maximum score is 39 points. The SCQ has well established validity and reliability and was used in studies of patients with a variety of chronic conditions[21-25].

The occurrence of breast pain prior to surgery was determined by asking 'Are you experiencing pain in your affected breast?". If women responded yes, they rated the severity of their average and worst pain using a 0 (no pain) to 10 (worst pain imaginable) numeric rating scale (NRS)[26-28]. Women were asked how many days a week and how many hours a day they experienced significant pain (i.e., How many days out of a typical week do you currently have pain in your affected breast that interferes with your mood and/or activities? On those days when you have pain in your affected breast, how many hours of the day does it currently last?).

The 21-item General Sleep Disturbances Scale (GSDS) was used to evaluate overall sleep disturbance over the past week. Each item is rated on a scale that ranges from 0 (never) to 7 (everyday). The GSDS consists of seven subscales (i.e., quality of sleep, quantity of sleep, sleep onset latency, mid-sleep awakenings, early awakenings, medications for sleep, excessive daytime sleepiness) that can range from 0 to 7 and a total score that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). A total GSDS score of ≥43 indicates a clinically meaningful level of sleep disturbance[29]. Subscale scores represent the number of days a week a patient finds the sleep parameter

problematic and a score ≥ 3 indicates a clinically meaningful level of disturbance. The GSDS has high internal consistency reliability among oncology samples[30-34]. The Cronbach's alpha for the GSDS total score was 0.86.

The Sleep Interference Scale (SIS) evaluated the level of interference that sleep disturbance had on seven aspects of daily living (i.e., general activity, mood, walking ability, normal work, relations with other people, enjoyment of life, sexual activity). The SIS was developed for this study and modeled after the interference scales from the Brief Pain Inventory[35] and the Brief Fatigue Inventory[36]. Interference with each of the 7 items is rated on a 0 (does not interfere at all) to 10 (completely interferes) NRS. A mean interference score was calculated for the 7 items. The Cronbach's alpha for the SIS was 0.91.

Lee Fatigue Scale (LFS) consists of 18 items designed to assess physical fatigue and energy[37]. Each item is rated on a 0 (not at all) to 10 (extremely) NRS. Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the 5 energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Respondents were asked to rate each item based on how they felt "right now". The LFS was chosen for this study because it is relatively short, easy to administer, and has well established validity and reliability. The LFS was used with healthy individuals[37,38] and in patients with cancer and HIV[32,39-41]. In this study, Cronbach's alphas for the fatigue and energy subscales were .96 and .93, respectively.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Boards at each of the study

sites. During the patient's preoperative visit, a clinical staff member explained the study

to the patient and determined her willingness to participate. For those women who were

willing to participate, the staff member introduced the patient to the research nurse. Prior

to surgery, the research nurse met with the women, determined eligibility, and obtained

written informed consent. After signing the consent, the patients completed the baseline

study questionnaires. Following the completion of these questionnaires, the research

nurse obtained the patients' height and weight.

Statistical Analysis

Data were analyzed using SPSS version 18[42]. Descriptive statistics and frequency

distributions were generated on sample characteristics and symptom severity total and

subscale scores. Clinically meaningful cutpoints for sleep disturbance (i.e., GSDS total

score ≥43), fatigue (i.e., fatigue severity score ≥4.4 on the LFS), and energy (i.e., energy

decrement score ≤4.8 on the LFS), as well as the presence or absence of breast pain were

used to determine the occurrence rates for these symptoms. Women were categorized into

breast pain (n=110; 28.2%) and no breast pain (n=280; 71.8%) groups. Differences in

demographic and clinical characteristics between the pain and no pain groups were

determined using Independent sample t-tests, Mann-Whitney U tests, and Chi Square

analyses.

Based on these initial analyses, significant differences in age, KPS scores,

menopausal status, and ethnicity were found between the two pain groups. Because

differences in sleep disturbance and fatigue are associated with age[43-45], KPS

scores[31,46,47], ethnicity[6], and menopausal status[48-50], age and KPS score (as continuous

variables) as well as ethnicity (white versus nonwhite) and menopausal status (yes/no; as

dichotomous variables) were entered as covariates and pain group (as a dichotomous

variable) was entered as a fixed factor in the univariate analyses of covariance

(ANCOVAs) that evaluated for differences in sleep and fatigue parameters between

women with and without breast pain. All analyses used actual values. Adjustments were

not made for missing data. Therefore, the cohort for each analysis was dependent on the

largest set of available data for each group. A p-value of <0.05 was considered

statistically significant.

Results

Differences in Demographic and Clinical Characteristics Between Women with and

without Breast Pain

Differences in demographic and clinical characteristics between women with

(n=110, 28.2%) and without (n=280, 71.8%) breast pain prior to breast cancer surgery are

summarized in Tables 1 and 2. Women who reported breast pain prior to surgery were

significantly younger (50.85±9.81) than those without breast pain (56.48±11.77,

p≤0.0001). A significantly higher percentage of non-white women (35.5%) had breast

pain compared to white women (24.0%, FE=0.018). No differences in education, marital

status, living arrangements, employment status, and income were found between the two

pain groups.

As shown in Table 2, no significant differences were found in the majority of

clinical characteristics between women with and without breast pain. Significantly fewer

women with breast pain had gone through menopause (53.8%) compared to women

without breast pain (67.9%, p=0.012). Women with breast pain reported a significantly

lower mean KPS score (90.93±10.05) than women without breast pain (94.04±10.33,

p=0.008). In addition, women with breast pain underwent significantly more biopsies in the previous year (1.61±0.82) than women without breast pain (1.45±0.80, p=0.006). Among the women who reported pain in the breast, the mean worst pain score was 3.58±2.39 and average daily pain intensity was 2.23±2.12. These women had significant pain an average of 6.16±7.90 hours per day on 2.86±2.75 days per week.

Differences in Occurrence Rates for Sleep Disturbance, Fatigue, and Energy

As shown in Figure 1, a significantly higher percentage of patients with breast pain (66.7%) had a total GSDS score of ≥43 than patients without breast pain (53.5%, p = 0.02). No between group differences were found in the percentage of patients who reported clinically meaningful levels of fatigue (≥4.4) or decrements in energy (≤4.8) on the LFS.

Differences on Sleep Parameters Between Women with and without Breast Pain

As shown in Figure 2, after controlling for age, KPS scores, ethnicity, and menopausal status, no differences were found in any subscale or total GSDS scores between the two pain groups. In addition, except for interference with sexual activity item, no differences were found in any individual item or total sleep interference scores (see Figure 3). Women without breast pain reported significantly higher sleep interference scores with sexual activity (2.96±0.39) than women with breast pain (1.62±0.48, p<0.04).

Differences on the Fatigue and Energy Scores Between Women with and without

Breast Pain

As shown in Figure 4, after controlling for age, KPS score, ethnicity, and menopausal status, no differences were found in fatigue and energy scores between the two pain groups.

Discussion

This study is the first to evaluate the effects of breast pain on self-reported sleep disturbance, fatigue, and energy levels in a large sample of women prior to surgery for breast cancer. While the occurrence of clinically meaningful levels of sleep disturbance was significantly higher in the pain group, 53.5% of women in the no pain group reported sleep disturbance. This finding is consistent with previous reports[7,8] and suggests that sleep disturbance is a common problem in these patients. In contrast, the occurrence rates for clinically meaningful levels of fatigue and decreased energy were similar between the two groups. Consistent with one study[10] but lower than occurrence rates reported in another study[7], 32% of the sample reported fatigue. Taken together, the high rates of sleep disturbance and fatigue suggest that a substantial percentage of women experience clinically meaningful levels of these symptoms with or without pain. Additional studies are needed to determine the factors associated with these symptoms as well as how these symptoms change over time.

No studies were found that evaluated energy levels in women prior to surgery for breast cancer. While the concept of energy may appear to be the inverse of fatigue, it is a unique concept. Energy was assessed by asking questions about levels of activity, vigor, feeling lively, efficiency, and overall energy. In comparison the questions that were used

to assess fatigue included ratings of exhaustion, difficulty concentrating, ability to make body movements, and ability to carry on a conversation. The hypothesis that diminished energy is a distinct concept is further supported by the fact that almost 50% of the patients in this study reported clinically meaningful decrements in energy. Additional research is warranted to identify phenotypic and genotypic characteristics that contribute to increases in fatigue and decrements in energy in patients with breast cancer.

Of note, no differences were found in any GSDS subscale or total scores. However, except for the "use of sleep medications" subscale, scores on the other six GSDS subscales ranged from 2.1 to 4.8. These scores are interpreted as the number of days per week a patient experiences a particular problem and a score of ≥3 indicates a clinically meaningful problem. Women in this study experienced problems with sleep quality, quantity, mid-sleep awakenings, and early awakenings on three or more days per week, which suggests a problem with sleep maintenance. In addition, the very low scores on the use of sleep medications subscale suggests that women are not prescribed or are not taking medications to alleviate sleep disturbance. Given the significant number of patients with and the severity of sleep disturbance, future studies are needed to identify predictors of sleep disturbance so that interventions can be developed and tested to alleviate this significant clinical problem.

It is not entirely clear why the presence of breast pain did not increase the severity of sleep disturbance. Only one study found that increased pain severity was associated with lower sleep efficiency scores[6]. In this study, higher preoperative pain scores were weakly correlated with increased sleep disturbance (r=0.22), poorer sleep quality (r=0.15), increased sleep onset latency (r=0.16), increased number of early awakenings

(r=0.13), and excessive daytime sleepiness (r=0.21, all p≤0.02). The weak associations between GSDS and pain scores may be related to relatively lower levels of pain reported by these patients.

This study is the first to report sleep interference scores in women prior to surgery for breast cancer. With the exception of sexual activity, pain group membership did not influence sleep interference scores. The individual item and total SIS scores ranged from 1.4 to 3.7. These findings suggest that on average these women had mild to moderate levels of sleep interference. Finally, women without breast pain reported that their level of sleep disturbance interfered more often with their sexual activity than women with breast pain. While no studies were found on the impact of sleep disturbance on sexual activity in women with breast cancer, in women with fibromyalgia sleep disturbance and/or pain may diminish sexual activity[51]. Additional research is warranted on the impact of sleep disturbance on patients' ability to function.

Several study limitations need to be acknowledged. Sleep disturbance was assessed using only a subjective measure. Future studies need to evaluate both objective and subjective measures and evaluate for the existence of a sleep problem prior to the diagnosis of breast cancer. The exact etiology of the patients' breast pain warrants more detailed evaluation. Given that 28.2% of the patients reported breast pain, future studies need to include a more detailed examination of the painful site. Finally, since the majority of the sample was well educated, findings cannot be generalized to individuals with lower levels of education.

Despite these limitations, findings from this study suggest that sleep disturbance and decreased levels of energy are significant problems for women prior to breast cancer

surgery. Future studies need to evaluate which phenotypic and genotypic characteristics place women at greater risk for sleep disturbance and decreased energy. In addition, future studies need to determine the mechanisms that underlie sleep disturbance, increased fatigue, decreased energy, and breast pain prior to surgery, as well as evaluate for changes in these symptoms over time. This type of detailed characterization of these symptoms in women prior to and during treatment for breast cancer will facilitate the development and testing of interventions to relieve these symptoms.

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Figure Legends

Figure 1. Differences in occurrence rates for sleep disturbance (i.e., General Sleep Disturbance Scale ≥43), fatigue (i.e., Lee Fatigue Scale (LFS) Score ≥4.4), and decreased levels of energy (i.e., Energy subscale of LFS ≤4.8) by pain group. All values are plotted as percentages by pain group.

Figure 2. Differences in total and subscale scores on the General Sleep Disturbance Scale between women with and without breast pain. All values are plotted as means ± standard errors of the mean.

Figure 3. Differences in the total and item scores on the Sleep Interference Scale between women with and without breast pain. All values are plotted as means ± standard errors of the mean.

Figure 4. Differences in the fatigue and energy subscale scores on the Lee Fatigue Scale between women with and without breast pain. All values are plotted as means ± standard errors of the mean.

Table 1. Differences in demographic characteristics between women with (n=110) and without (n=280) breast pain prior to breast cancer surgery

		No Breast Pain 71.8% (n=280)	Breast Pain 28.2% (n=110)	
Characteristic		Mean (SD)	Mean (SD)	Statistics
Age (years)		56.48 (11.77)	50.85 (9.81)	t=4.81, p<0.0001
Education (years)		15.81 (2.69)	15.38 (2.62)	n.s.
		% (n)	% (n)	
Ethnicity	Non-white	31.9 (89)	45.0 (49)	F.E.=0.018
Marital Status	Married	41.9 (117)	43.0 (46)	
	Non-married	58.1 (162)	57.0 (61)	n.s.
Lives alone		24.1 (67)	25.2 (27)	n.s.
Works for pay		48.4 (134)	50.0 (55)	n.s.
Income	<$30,000	12.6 (29)	25.3 (23)	
	$30,000-$99,999	47.4 (109)	40.7 (37)	
	≥$100,000	40.0 (92)	34.1 (31)	n.s.

n.s. = not significant

Table 2. Differences in clinical characteristics between women with (n=110) and without (n=280) breast pain prior to breast cancer surgery

| Characteristic		No Breast Pain 71.8% (n=280)	Breast Pain 28.2% (n=110)	Statistics
		Mean (SD)	Mean (SD)	
Body mass index (kg/m^2)		26.98 (6.33)	26.12 (5.66)	n.s.
Karnofsky performance status score		94.04 (10.33)	90.93 (10.05)	t=2.66, p=0.008
Self-administered comorbidity questionnaire score		4.33 (2.75)	4.20 (3.09)	n.s.
Number of biopsies in the last year		1.45 (0.80)	1.61 (0.82)	U= 12887.0, p=0.006
		% (n)	% (n)	
	Stage 0	17.7 (47)	16.0 (17)	
Stage of Disease	Stage I	39.6 (105)	31.1(33)	
	Stage IIA/IIB	34.7 (92)	40.6 (43)	
	Stage IIIA-IV	7.9 (21)	12.3 (13)	n.s.
Mastitis		11.6 (32)	14.0 (15)	n.s.
Fibrocystic or cystic breast disease		17.8 (48)	22.9 (24)	n.s.
Non-cancer surgery on the affected breast		10.0 (28)	12.7 (14)	n.s.
Non-cancer surgery on the affected arm		4.3 (12)	1.8 (2)	n.s.
Non-cancer surgery on the affected hand		5.0 (14)	6.4 (7)	n.s.
Injury on the affected arm		15.0 (42)	14.5 (16)	n.s.
Injury on the affected hand		9.6 (27)	10.9 (12)	n.s.
Gone through menopause		67.9 (186)	53.8 (57)	F.E.=0.012
Received neoadjuvant therapy		21.1 (59)	17.3 (19)	n.s.

n.s. = Not significant
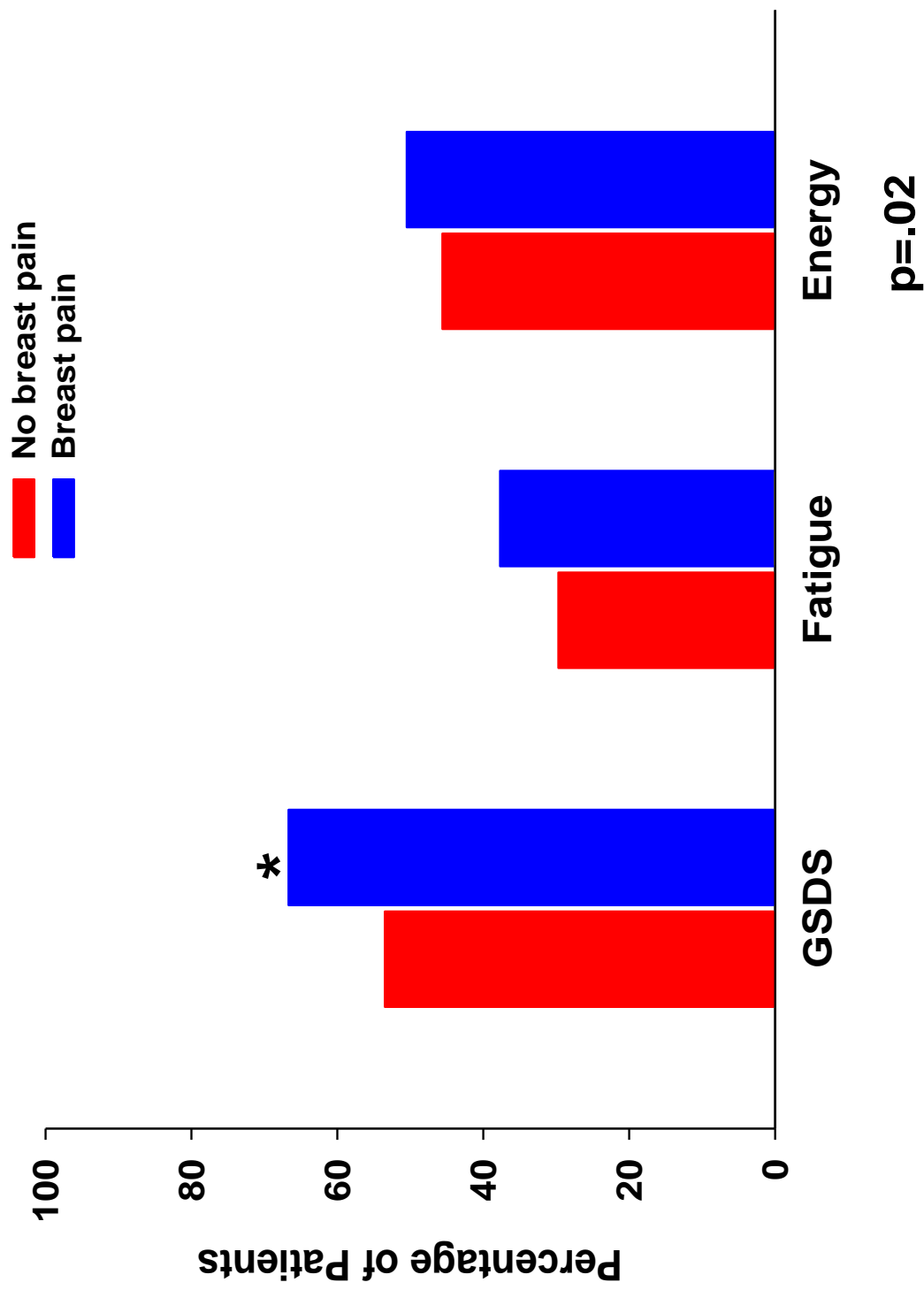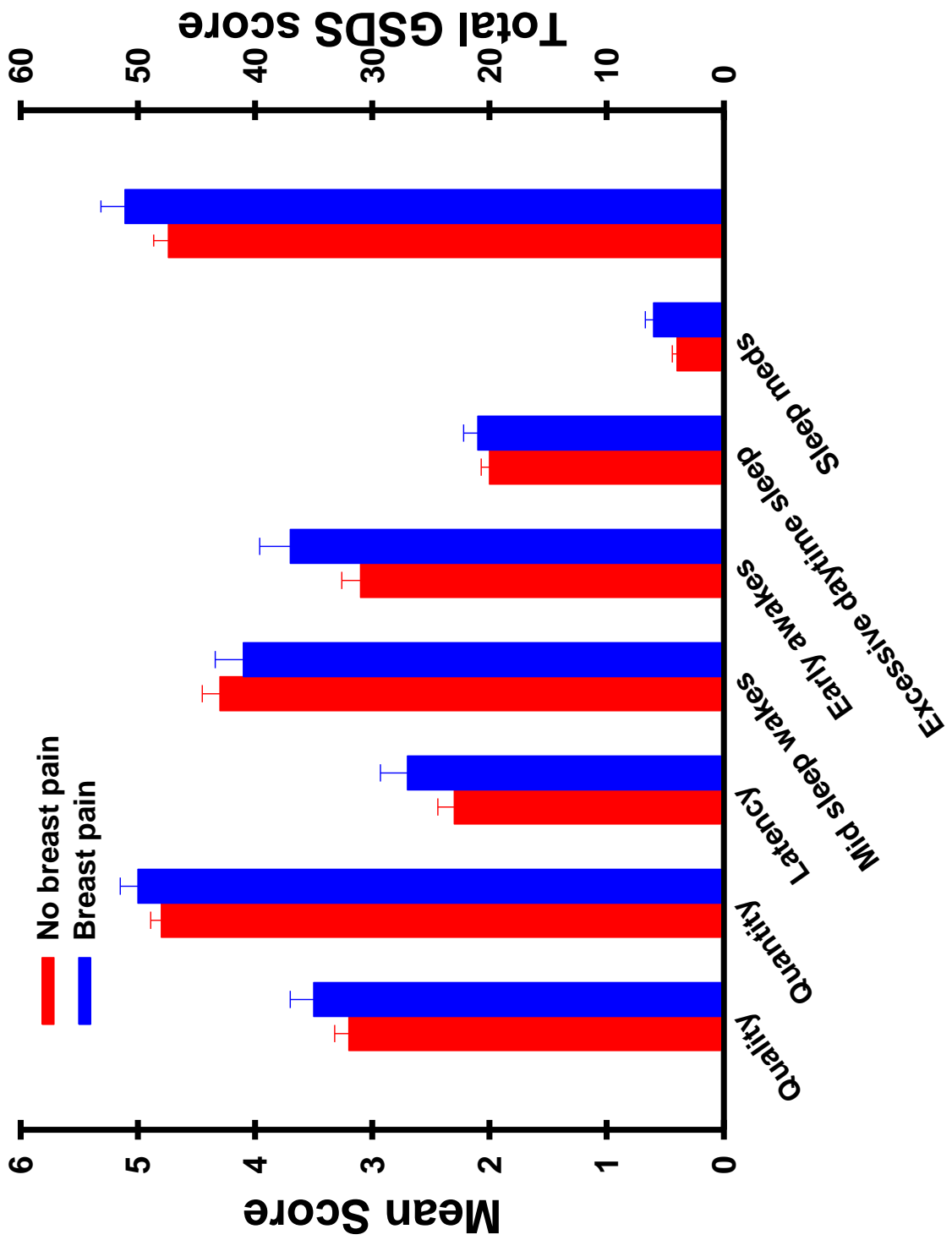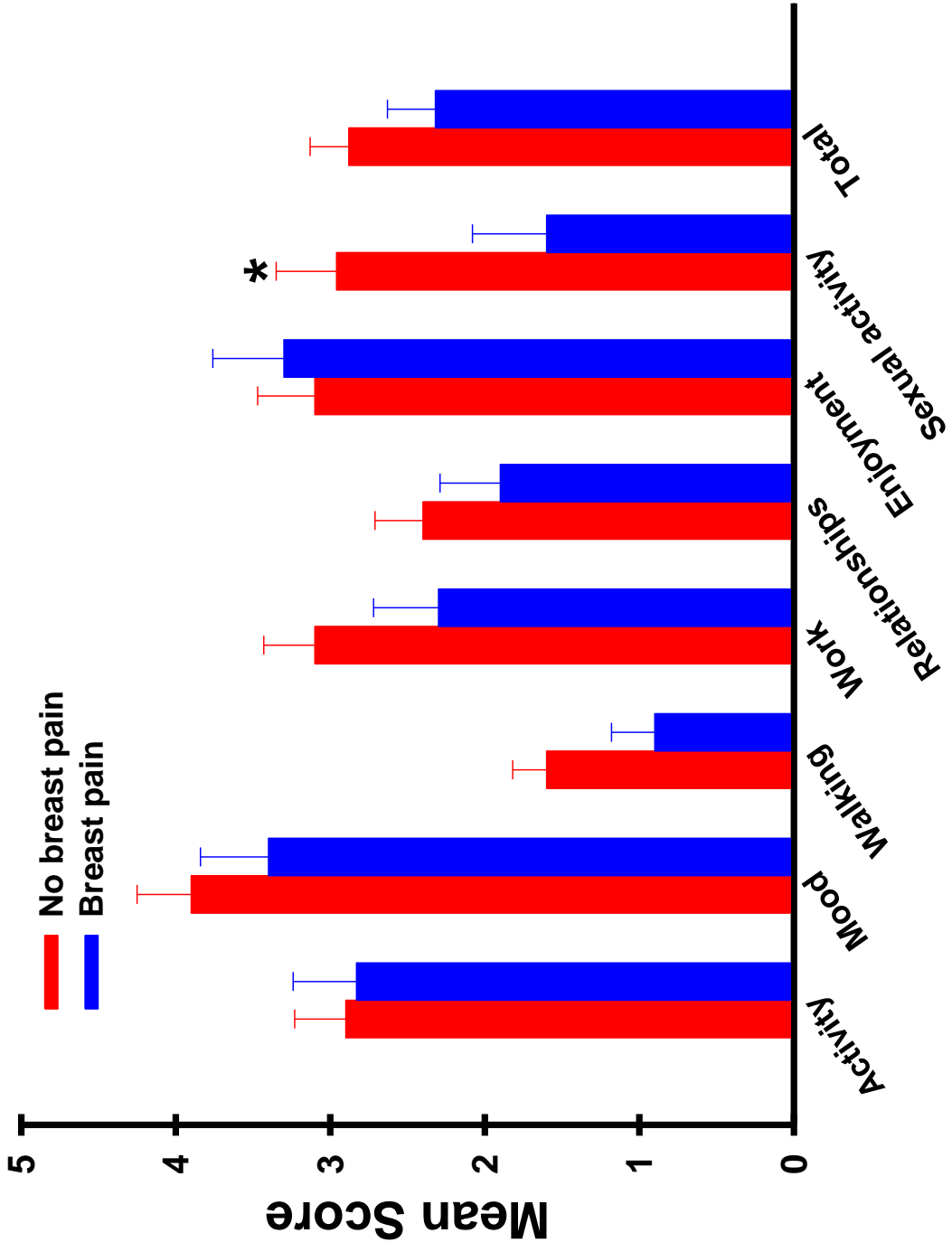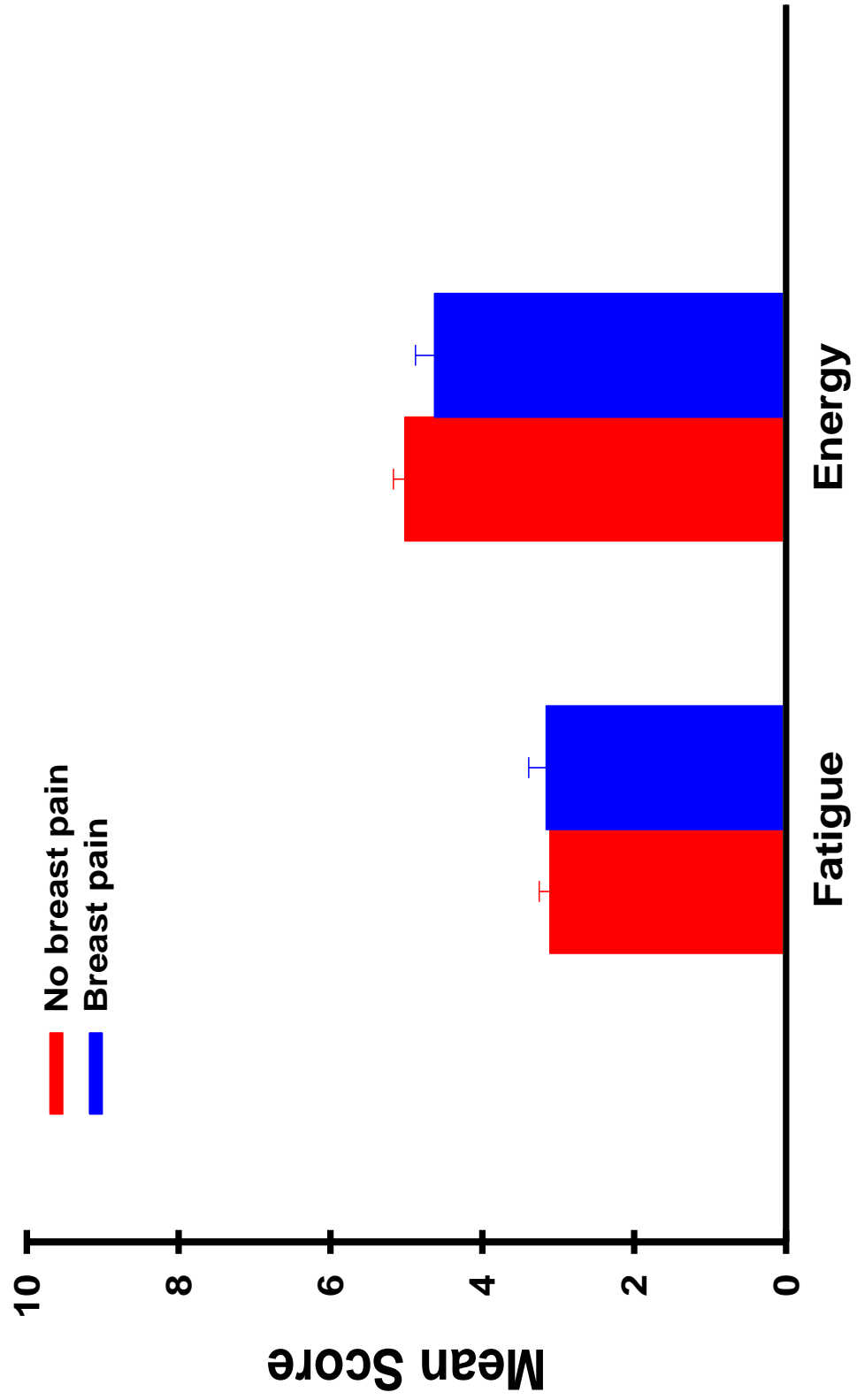
Trajectories of Sleep Disturbance and Daytime Sleepiness in Women Before and

After Surgery for Breast Cancer

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ABSTRACT

Introduction: Sleep disturbance and (DS) are significant problems for women with breast cancer. No studies have examined the predictors of sleep disturbance and DS in women prior to and after surgery for breast cancer.

Purpose: To examine how self-reports of sleep disturbance and DS changed from the time prior to surgery to six months following surgery and to evaluate whether certain characteristics predicted the initial levels of these sleep parameters and/or characteristics of the trajectories of these sleep parameters.

Methods: The sample consisted of 396 women who were about to undergo surgery for breast cancer. Using Hierarchical Linear Modeling, a number of demographic, clinical, symptom, and psychosocial adjustment characteristics were evaluated as predictors of initial levels of and trajectories of sleep disturbance and DS. Patients were followed every month for six months after surgery. The General Sleep Disturbance Scale (GSDS) was used to assess sleep disturbance and DS.

Results: Sleep disturbance scores prior to and for six months following surgery remained above the cutoff for clinically meaningful levels of sleep disturbance. Lower performance status, higher comorbidity, more severe hot flashes, higher attentional fatigue, and higher physical fatigue predicted higher levels of sleep disturbance prior to surgery for breast cancer. Higher levels of education predicted higher sleep disturbance scores over time. Finally, higher depressive symptoms scores predicted higher levels of sleep disturbance prior to surgery, which slowly declined throughout the study. Lower performance status, higher body mass index (BMI), higher fear of future diagnostic tests, not having had SLNB, having had an ALND, higher depressive symptom scores, higher fatigue, and

higher attentional fatigue predicted increased DS prior to surgery for breast cancer. Higher levels of education, not working for pay, and not having undergone adjuvant chemotherapy (CTX) predicted higher DS scores over time.

Conclusions: Sleep disturbance is a significant and persistent problem for patients with breast cancer. Additional research is needed to replicate these findings and evaluate the associations between the predictors for sleep disturbance and DS.

INTRODUCTION

Sleep disturbance is a commonly reported and disturbing symptom in women with breast cancer[1,2]. Sleep disturbance has deleterious effects on quality of life (QOL) before, during, and after treatment for breast cancer[3,4]. Prior to surgery for breast cancer, the occurrence of sleep disturbance ranges from 36%[5] to 88%[6]. In addition, during adjuvant chemotherapy (CTX) and radiation therapy (RT) reports of sleep disturbance range from 48%[7] to 66%[8].

Several studies have evaluated for changes in sleep disturbance in women during and after CTX and RT[5,8-14]. While the exact measurement times differed across these studies, sleep disturbance increased during CTX and then decreased following the completion of CTX[5,11,12,14]. In the two studies that evaluated sleep disturbance during RT, the results are inconsistent. In one study[13], sleep onset latency and sleep disturbance improved throughout RT. In contrast, in a study that evaluated women who were undergoing CTX or RT, 66% had sleep disturbance[8]. No longitudinal studies were found that evaluated sleep disturbance in women with breast cancer prior to surgery and followed them during the immediate postoperative period and during adjuvant treatment for breast cancer.

Daytime sleepiness describes the inability of an individual to remain awake during the daytime that results in drowsiness or sleep[15]. The prevalence of and changes over time in daytime sleepiness in women with breast cancer are not well characterized. In two studies[2,16], daytime sleepiness was described as a mild problem for most women prior to adjuvant treatment for breast cancer. In one study[17], daytime sleepiness increased during CTX administration.

Predictors of Sleep Disturbance and Daytime Sleepiness Prior to and After Surgery for Breast Cancer

Findings from several studies of patients with breast cancer suggest that increased levels of sleep disturbance are associated with higher levels of depressive symptoms[2,8] and fatigue[2,9,16,18]. Less consistent associations were found between hot flashes and sleep disturbance. The majority of these studies were conducted after treatment or among survivors[19-23]. In four of these studies, including one by Kim and colleagues[8] that evaluated women prior to adjuvant treatment, the presence or increases in hot flashes were associated with increased sleep disturbance. In two studies[19,23], no associations were found between hot flashes and sleep disturbance. These inconsistent findings may be related to differences in when the evaluations were done in relationship to the patients' treatment trajectories, as well as sample size constraints.

Only two studies[16,24] were indentified that evaluated for predictors of (DS). In one study of women with metastatic breast cancer[24], increased baseline and ongoing depression predicted increased daytime sleepiness throughout the study. In another study of women prior to adjuvant CTX[16], increased fatigue was associated with DS.

While several studies have identified sleep disturbance as a problem for women with breast cancer, no studies have identified predictors of sleep disturbance in the period prior to surgery and during adjuvant treatment. Additional research is warranted to determine which factors place women at higher risk for more severe problems with sleep disturbance prior to surgery and during subsequent treatments for breast cancer. Therefore, the purposes of this study, in a sample of women who underwent surgery for breast cancer (n=396), were to examine how self-reports of sleep disturbance and DS

changed from the time prior to surgery to six months following surgery and to evaluate whether specific demographic, clinical, symptom, and psychosocial adjustment characteristics predicted the initial levels of these sleep parameters and/or characteristics of the trajectories of these sleep parameters.

METHODS

Patients and settings

This analysis, drawn from a descriptive, longitudinal study, analyzed data from 396 women who underwent surgery for breast cancer. Patients were identified and their willingness to participate was determined by clinicians at each of the study sites (i.e., university-based comprehensive cancer center, two public hospitals, three community-based oncology programs). Women who were willing to participate met with a research nurse to determine eligibility based on a number of inclusion and exclusion criteria. Women were eligible to participate if they: were >18 years of age; diagnosed with unilateral breast cancer; about to undergo surgery for breast cancer; were able to read, write, and understand English; and provided written informed consent. Women were excluded if they had distant metastasis at the time of diagnosis, had bilateral breast cancer, and/or were undergoing a bilateral mastectomy (including prophylactic mastectomy).

A total of 516 patients were approached and 410 enrolled in the study (response rate of 79.4%). The major reasons for refusal were: too busy, overwhelmed with the cancer diagnosis, or insufficient time available to do the baseline assessment prior to surgery.

40

Instruments

The study instruments included a Patient Information Questionnaire, the Self-Administered Comorbidity Questionnaire (SCQ) the General Sleep Disturbance Scale (GSDS), the Center for Epidemiological Studies-Depression Scale (CES-D), the Spielberg State-Trait Anxiety Inventories (STAI-S ad STAI-T), the Lee Fatigue Scale (LFS), the Attentional Function Index (AFI), descriptive numeric rating scales (NRSs) for worst and average pain intensity, and an evaluation of the frequency of breast pain, NRSs for severity and distress of hot flashes, and the Quality of Life Scale-Patient Version (QOL-PV).

The Patient Information Questionnaire obtained demographic and clinical information about age, gender, educational level, ethnicity, marital status, employment status, financial status, Karnofsky Performance Status (KPS) score[25,26], and current and past medical history. In addition, patients' medical records were reviewed for disease and treatment information.

The SCQ was designed to ascertain comorbidity in clinical and health service research settings[27]. The questionnaire consists of 13 common medical conditions that were simplified into language that could be understood without any prior medical knowledge. The patient indicated if they had the condition using a dichotomous "yes/no" format. If they indicated that they had a condition, they were asked if they received treatment for it (yes/no; proxy for disease severity) and did it limit their activities (yes/no; indication of functional limitations). Patients could add two additional conditions not listed on the instrument. For each condition, a patient could receive a maximum of 3 points. Because 13 defined medical conditions are listed, the maximum score is 39 points.

The SCQ has well established validity and reliability and was used in studies of patients with a variety of chronic conditions[27-31].

The 21-item GSDS was used to evaluate overall sleep disturbance over the past week. Each item is rated on a scale that ranges from 0 (never) to 7 (everyday). The GSDS consists of seven subscales (i.e., quality of sleep, quantity of sleep, sleep onset latency, mid-sleep awakenings, early awakenings, medications for sleep, DS). The total score can range from 0 (no disturbance) to 147 (extreme sleep disturbance). A total GSDS score of $\geq$43 indicates a clinically meaningful level of sleep disturbance[32]. The GSDS has high internal consistency reliability among oncology samples[33-37]. The Cronbach's alpha for the GSDS total score was 0.86. The total GSDS score and the subscale score for DS were used in these analyses.

DS was evaluated using the seven items from the GSDS that make up the DS subscale[38]. This subscale ascertains the level of daytime sleepiness by asking questions about ability to stay awake and scheduled and unscheduled napping during the day. Additional questions evaluate irritability, alertness, and sleepiness during the daytime hours. Scores can range from 0 to 7 and represent the number of days a week a patient finds that DS is problematic. A score $\geq$3 indicates a clinically meaningful level of disturbance.

The CES-D scale consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60, with scores of ≥ 16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well established concurrent and construct validity[39-41]. In the current study, the Cronbach's alpha for the CES-D was .90.

The STAI-T and STAI-S consist of 20 items each that are rated from 1 to 4. The scores for each scale are summed and can range from 20 to 80. A higher score indicates greater anxiety. The STAI-T measures an individual's predisposition to anxiety determined by his/her personality and estimates how a person generally feels. The STAI-S measures an individual's transitory emotional response to a stressful situation. It evaluates the emotional responses of worry, nervousness, tension, and feelings of apprehension related to how a person feels "right now" in a stressful situation. Cutoff scores of $\geq$ 31.8 and $\geq$ 32.2 indicate high levels of trait and state anxiety, respectively. The STAI-S and STAI-T inventories have well established criterion and construct validity and internal consistency reliability coefficients[42-44]. In the current study, the Cronbach's alphas for the STAI-T and STAI-S were .88 and .95, respectively.

The LFS consists of 18 items designed to assess <u>physical</u> fatigue and energy[45]. Each item is rated on a 0 (not at all) to 10 (extremely) NRS. Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the 5 energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Respondents were asked to rate each item based on how they felt "right now". The LFS was chosen for this study because it is relatively short, easy to administer, and has well established validity and reliability. The LFS was used with healthy[45,46] and in patients with cancer and HIV[35,47-49]. In this study, Cronbach's alphas for the fatigue and energy subscales were .96 and .93, respectively.

The AFI consists of 16-items designed to measure <u>attentional</u> fatigue in patients with cancer. Each item is rated on a 0 to 10 NRS. A mean AFI score was calculated, with higher scores indicating greater capacity to direct attention and, therefore, lower levels of

attentional fatigue[50]. Based on a previously conducted analysis of the frequency distributions of the AFI scores, attentional fatigue can be grouped into categories of functional status (i.e., patients who score <5.0 functioning poorly and experiencing high levels of attentional fatigue, patients who score 5.0 to 7.5 functioning moderately well and experiencing moderate levels of attentional fatigue, patients who score >7.5 functioning well and experiencing low levels of attentional fatigue[51]). The AFI has established reliability and validity[50,52]. In the current study, Cronbach's alpha for the AFI was .95.

The occurrence of breast pain prior to surgery was determined by asking 'Are you experiencing pain in your affected breast?". If women responded yes, they rated the severity of their average and worst pain using a 0 (no pain) to 10 (worst pain imaginable) NRS[53-55]. Women were asked how many days a week and how many hours a day they experienced significant pain (i.e., How many days out of a typical week do you currently have pain in your affected breast that interferes with your mood and/or activities? On those days when you have pain in your affected breast, how many hours of the day does it currently last?).

The occurrence of hot flashes prior to surgery was determined by asking "Did you have hot flashes in the last week?". If women responded yes, they rated the severity and distress related to the hot flashes on a scale from 0 (none and not at all distressing, respectively) to 10 (intolerable and very distressing, respectively). This scale was developed using the format of the Memorial Symptom Assessment Scale[56].

QOL-PV is a 41-item instrument that measures four dimensions of QOL in cancer patients (i.e., physical well-being, psychological well-being, spiritual well-being, social

well-being) as well as a total QOL score. The QOL-PV has established validity and reliability[57-60]. In the current study, the Cronbach's alpha for the QOL-PV total score was .86.

Individual items from the QOL-PV were used to assess coping, distress, fear, and control. One item asked the patient to rate the difficulty with coping as a result of cancer and treatment. Another item asked the patients to rate the distress of the cancer diagnosis. Fear was assessed with two questions, one regarding fear of future diagnostic tests and another regarding fear of developing a second cancer. Finally, one question asked if a patient feels like she is in control of things in her life. Each item is scored on a 0 to 10 scale with higher scores indicating a better QOL.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Board at each of the study sites. During the patient's preoperative visit, a clinical staff member explained the study to the patient and determined her willingness to participate. For those women who were willing to participate, the staff member introduced the patient to the research nurse. Prior to surgery, the research nurse met with the women, determined eligibility, and obtained written informed consent. After signing the consent, patients completed the baseline study questionnaires. Following the completion of these questionnaires, the research nurse obtained the patients' height and weight. The research nurse contacted the patient two weeks after surgery to schedule the first postoperative visit. Visits took place in either the participant's home or in the clinical research center at 1, 2, 3, 4, 5, and 6 months after surgery.

Statistical Analysis

Descriptive statistics and frequency distributions were generated on the sample characteristics, baseline symptom severity scores, and QOL-PV scores using SPSS version 18[61]. For each of the seven assessments, mean total GSDS and DS subscale scores were calculated for use in the subsequent statistical analyses.

Hierarchical linear modeling (HLM), based on full maximum likelihood estimation, was done using the software developed by Raudenbush and Bryk[62]. The repeated measures of overall sleep disturbance and DS were conceptualized as being nested within individuals. Compared with other methods of analyzing change, HLM has two major advantages. First, HLM can accommodate unbalanced designs, which allows for the analysis of data when the number and the spacing of the assessments vary across respondents. Second, HLM has the ability to model individual change, which helps to identify more complex patterns of change that are often overlooked by other methods[62,63].

With HLM, the repeated measures of the outcome variables (i.e., overall sleep disturbance and DS) are nested within individuals and the analysis of change in these scores has two levels; within persons (level 1) and between persons (level 2). At level 1, the outcome is conceptualized as varying within individuals and is a function of person-specific change parameters plus error. At level 2, these person-specific change parameters are multivariate outcomes that vary across individuals. These level 2 outcomes can be modeled as a function of demographic, clinical, and symptom characteristics that vary between individuals, plus an error associated with the individual. Combining level 1 and level 2 results in a mixed model with both fixed and random effects[62,64,65].

Separate HLM analyses were done to evaluate changes over time in ratings of overall sleep disturbance and DS. Each HLM analysis proceeded in 2 stages. First, intra-individual variability in the sleep parameter over time was examined. In this study, time, in months, refers to the length of time from the preoperative visit to six months after the completion of surgery (i.e., six months with a total of seven assessments). Three level 1 models, which represented that the patients' sleep parameter levels a) did not change over time (i.e., no time effect), b) changed at a constant rate (i.e., linear time effect), and c) changed at a rate that accelerates or decelerates over time (i.e., quadratic effect), were compared. At this point, the level 2 model was constrained to be unconditional (i.e., no predictors), and the likelihood ratio tests were used to determine the best model.

The second stage of the HLM analysis, which answered the second research question, examined interindividual differences in the trajectories of overall sleep disturbance and DS by modeling the individual change parameters (i.e., intercept, linear, and quadratic slopes) as a function of proposed predictors at level 2. Table 1 presents a list of the proposed predictors that was developed based on a review of the literature of sleep disturbance in women with breast cancer[2,8,9,16,18-24]. To improve estimation efficiency and construct a model that was parsimonious, an exploratory level 2 analysis was done in which each potential predictor was assessed to see it if would result in a better fitting model if it alone was added as a level 2 predictor. Predictors with a t value of less than 2.0, which indicates a lack of a significant effect, were dropped from subsequent model testing. All of the potentially significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Only predictors that maintained a significant contribution in conjunction with

other variables were retained in the final model. A p-value of <0.05 indicates statistical significance.

RESULTS

Patient Characteristics and Symptom Severity Scores

Table 2 summarizes the demographic and clinical characteristics of the 396 women in this study. The mean age of the women was 55 years. These women were well educated (15.7 years), had a mean SCQ score of 4.3 (2.8), and 35% were non-white. Of this sample, approximately 48% were employed, 24% lived alone, and 41% were married. Approximately 38% had Stage I disease and 35% had Stage II disease. The majority of these women had gone through menopause (65%) and 32% were experiencing hot flashes. Only 20% of these women had undergone neoadjuvant CTX. The majority of the sample had breast conserving surgery (80%) and a sentinel node biopsy (83%). Almost 22% underwent reconstruction of the affected breast at the time of surgery. The mean baseline symptom severity scores for the 396 women are listed in Table 2.

Individual and Mean Change in Overall Sleep Disturbance and DS

The first HLM analyses examined how overall sleep disturbance and DS changed from the time of the preoperative visit to six months after surgery. Two models were estimated in which the function of time was linear and quadratic. For both sleep parameters, the goodness-of-fit tests of the deviance between the linear and quadratic models indicated that a quadratic model fit the data significantly better than did a linear model (both, p<0.001).

Sleep Disturbance

The estimate of the quadratic change model is presented in Table 3 (unconditional model). Because the model had no covariates (i.e., unconditional), the intercept represents the estimated amount of sleep disturbance (i.e., 48.313 on a 0 to 147 point scale) at the preoperative assessment. The estimated linear rate of change in sleep disturbance, for each additional month was 0.449 (p=0.346), and the estimated quadratic rate of change per month was -0.159 (p<0.05). The weighted combination of the linear and quadratic terms defines each curve. As shown in Figure 1A, sleep disturbance increased slightly during the first month and then slowly declined over the remainder of the study. It should be noted that the mean sleep disturbance and DS scores for the various groups depicted in all of the figures are estimated or predicted means based on the HLM analyses.

As shown in Table 3, in the unconditional model, the intercept represents the estimated amount of DS (i.e., 2.079 on a 0 to 7 scale) at the preoperative assessment. The estimated linear rate of change in DS, for each additional month, was 0.080 (p<0.05), and the estimated quadratic rate of change per month was -0.020 (p<0.01). As shown in Figure 1B, DS increased from the time prior to surgery to two months after surgery and then slowly declined throughout the remainder of the study.

Although the results indicate a samplewide increase followed by a decrease in both sleep disturbance and DS, they do not imply that all patients exhibited the same trajectories. The variance in individual change parameters estimated by the models (i.e., variance components; Table 3) suggested that substantial interindividual differences

existed in the trajectories of sleep disturbance and DS. These results suggest that further examination of interindividual differences in the individual change parameters was warranted.

Interindividual Differences in the Trajectories of Sleep Disturbance and DS

The second stage of the HLM analyses tested if the pattern of change over time in sleep disturbance and DS varied based on specific demographic, clinical, symptom or psychosocial adjustment characteristics that were found to influence sleep disturbance and/or DS levels of patients with breast cancer. Exploratory analyses were done with the potential predictors listed in Table 1.

<div align="center">Sleep Disturbance</div>

As shown in the final model in Table 3, the six variables, assessed prior to surgery that predicted interindividual differences in the intercept for sleep disturbance were: performance status (KPS score), comorbidities (SCQ score), depressive symptoms (CES-D score), physical fatigue (LFS score), severity of hot flashes, and attentional fatigue (AFI score). The variables assessed prior to surgery that predicted interindividual differences in the slope parameters for sleep disturbance were education and depressive symptoms (CES-D score).

To illustrate the effects of the demographic predictors on patients' trajectories of sleep disturbance, Figure 2A displays the adjusted change curves of sleep disturbance that were based on the differences in education (i.e., lower/higher education calculated based on 1 standard deviation (SD) above and below the mean education (years)). Figures 2B and 2C illustrate the effects of the two clinical predictors displayed as adjusted change curves of sleep disturbance based on the differences in performance status scores (i.e.,

low/high performance status calculated based on 1 SD above and below the mean KPS score, Figure 2B) and comorbidities score (i.e., low/ high SCQ score calculated based on 1 SD above and below the mean SCQ score, Figure 2C). To illustrate the effects of the four symptom predictors on patients' trajectories of sleep disturbance, Figure 3 displays the adjusted change curves of sleep disturbance that were based on the differences in severity of hot flashes (i.e., low/high hot flash severity score calculated based on 1 SD above and below the mean hot flash severity score, Figure 3A), attentional fatigue (i.e., low/ high AFI calculated based on 1 SD above and below the mean AFI score, Figure 3B), physical fatigue (i.e., low/ high fatigue calculated based on 1 SD above and below the mean LFS score, Figure 3C), and depressive symptoms (i.e., low/ high CES-D calculated based on 1 SD above and below the mean CES-D score, Figure 3D).

As shown in the final model in Table 3, the seven variables assessed prior to surgery that uniquely predicted interindividual differences in the intercept for DS were: performance status (KPS score), body mass index (BMI), depressive symptoms (CES-D score), fatigue (LFS score), and attentional fatigue (AFI score), as well as underwent a sentinel lymph node biopsy (SLNB) during surgery, and underwent an axillary lymph node dissection (ALND) during surgery. The four variables assessed prior to surgery that uniquely predicted interindividual differences in the slope parameters for DS were: education, being employed, fear of future diagnostic testing, and received neo-adjuvant CTX.

To illustrate the effects of the two demographic predictors on patients' trajectories of DS, Figure 4 displays the adjusted change curves for DS that were estimated based on

education (i.e., higher/ lower education based on 1 SD above and below the mean education (years), Figure 4A) and employment status (i.e., employed or not employed, Figure 4B). To illustrate the effects of the clinical predictors on patients' trajectories of DS, Figure 5 displays the adjusted change curves for DS that were estimated based on baseline performance status (i.e., high/ low performance status score calculated based on 1 SD above and below the mean KPS, Figure 5A), baseline BMI (i.e., high/ low BMI calculated based on 1 SD above and below the mean BMI, Figure 5B), fear of future diagnostic testing (i.e., low/ high fear calculated based on 1 SD above and below the mean fear of future diagnostic testing rating, Figure 5C), underwent SLNB (i.e., had or did not have SLNB, Figure 5D), underwent ALND (i.e., had or did not have ALND, Figure 5E), and neo-adjuvant CTX (i.e., had or did not have neo-adjuvant CTX, Figure 5F). Finally, Figure 6 displays the effects of the three symptom predictors displayed as adjusted change curves for DS that were estimated based on the differences in depressive symptoms (i.e., low/ high CES-D calculated based on 1 SD above and below the mean CES-D score, Figure 6A), physical fatigue (i.e., low/ high fatigue calculated based on 1 SD above and below the mean LFS score, Figure 6B), and baseline attentional fatigue (i.e., low/ high AFI calculated based on 1 SD above and below the mean AFI score, Figure 6C).

Discussion

Sleep Disturbance Trajectory

This study is the first to evaluate for preoperative levels of sleep disturbance and changes in sleep disturbance over time in women with breast cancer. Consistent with previous studies that used the GSDS to evaluate sleep disturbance in women with breast

cancer prior to RT[33,66], the preoperative GSDS score of 48.1 is above the cutoff for clinically meaningful levels of sleep disturbance (≥43). In addition, these findings are consistent with high levels of sleep disturbance reported by women prior to[2,16,18,67] and during CTX[67] for breast cancer. Of note, while these women reported a slight increase followed by a decrease in GSDS scores, at the six month follow-up GSDS scores remained high. This trajectory is similar, although less dramatic, than women prior to (i.e., 42.3), three weeks after (i.e., 45.7), and six weeks after (i.e., 39.1)[68] undergoing a hysterectomy. Of note, only women who were pregnant (i.e., 62.8[69]), postpartum (i.e., 56.2[69]), rotating (i.e., 56.6[38]), and night shift workers (i.e., 60.5[38]) had higher sleep disturbance scores on the GSDS than the women in our sample.

Predictors of the Trajectories of Sleep Disturbance

Only one demographic characteristic, namely education, predicted changes in the trajectory of sleep disturbance over time. Women with more education showed a slight increase in sleep disturbance over the first three months of the study followed by a gradual decline over the last three months. In contrast, women with less education had a small and steady decrease in sleep disturbance over the six months of the study. This finding is consistent with a previous report of breast cancer patients one year after the initiation of CTX[70], that found that higher levels of education were associated with poorer sleep quality. One potential explanation for the positive association between education and sleep disturbance is that women with more education may experiences higher levels of distress related to increased knowledge about their disease and its treatment. Additional research is needed to confirm the association, as well as, the reasons for this association.

KPS and SCQ scores were the only two clinical characteristics that predicted baseline levels of sleep disturbance. Consistent with previous reports from heterogeneous samples of oncology patients[35,71,72], lower KPS scores were associated with higher levels of sleep disturbance. While a study of breast cancer patients one year after diagnosis[73], did not find an association between comorbidities and sleep disturbance, studies of patients with other chronic medical conditions[74-77] found that an increase in comorbidities was associated with insomnia.

The symptoms that predicted higher preoperative levels of sleep disturbance included depressive symptoms, physical fatigue, attentional fatigue, and hot flash severity (Figure 3). In addition, depressive symptoms predicted changes in the trajectories of sleep disturbance over time. Higher preoperative levels of depressive symptoms were associated with increased baseline sleep disturbance that slowly decreased over the six months of the study. In contrast, women with lower depressive symptom scores had sleep disturbance scores that worsened and then improved after three months. However, for both growths GSDS scores remained above the clinically meaningful cutoff score. While no studies were found that evaluate the effects of depressive symptoms on the trajectories of sleep disturbance, studies that evaluated women during CTX and/or RT found that higher levels of depressive symptoms were associated with subjective reports of increased sleep disturbance[2,8,13,14]. In contrast, in studies that evaluated women prior to surgery[78] and during CTX[2], depression was not associated with measures of objective sleep disturbance. The reason for these inconsistencies may be related to the methods used to assess sleep disturbance (i.e., subjective versus objective measures). Studies in breast cancer patients[2,16] have demonstrated small to no correlation between subjective

and objective sleep parameters, with overestimation of subjective sleep problems. It is possible that only perceived sleep disturbance is associated with depressive symptoms.

Consistent with previous reports of women before and during primary treatment for breast cancer[2,8,9,12,14,16,18,67,70,79] higher levels of sleep disturbance were associated with higher levels of physical fatigue. While the causal relationship between fatigue and sleep disturbance has not been demonstrated in these studies[2,9,16], one study found that a behavioral intervention improved sleep quality, but not fatigue, reinforcing the distinct differences between these two symptoms[70]. Of note, both higher and lower fatigue scores predicted GSDS scores above the cutoff for clinically meaningful sleep disturbance prior to surgery.

Consistent with a study of breast cancer patients prior to initiation or RT[80], higher levels of attentional fatigue were associated with higher baseline sleep disturbance scores. Several of the questions on the AFI assess disorganized thought processes and inability to complete tasks[51]. It is possible that these disorganized thoughts and/or distress related to incomplete tasks during the day (i.e., higher attentional fatigue) lead to an inability to fall asleep or maintain sleep (i.e., increased sleep disturbance). This hypothesis is supported by one study of breast cancer survivors[81], which found that dysfunctional sleep related thoughts (e.g., anxiety about sleep) predicted decreased sleep efficiency and sleep quality.

Finally, higher hot flash severity ratings were associated with higher baseline GSDS scores. This finding is consistent with previous studies of women prior to[8,82] and during adjuvant treatment[82,83] for breast cancer. Prospective studies of women during the menopausal transition[84-89] found that the onset of hot flashes is associated with sleep

disturbance. While hot flashes are commonly measured by incidence or frequency, it may be just as important to evaluate the severity of hot flashes. Only two studies evaluated the severity of hot flashes in relation to sleep disturbance in women during treatment for breast cancer[8,82]. It is plausible that more severe hot flashes result in awakenings during the night, adversely effecting sleep quality. However, additional research is warranted to confirm this hypothesis.

DS Trajectory

Consistent with a previous study that used the GSDS to evaluate DS in women with breast cancer prior to RT[66], the preoperative DS score of 2.1 is below the cutoff for clinically meaningful DS ($\geq$3). The DS subscale can be interpreted as the number of days per week that DS is experienced. Therefore, on average these women report DS two days per week before undergoing surgery for breast cancer. A slight increase in DS scores occurred through month two followed by a slight decline through month six. However, the scores remained below the cutoff score for clinically meaningful DS throughout the study. Taken together, these findings suggest that women with breast cancer have some problem with DS that remains essentially stable in the six months following surgery. These findings are similar to reports of women prior to CTX[2,16] and during CTX[17,67] for breast cancer. In addition, these findings are consistent with reports of women during (i.e., 2.7) and after pregnancy (i.e., 2.2[90]). In contrast, these findings are lower than those reported by women who work night shifts (i.e., 3.4) and rotating shifts (3.0[38]). Since no study was found that included changes over time in DS in breast cancer patients, these findings warrant confirmation in future studies.

Predictors of the Trajectories of DS

Education and being employed were the only two demographic characteristics that predicted the trajectories of DS. Higher levels of education and not being employed predicted a small increase in DS from before to three months after surgery followed by a gradual decline. Similar to our findings for sleep disturbance, women with higher levels of education may have more distress related to increased information that results in sleep disturbance, as well as DS. In terms of employment status, our finding is consistent with a study of breast cancer patients[91], in which women who worked for pay had lower fatigue severity than women who did not work. In addition, in a study of breast cancer survivors[92], not working resulted in a disruption of daily life. This disruption of daily life may result in sleep disturbance and subsequent levels of DS. However, this hypothesis warrants confirmation in future studies.

While their effect was relatively small, lower performance stats and higher BMI were associated with higher levels of DS prior to surgery. While lower performance status scores were associated with higher levels of sleep disturbance in heterogeneous samples of cancer patients[35,72,93], no studies were found that evaluated the association between performance status and DS in breast cancer patients. In a study that evaluated sleep disturbance and weight in breast cancer patients[94], weight gain after diagnosis was associated with temporary or ongoing sleep problems up to 39 months after diagnosis. In contrast, in a study of breast cancer survivors[95], no association was found between insomnia and BMI. Since studies were found that evaluated the association between DS and BMI in breast cancer patients, additional research is warranted to refute or confirm this finding.

Women who did not undergo a SLNB at the time of surgery had had slightly higher levels of DS prior to surgery than women who underwent a SLNB. These women were more likely to be diagnosed Stage 0, to not undergo reconstruction at the time of surgery, and to not have undergone adjuvant CTX (all $p<0.03$). The exact reason for this relationship is not readily apparent and warrants investigation in future studies.

Women who underwent an ALND at the time of surgery had slightly higher levels DS prior to surgery than women who did not undergo an ALND. One possible explanation for this relationship is that women who would undergo an ALND had more distress associated with their disease and subsequent treatment trajectory. Since no studies were identified that evaluated the associations between SLNB and ALND and DS additional research is warranted to confirm these findings. Therefore, further investigation is warranted to understand these relationships.

Fear of diagnostic tests and receipt of neo-adjuvant CTX predicted the trajectories of DS. Women who reported a lower fear of diagnostic testing had a slightly increased DS from the time prior to surgery through month three, followed by a slow decline through month six. No other studies support this finding. This association is not well understood and requires further research to refute or confirm. Women who did not undergo neo-adjuvant CTX had a small increase in DS from baseline through month three, followed by a slow decline through month six. One possible explanation for this finding is that women who did not undergo neoadjuvant treatment underwent adjuvant treatment with RT that resulted in fatigue and DS.

Similar to sleep disturbance, symptoms that predicted baseline levels of DS were depressive symptoms, physical fatigue, and attentional fatigue. Higher levels of

depressive symptoms, physical, and attentional fatigue predicted poorer DS prior to surgery for breast cancer. The association between depressive symptoms and DS is consistent with a study of women with metastatic breast cancer prior to and up to twelve months after administration of a group therapy intervention[24]. The association between physical fatigue and DS is consistent with studies of women prior to[16] and during CTX[9] for breast cancer. It is likely that fatigue throughout the day leads to daytime sleepiness. No studies were found that examined the relationship between attentional fatigue and DS in women with breast cancer. One possible explanation is that sleep disturbance during the night influences both attentional fatigue and DS. Of note, both higher and lower CES-D, LFS, and AFI scores predicted DS scores below the cutoff for clinically meaningful DS prior to surgery for breast cancer.

Some limitations of the study warrant discussion. No objective measure of sleep disturbance was used to corroborate self-reported sleep disturbance. In addition, the measure used to evaluate DS is not a standardized measure of daytime sleepiness. Further evaluation of sleepiness should utilize a standardized measure of daytime sleepiness to replicate these findings.

Despite these limitations the findings from this study suggest that sleep disturbance is a problem for women prior to and following surgery. Further understanding and replication of the findings between sleep disturbance and neo-adjuvant CTX, SLNB, ALND, fear, and education are needed. Future research should focus on replicating these findings in other breast cancer patients, as well as developing an intervention that can be given prior to after surgery to alleviate ongoing sleep disturbance.

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Figure Legends

Figure 1. Trajectory of sleep disturbance (A) and DS (B) over the six months of the study.

Figure 2. Influence of education (A) on the slope parameters for sleep disturbance and influence of performance status (B) and comorbidities (C) on interindividual differences in the intercept for sleep disturbance.

Figure 3. Influence of severity of hot flashes (A), attentional fatigue (B), physical fatigue (C) on interindividual differences in the intercept for sleep disturbance and influences of depressive symptoms (D) on interindividual differences in the intercept and slope parameters for sleep disturbance

Figure 4. Influence of education (A) and employment status (B) on the slope parameters for sleep DS.

Figure 5. Influence of performance status (A), body mass index (B), underwent an ALND (D), and underwent a SLNB (E) on interindividual differences in the intercept for DS and influence of fear of future diagnostic tests (C) and neo-adjuvant chemotherapy (F) on the slope parameters for DS.

Figure 6. Influence of depressive symptoms (A), physical fatigue (B), and attentional fatigue (C) on interindividual differences in the intercept for DS.

Table 1. Potential Predictors of Intercept (I), Linear Coefficient (LC), and Quadratic Coefficient (QC) for the Overall Sleep Disturbance and Excessive Daytime Sleepiness

Characteristics	Overall Sleep Disturbance			Excessive Daytime Sleepiness		
	I	LC	QC	I	LC	QC
Demographic						
Age						
Lives alone						
Marital status						
Education		■	■		■	■
Ethnicity						
Employed					■	■
Clinical						
Body mass index				■		
SCQ score	■					
Karnofsky Performance Status	■			■		
Stage of disease						
Neoadjuvant chemotherapy	■				■	
Type of surgery					■	
Sentinel node biopsy				■		
Axillary node dissection				■		
Breast reconstruction					■	
Menopausal status						
Symptoms						
CES-D score	■	■	■	■		
Trait Anxiety score	■					
State Anxiety score		■	■	■		
Attentional Fatigue score	■			■		
LFS Fatigue score	■	■		■	■	
LFS Energy score						
Presence of hot flashes	■					
Severity of hot flashes						
Distress of hot flashes						
Presence of breast pain						
Worst pain score						
Average pain score						
No. of days per week in pain						
No. of hours per day in pain						
Psychosocial Adjustment						
Coping	■	■	■		■	■
Distress of diagnosis	■					
Fear of future diagnostic tests		■	■		■	■
Fear of metastasis	■					
Control	■	■				■

CES-D- Center for Epidemiological Studies-Depression Scale; GSDS-General Sleep Disturbance Scale; LFS-Lee Fatigue Scale; SCQ-Self-Administered Comorbidity Questionnaire

■ = From exploratory analysis had a *t* value of greater than 2.00.

Table 2. Demographic, Clinical, and Symptom Characteristics of the Patients (n=396)

Characteristic	Mean (SD)
Age (years)	54.9 (11.6)
Education (years)	15.7 (2.7)
Karnofsky Performance Status score	93.2 (10.3)
Self-Administered Comorbidity Questionnaire	4.3 (2.8)
Body mass index (kg/m^2)	26.8 (6.2)
Gone through menopause, % (n)	62.3 (248)
Experiencing hot flashes, % (n)	31.9 (127)
Lives alone, % (n)	23.9 (95)
Married, % (n)	41.5 (165)
Non-white, % (n)	35.4 (141)
Employed, % (n)	47.5 (189)
Stage, % (n)	
0	18.3 (73)
I	37.9 (151)
IIA, IIB	35.4 (141)
IIIA, IIIB, IIIC, IV	8.3 (33)
Neoadjuvant chemotherapy received, % (n)	19.8 (79)
Type of surgery, % (n)	
Breast conservation	79.9 (318)
Mastectomy	20.1 (80)
Underwent reconstruction to breast at the time of surgery, % (n)	21.6 (86)
Underwent sentinel node biopsy, % (n)	82.4 (328)
Underwent axillary lymph node dissection, % (n)	37.4 (149)
Pain in the affected breast, % (n)	28.2 (110)
Mean symptom severity scores at baseline	
Center for Epidemiological Studies-Depression Scale score	13.7 (9.8)
Trait Anxiety score	35.3 (9.0)
State Anxiety score	41.8 (13.5)
Attentional Fatigue score	6.6 (1.9)
LFS Fatigue score	3.1 (2.4)
LFS Energy score	4.9 (2.5)

LFS-Lee Fatigue Scale

Table 3. Hierarchical Linear Models of Sleep Disturbance and Excessive Daytime Sleepiness

| | Coefficient (SE) | |
	Unconditional Model	Final Model
Variable		
Sleep Disturbance		
Fixed effects		
Intercept	48.313 (1.072)[b]	48.340 (0.778)[b]
Time[a] (linear rate of change)	0.449 (0.475)[ns]	0.440 (0.463)[ns]
Time^2 (quadratic rate of change)	-0.159 (0.073)[d]	-0.158 (0.072)[d]
Time invariant covariates		
Intercept		
KPS score		-0.204 (0.074)[c]
SCQ score		0.646 (0.254)[d]
CES-D		0.722 (0.096)[b]
Fatigue (LFS)		2.263 (0.365)[b]
Hot flash severity rating		0.626 (0.297)[d]
AFI		-1.475 (0.492)[c]
Linear		
Education (yrs) x time		0.394 (0.161)[d]
CES-D x time		-0.206 (0.048)[b]
Quadratic		
Education (yrs) x time^2		-0.058 (0.026)[d]
CES-D x time^2		0.025 (0.007)[c]
Variance components		
In intercept	363.104[b]	148.545[b]
In linear rate	30.489[b]	26.325[b]
In quadratic fit	0.596[b]	0.524[b]
Goodness-of-fit deviance (parameters estimated)	20621.422 (10)	20353.273 (20)
Model comparison (χ^2_{10})		268.149 (10)[b]
Excessive Daytime Sleepiness		
Fixed effects		
Intercept	2.079 (0.064)[b]	2.265 (0.097)[b]
Time[a] (linear rate of change)	0.080 (0.031)[d]	0.197 (0.045)[b]
Time^2 (quadratic rate of change)	-0.020 (0.005)[b]	-0.034 (0.007)[b]
Time invariant covariates		
Intercept		
KPS score		-0.014 (0.004)[c]
SLNB		-0.350 (0.099)[c]
ALND		0.274 (0.081)[c]
Body mass index (kg/m^2)		0.020 (0.006)[c]
CES-D		0.025 (0.005)[b]
Fatigue (LFS)		0.169 (0.020)[b]
AFI		-0.092 (0.026)[c]
Linear		
Education (yrs) x time		0.034 (0.010)[c]
Employed x time		-0.155 (0.055)[c]
Fear of future diagnostic tests x time		0.021 (0.008)[d]

Neo-adjuvant chemotherapy x time		-0.197 (0.071)[c]
Quadratic		
Education (yrs) x time^2		-0.005 (0.002)[c]
Employed x time^2		0.020 (0.009)[d]
Fear of future diagnostic tests x time^2		-0.003 (0.001)[d]
Neo-adjuvant chemotherapy x time^2		0.022 (0.012)[ns]
Variance components		
In intercept	1.160[b]	0.376[b]
In linear rate	0.097[b]	0.083[b]
In quadratic fit	0.002[c]	0.001[c]
Goodness-of-fit deviance (parameters estimated)	7000.780 (10)	6695.150 (25)
Model comparison (χ^2_{15})		305.63 (15)[b]

KPS- Karnofsky Performance Status

SCQ-Self-Administered Comorbidity Questionnaire

CES-D- Center for Epidemiological Studies-Depression Scale

LFS-Lee Fatigue Scale

AFI-Attentional Fatigue Index

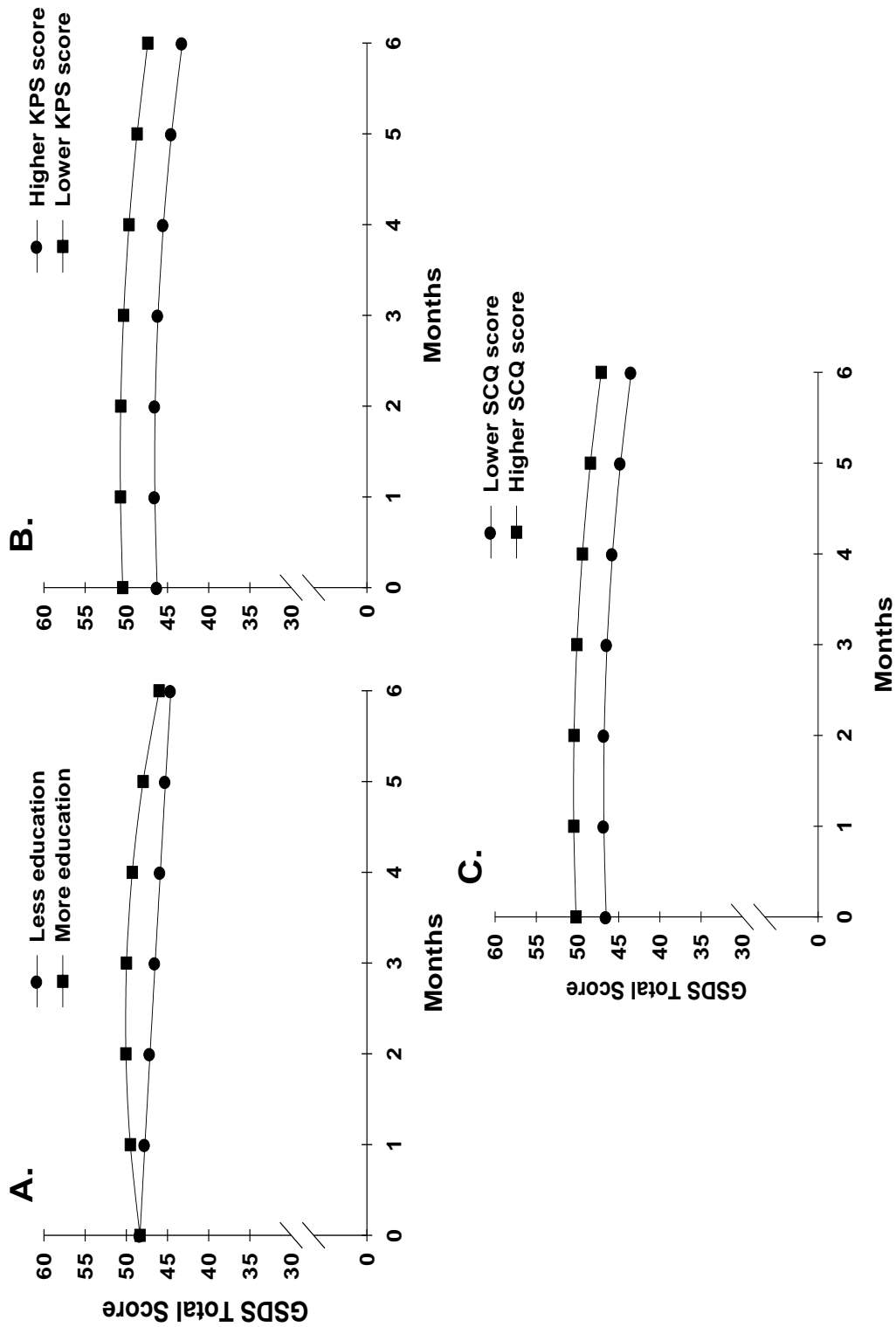SLNB-Sentinel lymph node biopsy

ALND-Axillary lymph node biopsy

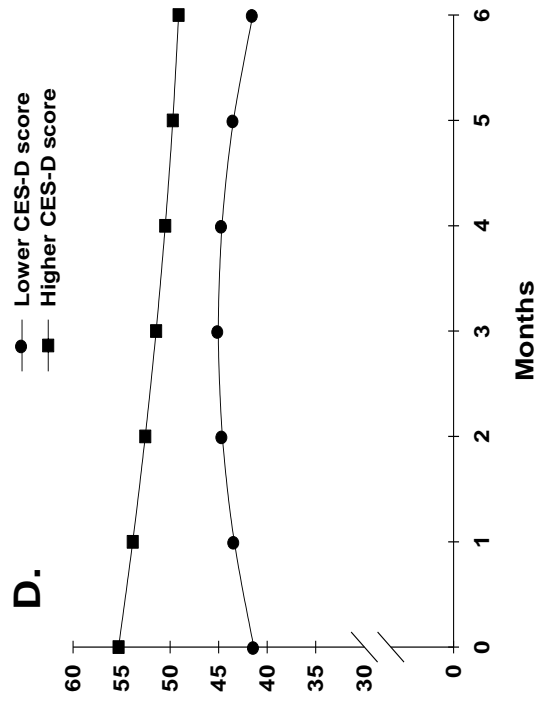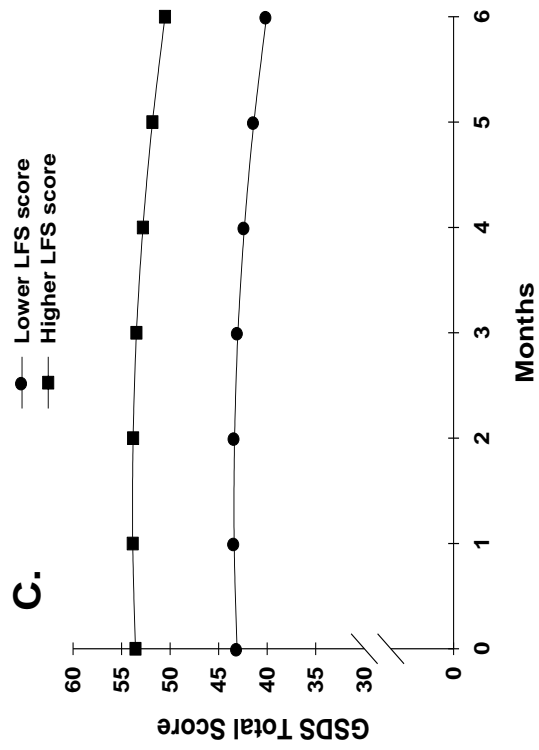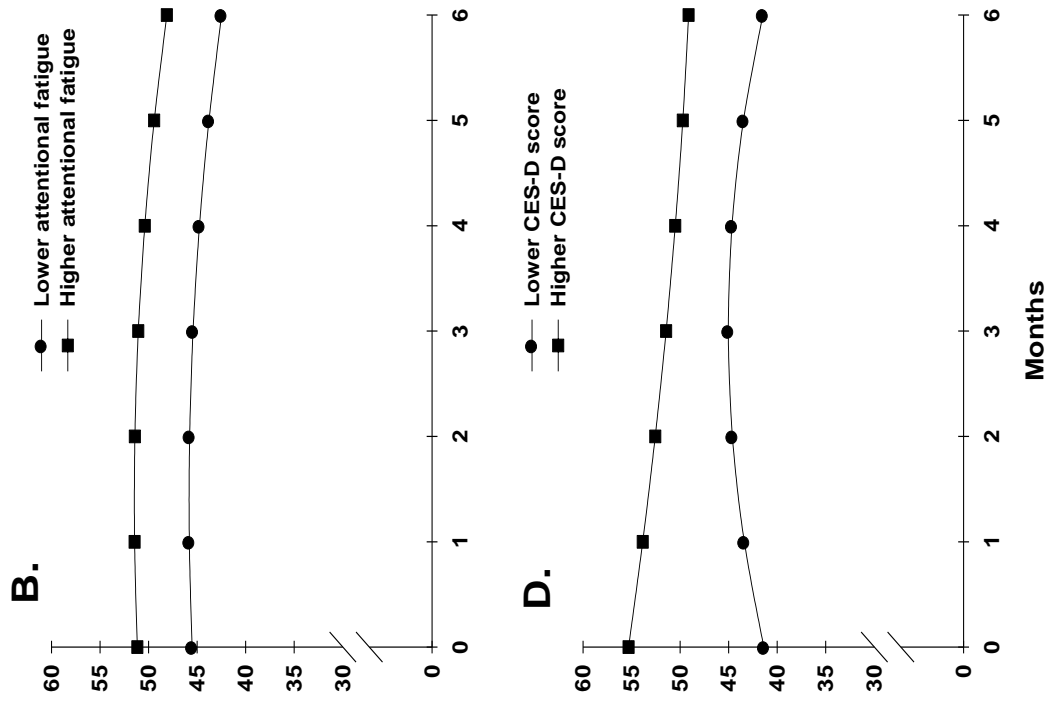[a]Time was coded 0 at the time just prior to surgery

[b]$p<0.001$

[c]$p<0.01$

[d]$p<0.05$

A.

B.

A.

Excessive Daytime Sleepiness Score

- ● Higher KPS score
- ■ Lower KPS score

B.

Excessive Daytime Sleepiness Score

- ● Lower BMI
- ■ Higher BMI

C.

Excessive Daytime Sleepiness Score

- ● Higher fear of future diagnostic tests
- ■ Lower fear of future diagnositic tests

Months

D.

- ● SLNB
- ■ No SLNB

E.

- ● No ALND
- ■ ALND

F.

- ● Neoadjuvant treatment
- ■ No neoadjuvant treatment

Months
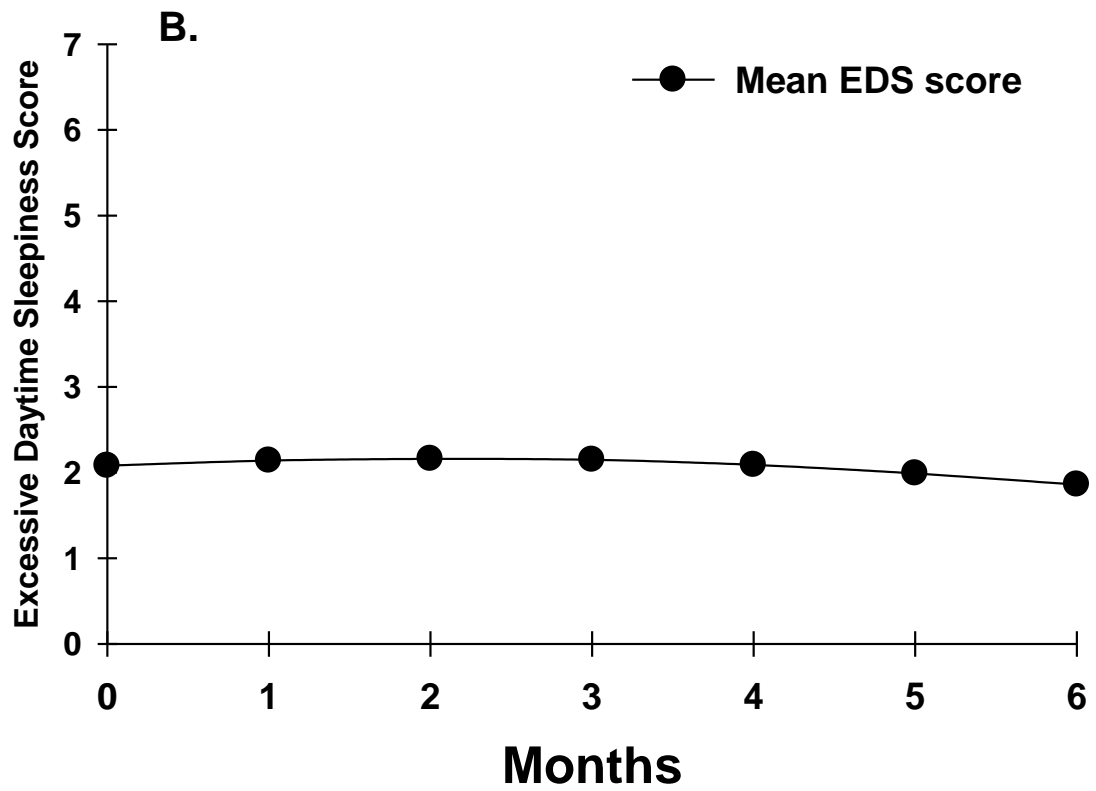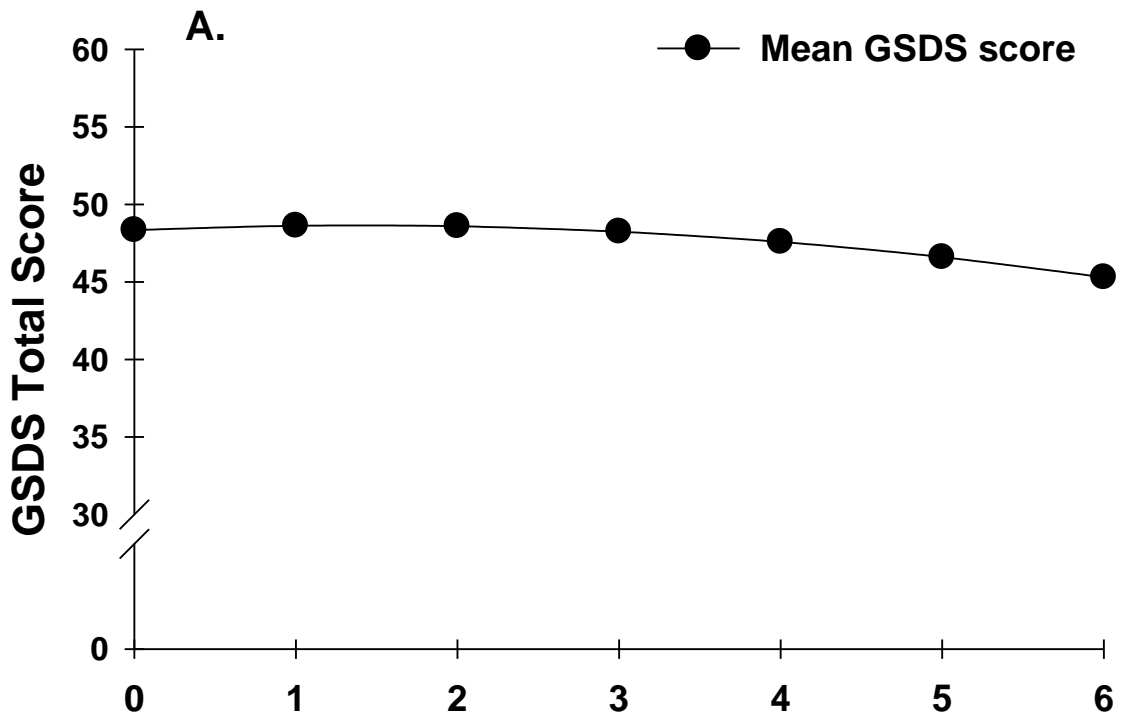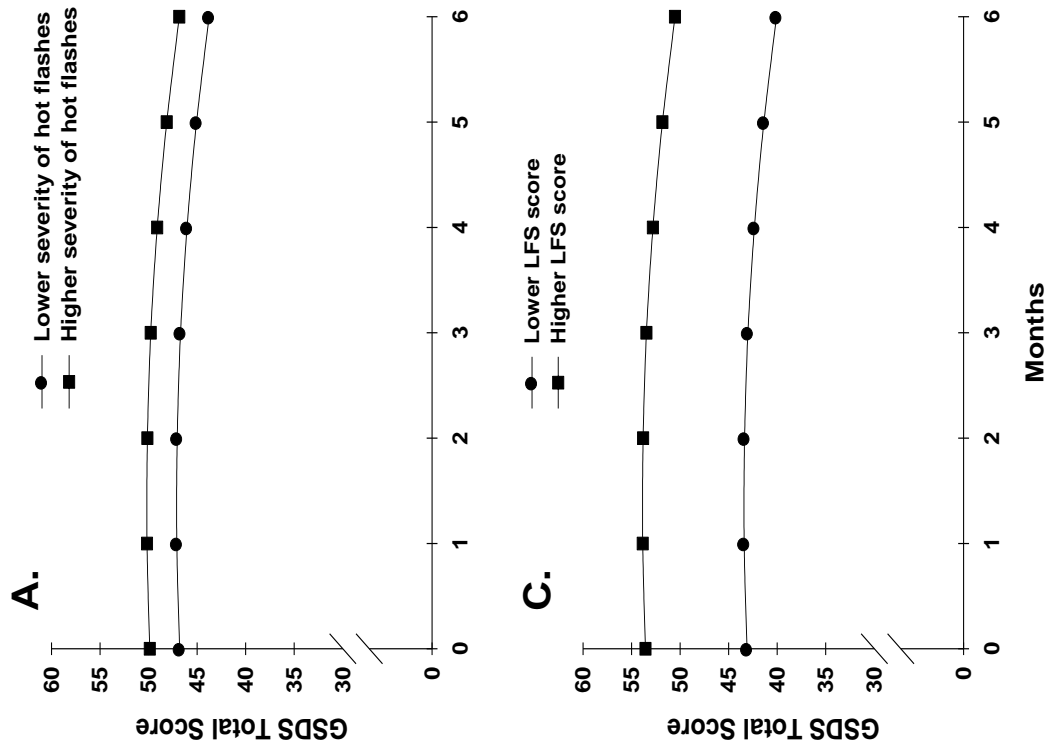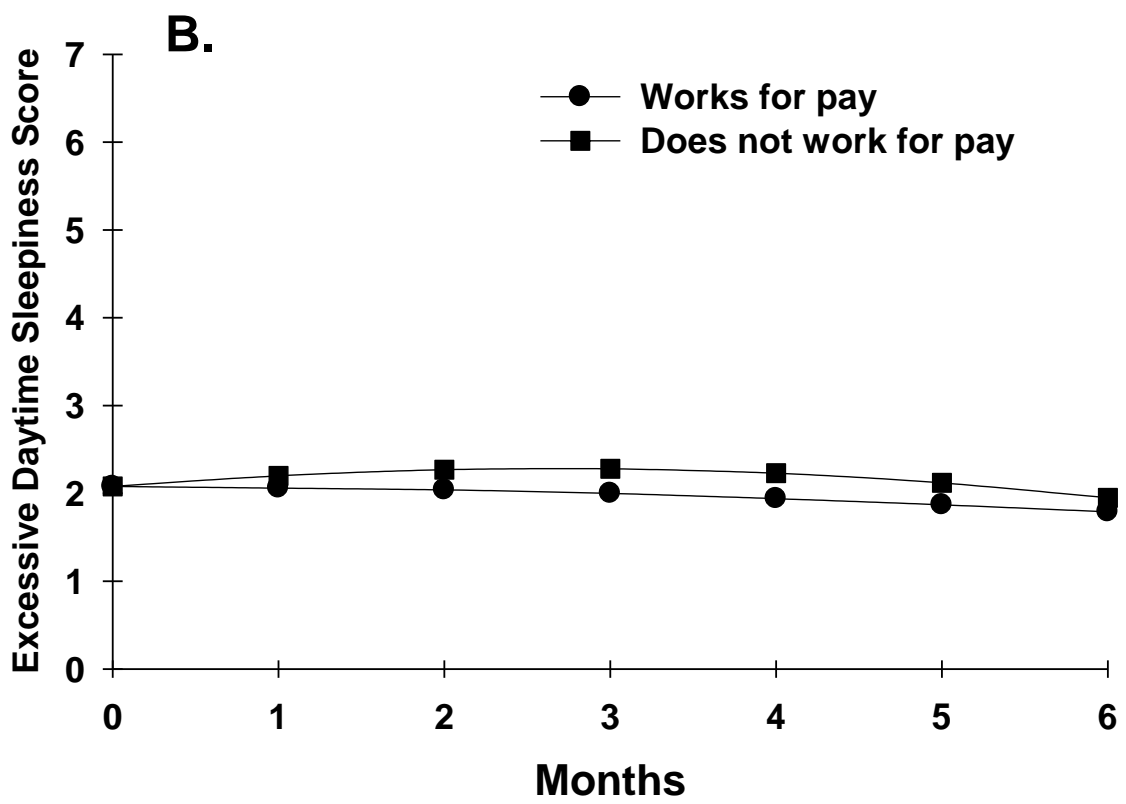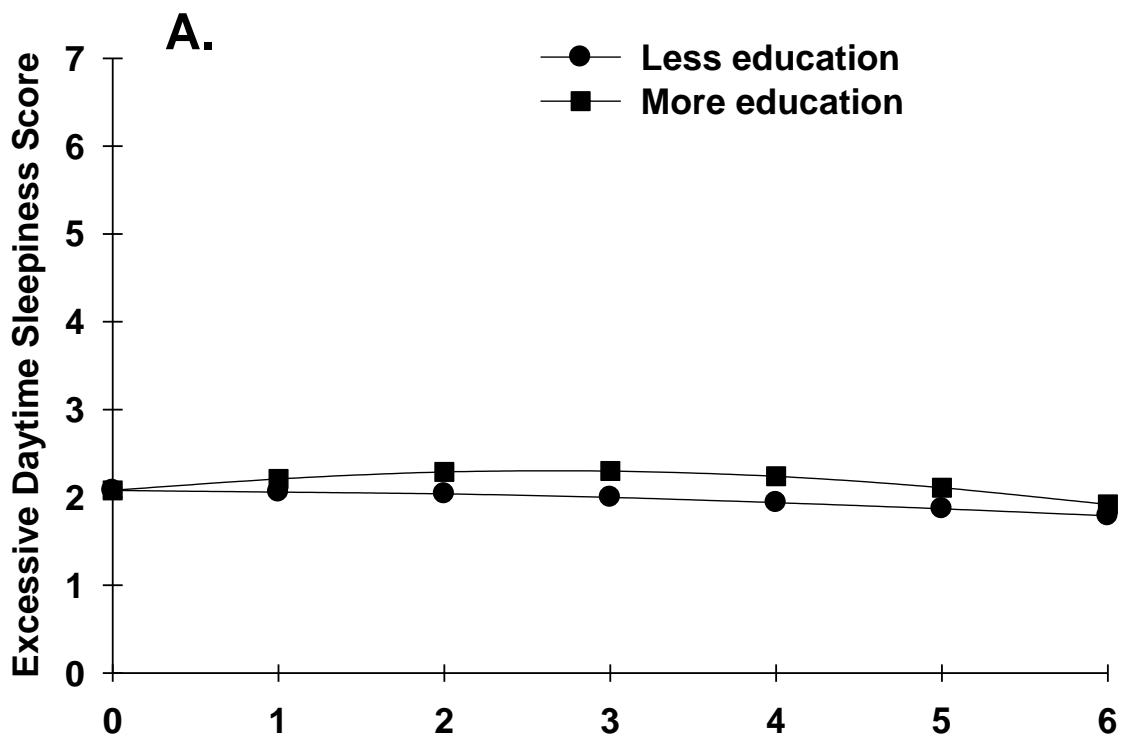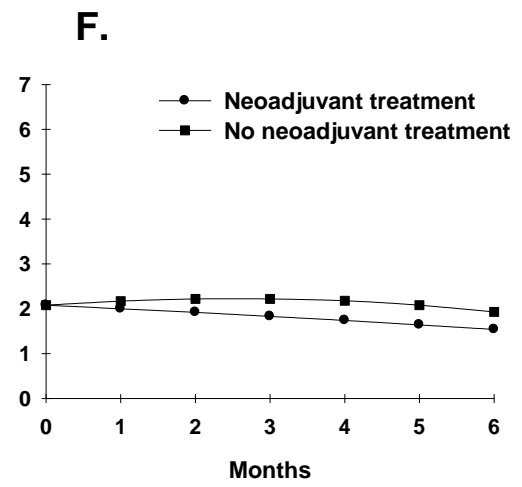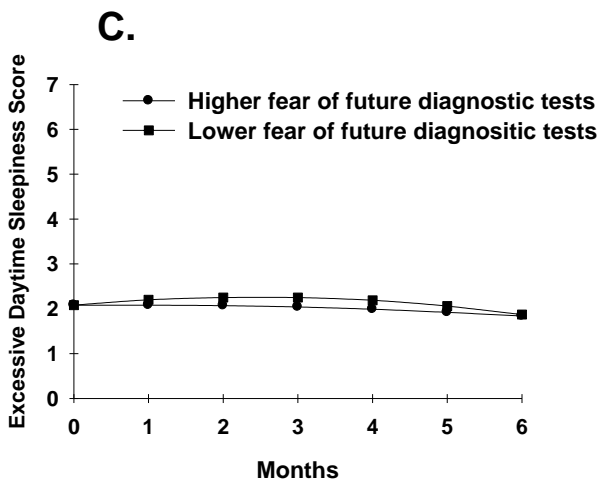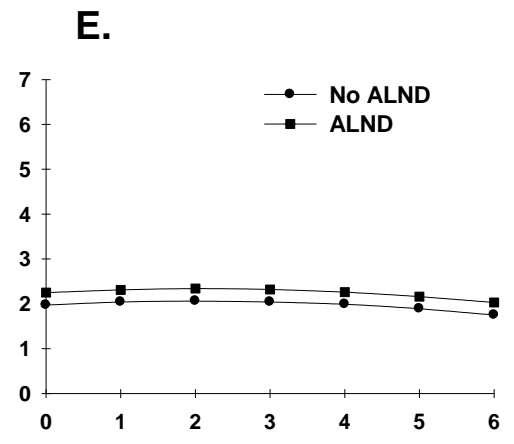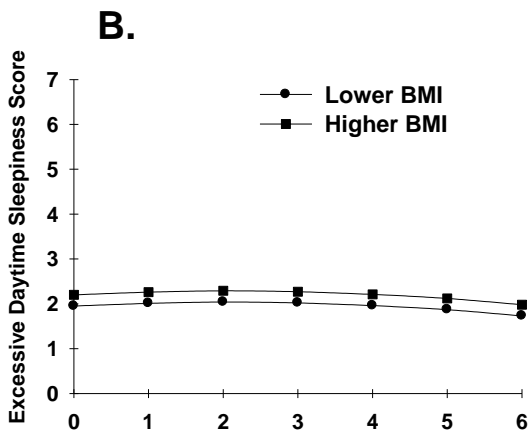
Identification of Distinct Subgroups of Breast Cancer Patients Based on Self-Reported Changes in Sleep Disturbance

Christina Van Onselen, RN, CNS, PhD(c)

ABSTRACT

Study Objectives: Identify distinct latent classes of breast cancer patients based on self-reported sleep disturbance from the time prior to surgery through six months and to evaluate for differences in baseline demographic, clinical, and symptom characteristics among these latent classes.
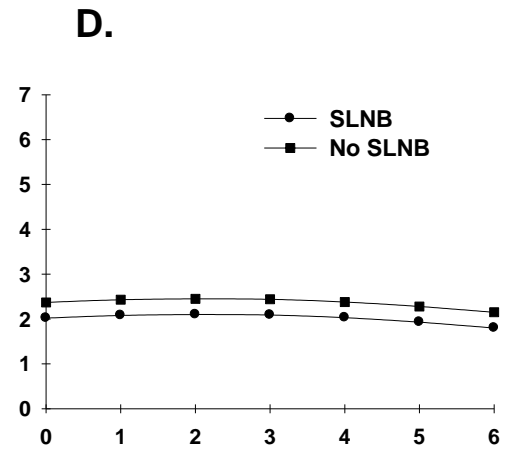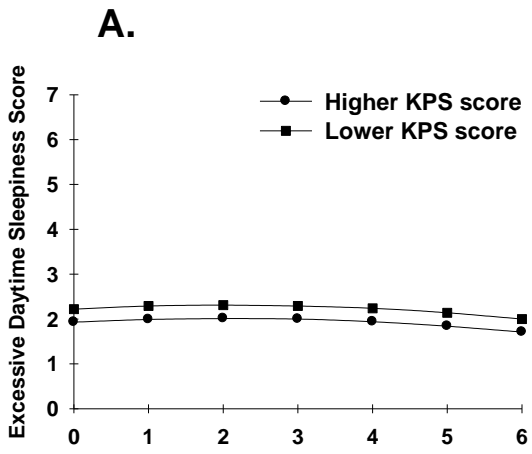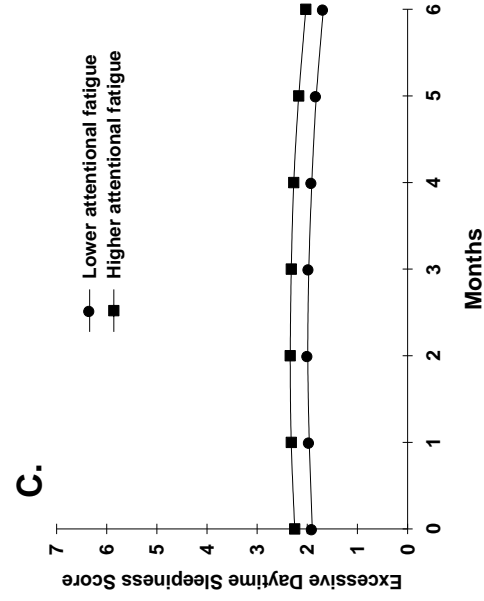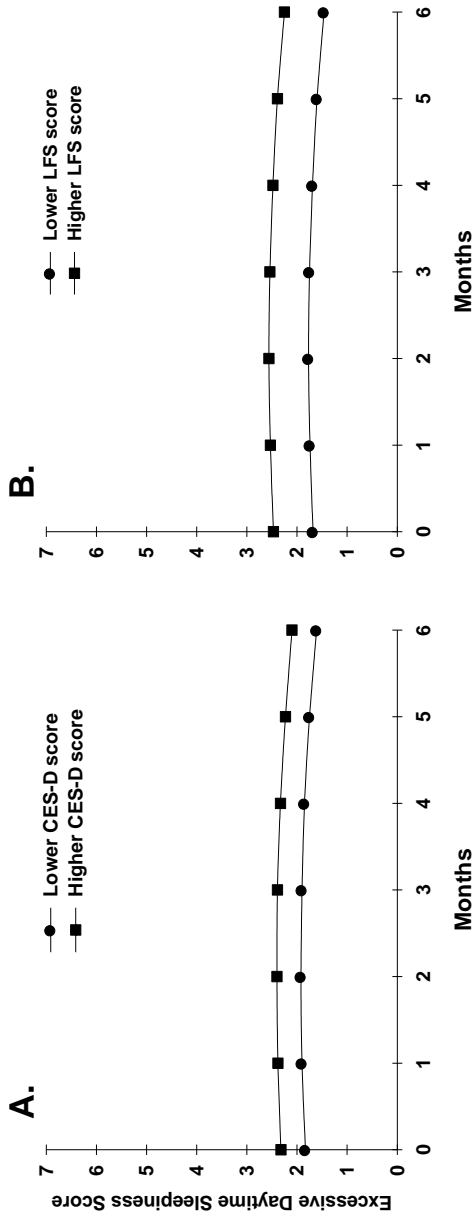
Methods: The sample included 398 women who underwent unilateral breast cancer surgery. Patients completed Karnofsky Performance Status scale, General Sleep Disturbance Scale (GSDS), Lee Fatigue Scale, Attentional Function Index, Center for Epidemiological Studies-Depression Scale, and Spielberger State-Trait Anxiety Inventories. Questionnaires were completed prior to surgery and every month for six months.

Results: Three distinct classes of sleep disturbance trajectories were identified. The High Sustained class (55.0%) had a high GSDS score prior to surgery that persisted for six months. The Low class (39.7%) had a low GSDS score at baseline that remained low. The Decreasing class (5.3%) had high GSDS score prior to surgery that decreased over time. The High Sustained class was significantly younger, more comorbidity and poorer function compared to the Low class. More women with hot flashes were in the High Sustained compared to the Low class. More women who underwent mastectomy or breast reconstruction were in the Decreasing class compared to the High Sustained and Low classes. The Decreasing and High Sustained classes reported higher levels of physical fatigue, attentional fatigue, depressive symptoms, and trait anxiety compared to the Low class.

Conclusion: A relatively high percentage of women with sleep disturbance prior to surgery for breast cancer will continue to have sleep problems during subsequent treatments. Clinicians should have a high index of suspicion for sleep disturbance when women are to undergo a mastectomy, reconstruction, are younger, or are experiencing hot flashes.

Keywords: cancer, surgery, latent, sleep, symptoms

INTRODUCTION

The occurrence of sleep disturbance varies widely in women with breast cancer, with prevalence rates ranging from 20% to 70% (1,2). Some of the variability may be related to the timing of the assessments in relationship to the patients' treatment trajectory. For example, in studies that evaluated sleep disturbance prior to surgery for breast cancer, 70% (3) to 88% (4) of these patients reported sleep disturbance (3-6). In one of these studies (3), a significant decrease in the prevalence of sleep disturbance was found between the preoperative assessment (69.6%) and the assessment two months after surgery (59.6%).

Studies that evaluated sleep disturbance after surgery and during adjuvant treatment (i.e., radiation therapy (RT), chemotherapy (CTX)) have produced rather consistent findings (7-13). In terms of occurrence rates, in two studies that evaluated patients prior to adjuvant treatment, between 59% (7) and 66% (9) of women reported sleep disturbance. Throughout CTX and RT, 66% of patients complained of sleep disturbance (7). Of note, 50% (7) to 58% (11) had sleep disturbance up to eight weeks after completion of adjuvant treatment.

In terms of symptom severity, in one study, women undergoing CTX for breast cancer slept less than healthy controls (12). In two longitudinal studies (9,13), hours of total sleep time decreased during the first two cycles and returned to pretreatment levels during the third cycle of CTX. In contrast, in a study that evaluated patients receiving RT for breast cancer (8), the severity of sleep disturbance increased during and after RT.

Several investigators have tried to describe the types of sleep disturbance in women with breast cancer (e.g., problems with sleep onset latency, sleep maintenance, or

early awakening) (8,10,11). Across all of these studies, large amounts of inter-individual variability were found in occurrence rates, severity ratings, as well as in the impact of sleep disturbance on daytime function (3,8,9,13). However, no studies were found that attempted to evaluate for distinct subgroups of women with breast cancer (i.e., latent classes) based on changes in sleep disturbance over time. This type of evaluation using more sophisticated methods of longitudinal data analysis (i.e., latent class analysis (LCA)), may assist with the identification of distinct subgroups of patients who are at higher risk for more severe sleep disturbance.

Only one study (14) was found that used GMM to identify distinct subgroups of patients using their self-reports of types and duration of sleep disturbance as well as the type of functional impairment associated with sleep disturbance. This population-based study identified four distinct latent classes of patients with insomnia, namely distressed (i.e., having one sleep complaint that occurs weekly and has emotional distress), transient (i.e., having a variety of sleep related symptoms with different frequencies), difficulty maintaining sleep (DMS), and comorbid with non-restorative sleep (Comorbid and NRS). These four subgroups differed on the number of sleep disturbance symptoms, presence of non-restorative sleep and comorbidities, degree of daytime impairment and insomnia severity (as measured by the Insomnia Severity Index (ISI)). This study demonstrates the usefulness of using LCA to identify distinct subgroups of patients. However, the cross-sectional design did not allow for an evaluation of distinct subgroups of patients whose sleep disturbance might persist over a period of months or years.

Therefore, the purposes of this study were: to identify distinct latent classes of breast cancer patients based on self-reported sleep disturbance from the time prior to

surgery through six months after surgery and to evaluate for differences in baseline

demographic and clinical characteristics, as well as differences in the severity of other

common symptoms (i.e., fatigue, energy, attentional fatigue, depression, and anxiety)

among these latent classes. In addition, differences in the severity of a number of sleep

parameters prior to surgery were evaluated among the latent classes.

METHODS

Patients and Settings

This longitudinal study is part of a larger study that evaluated neuropathic pain

and lymphedema in a sample of women who underwent breast cancer surgery. Patients

were recruited from Breast Care Centers located in a Comprehensive Cancer Center, two

public hospitals, and four community practices. Women were eligible if they were $\geq$18

years of age; underwent breast cancer surgery on one breast; were able to read, write, and

understand English; and provided written informed consent. Patients were excluded if

they were: having bilateral breast cancer surgery and/or had distant metastasis at the time

of diagnosis. A total of 516 patients were approached and 410 enrolled in the study

(response rate 79.4%). Questionnaire booklets were completed by 398 women. The major

reasons for refusal were: too busy, overwhelmed with the cancer diagnosis, or insufficient

time available to complete the baseline assessment prior to surgery.

Instruments

At enrollment, demographic (age, gender, marital status, education, ethnicity,

employment status, living situation, financial status) and clinical (menopausal status,

body mass index (BMI)) information were obtained. At each subsequent assessment,

patients provided information on current treatments for breast cancer. Medical records

were reviewed to obtain information on stage of disease, surgical procedure, neoadjuvant treatment, and reconstructive surgery. Hot flashes were evaluated by asking women if they experienced hot flashes (0= no and 1= yes) during the past week.

The Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well established validity and reliability (15). Patients rated their functional status using the KPS scale that ranged from 30 ("I feel severely disabled and need to be hospitalized") to 100 ("I feel normal; I have no complaints or symptoms").

The Self-Administered Comorbidity Questionnaire (SCQ), which was developed to assess comorbidity in clinical and health service research settings (16), consists of 13 common medical conditions described in plain language (i.e., no prior medical knowledge needed). Patients were asked to indicate if they currently had the condition ("yes/no"), and if "yes," to indicate whether they received treatment for it ("yes/no") and whether it limited their activities ("yes/no"). Patients could add two additional conditions not listed on the instrument. Each condition yields a maximum of three points. Therefore, the maximum score totals 45 points if the open-ended items are used and 39 points if only the 13 closed-ended items are used. SCQ-13 scores are reported in this paper. The SCQ has well-established validity and reliability and has been used in studies of patients with a variety of chronic conditions (16,17).

The 21-item General Sleep Disturbance Scale (GSDS) was used to evaluate overall sleep disturbance during the past week. Each item is rated on a scale that ranges from 0 (never) to 7 (everyday). The GSDS consists of seven subscales (i.e., quality of sleep, quantity of sleep, sleep onset latency, mid-sleep awakenings, early awakenings,

medications for sleep, excessive daytime sleepiness) that can range from 0 to 7 and a total

score that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). A total

GSDS score of ≥43 indicates a clinically meaningful level of sleep disturbance (18).

Subscale scores represent the number of days a week a patient finds the sleep parameter

problematic and a score ≥3 indicates a clinically meaningful level of disturbance. The

GSDS has high internal consistency reliability among oncology samples (19-23). In this

study, the Cronbach's alpha for the GSDS total score was 0.86.

The Lee Fatigue Scale (LFS) consists of 18 items designed to assess physical

fatigue and energy (24). Each item is rated on a 0 (not at all) to 10 (extremely) numeric

rating scale (NRS). Total fatigue and energy scores were calculated as the mean of the 13

fatigue items and the 5 energy items, respectively. Higher scores indicate greater fatigue

severity and higher levels of energy. Respondents were asked to rate each item based on

how they felt "right now". The LFS was chosen for this study because it is relatively

short, easy to administer, and has well established validity and reliability. The LFS was

used with healthy individuals (24,25) and in patients with cancer and HIV (20,23,26,27).

In this study, Cronbach's alphas for the fatigue and energy subscales were .96 and .93,

respectively.

The Attentional Function Index (AFI) consists of 16-items designed to measure

attentional fatigue in patients with cancer. Each item is rated on a 0 to 10 NRS. A mean

AFI score was calculated, with higher scores indicating greater capacity to direct

attention (i.e., lower levels of attentional fatigue) (28). Based on a previously conducted

analysis of the frequency distributions of the AFI scores, attentional fatigue can be

grouped into categories of functional status (i.e., patients who score <5.0 functioning

poorly and experiencing high levels of attentional fatigue, patients who score 5.0 to 7.5 functioning moderately well and experiencing moderate levels of attentional fatigue, patients who score >7.5 functioning well and experiencing low levels of attentional fatigue (29). The AFI has established reliability and validity (28,30). In this study, Cronbach's alpha for the AFI was .95.

The Center for Epidemiological Studies-Depression Scale (CES-D) scale consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60, with scores of $\geq$ 16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well established concurrent and construct validity (31-33). In this study, the Cronbach's alpha for the CES-D was .90.

The Spielberg State-Trait Anxiety Inventories (STAI-T and STAI-S) consist of 20 items each that are rated from 1 to 4. The scores for each scale are summed and can range from 20 to 80. A higher score indicates greater anxiety. The STAI-T measures an individual's predisposition to anxiety determined by his/her personality and estimates how a person generally feels. The STAI-S measures an individual's transitory emotional response to a stressful situation. It evaluates the emotional responses of worry, nervousness, tension, and feelings of apprehension related to how a person feels "right now" in a stressful situation. Cutoff scores of $\geq$ 31.8 and $\geq$ 32.2 indicate high levels of trait and state anxiety, respectively. The STAI-S and STAI-T inventories have well established criterion and construct validity and internal consistency reliability coefficients (34-36). In this study, the Cronbach's alphas for the STAI-T and STAI-S were .88 and .95, respectively.

Study Procedures

The Committee on Human Research at the University of California, San

Francisco and the Institutional Review Boards at each of the study sites approved the

study. During the patient's preoperative visit, a staff member explained the study to the

patient. For those women who were willing to participate, the staff member introduced

the patient to the research nurse, who met with the women, determined eligibility, and

obtained written informed consent prior to surgery. After providing consent, the patient

completed the baseline study questionnaires (Assessment 0). Patients were contacted two

weeks after surgery to schedule the first post-surgical appointment. The research nurse

met with the patients in their home, the Clinical Research Center, or the clinic at 1, 2, 3,

4, 5, and 6 months after surgery. During each study visit, the women completed the study

instruments.

Statistical Analyses

Descriptive statistics and frequency distributions were calculated for patients'

demographic and clinical characteristics, as well as their symptom severity scores.

Unconditional growth mixture modeling (GMM) with robust maximum likelihood

estimation was carried out with Mplus Version 5.21 (37) to identify latent classes (i.e.,

subgroups of patients) with distinct sleep disturbance trajectories over the six months of

the study. In the basic latent growth curve analysis, a single growth curve representing

the "average" change trajectory is estimated for the whole sample. However, it is usually

true that substantial variation exists between the individual change trajectories and the

estimated mean growth curve for the sample. This heterogeneity may be due to "error."

However, it may represent meaningful differences between unknown groups of

individuals in the way they change across time. In the latter case, the possibility for examining the differences between these groups is lost when only a single growth curve is estimated (38) and (39).

GMM, an extension of latent growth curve analysis, extends the estimation of a single growth curve – represented as latent variables (i.e., intercept and slope coefficients and variance components for them) – to the estimation of a new latent categorical variable that identifies latent growth curves for two or more previously unknown groups, called "classes" (40-46). GMM can be employed in several ways. The basic GMM is the "unconditional model" in which separate growth classes are identified solely by examining differences in their growth trajectories (42,46). Classes can be distinguished due to differences in any combination of their intercepts, slopes (linear and nonlinear), and within-class variances in intercepts and slopes.

The simplest form of a latent class mixture model is the *latent class growth model* (LCGM; (47,48)). In the LCGM, within-class variances and covariances for intercepts and slopes are assumed to be zero, because the class membership is presumed to account for all variation between individuals (within classes) in their growth trajectories (43). It is useful in GMM to begin estimation of the number of latent classes with a latent class growth analysis using LCGM (46). GMM extends the estimation of multiple growth curves defined by the latent classes, such that covariances are not assumed to be zero within classes and may vary across classes.

The unconditional GMM may be extended through the incorporation of (1) covariates that characterize differences between observations; (2) concurrent events, or covariates or outcomes that are assessed and change across time; or (3) distal events, perhaps

94

consequences of the differing change processes (46,49). Muthén (44,45) refers to this extension as the general growth mixture model (GGMM).

The identification of the basic or unconditional growth model is the first step in such an analysis. It should be followed with an examination of how the latent classes differ on important covariates, and how class membership is associated with outcomes that depend on, or can be predicted by the differing change processes. The ideal approach is to examine covariates of the change processes that lead to different latent classes, and to validate the meaning of the latent classes through the examination of their associations with concurrent events or their differences on distal events, by incorporating these variables into increasingly complex structural models (41,46,49-51).

However, more complex models require larger samples, especially when the proportion of cases in some latent classes is small (e.g., perhaps only 10%). Tofighi and Enders (52) evaluated several indices useful for choosing the number of classes for a GMM, including and not including covariates. In their Monte Carlo study, they found that including covariates in fact made estimation of the correct number of classes less reliable unless the sample size was 1000 or more.

In this study, the number of latent growth classes that best fit the data was identified using guidelines recommended by Jung and Wickrama (40), Muthén (46), Nylund, Asparaouhov, & Muthén (53), and Tofighi and Enders (52). First, a model with two latent growth classes was fit to the data, then a model with three latent growth classes was fit, and the procedure was repeated until the final iteration of the model was not supported. Model fit for the GMM was assessed statistically by identifying the model with the lowest Bayesian Information Criterion (BIC), and by testing the "K" versus "K-

1" class models to determine whether a model with K classes fit the data better than a model with K-1 classes with the parametric bootstrapped likelihood ratio test (BLRT) (40,52,53). For example, after estimating the 3-class model (the K-class model), it was compared to the 2-class model (the K-1 class model) with the BLRT to determine whether the 3-class model fit the data better than the 2-class model. In addition to using the BLRT to compare models, we examined the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR) for the "K" versus "K-1" class models. The VLMR test was shown in Monte Carlo studies to be anti-conservative in identifying the "correct" number of classes in some mixture models. That is, it sometimes identifies a K-class model as fitting the data better than the K-1 class model when in fact the K-1 class model is correct. However, *when the VLMR test is non-significant*, it does provide evidence that the K-class model is not better than the K-1-class model (53).

The fourth index used to evaluate model fit was entropy (i.e., the proportion of latent versus predicted class membership). It was estimated for each solution, with $\geq .80$ being preferred. Better-fitting models should produce higher entropy values, indicating consistency between the latent and predicted class membership (54,55), perhaps analogous to classificiation indices for interrater agreement, or reliability coefficients. However, no fixed criterion exists for evaluating entropy. In addition, it was shown to be unreliable as a fit index with unbalanced class sizes (56). In addition to evaluating the fit indices, the best fitting model was visually inspected by plotting observed against model-predicted values to determine whether the predicted trajectories followed the empiric trajectories for the classes, and to evaluate whether the predicted plots "made sense" theoretically and clinically (46).

In summary, the criteria used for selecting the best fitting model in order of importance were the BIC followed by the BLRT. The VLMR was employed as a check against the extraction of too many classes by the BLRT, and the entropy measure was used descriptively to assess membership in the latent classes compared to the most likely class memberships predicted by the model. The model with higher entropy was preferred. Of course, none of these fit indices are relevant unless the smallest BIC can be reliably replicated with multiple random starts, or if the BLRT cannot reproduce the same log likelihood value in the majority of bootstrapped draws.

Intercepts and linear and quadratic slopes for each latent class were estimated for each model. Intercept variances were estimated for each class and were allowed to differ across classes. Given the relatively small sample size, the within-class linear and quadratic slope variance was fixed at zero for two classes, because estimation failed when they were free to vary. Even for the initial two-class model, it was necessary to fix the linear slope variance to zero for our largest class. Without setting the slope variance to zero, the model could not be estimated due to a non-positive definite covariance matrix. The change trajectory for this large class was flat with minimal within-class variance, similar to what would be expected in a latent class growth model (LCGM) (48,57). Mixture models are known to produce solutions at local maxima, so each model was fit with random starts to be sure that the solution for the model with the maximum log likelihood values was replicated (55).

After identifying the latent class solution that best fit our data, differences among the predicted classes were examined for important covariates and concurrent outcomes *outside our models*. Although this approach is not the ideal strategy (41,49-51), it was

97

judged to be more prudent given our relatively small sample and the large differences in latent class sizes. Missing data for the sleep disturbance scores were accommodated by Mplus Version 5.21 through the use of Full Information Maximum Likelihood and the use of the Expectation-Maximization algorithm. In this way, individuals are retained in the analysis even if their sleep disturbance scores were missing at one or more occasions, unlike traditional analyses of longitudinal data such as repeated measures analysis of variance (ANOVA), in which a case is dropped even if only a single measure is missing. This method assumes that any missing data are ignorable (e.g., missing at random) (50,58).

Data were analyzed using SPSS Version 18.0 (59) and Mplus Version 5.21 (37). ANOVA and Chi-square analyses were used to assess for differences in baseline demographic and clinical characteristics and baseline symptom severity scores (i.e., fatigue, energy, attentional fatigue) among the GMM latent classes. Post hoc contrasts were done using the Bonferroni procedure to control the overall familywise alpha level of the three pairwise contrasts for the three GMM classes at 0.05. For any of the three pairwise contrasts, a p-value of < 0.017 (.05/3) was deemed statistically significant.

RESULTS

Patient Characteristics

As summarized in Table 1, the majority of the sample was White (64.1%) and well educated (15.7±2.7 years). Approximately, 24% lived alone and 42% were married or partnered. The majority of patients had gone through menopause (64.1%).

Results for GMM Analysis

Three distinct predicted classes of sleep disturbance trajectories were identified using GMM (Figure 1). The fit indices for the various models are shown in Table 2. A three class model was selected because its BIC was smaller than the two-class and four-class models. In addition, comparisons of the other fit indices were used to determine the best model.

The parameter estimates for the three predicted classes are listed in Table 3. The majority of the patients were classified into the High Sustained class (55.0%). These patients had total GSDS scores that were high at baseline (59.3±19.2) and maintained a similar level of sleep disturbance throughout the study. Patients in the second largest class, the Low class, (39.7%), had total GSDS scores that were low at baseline (30.8±11.9) and maintained a similar level of sleep disturbance throughout the study. Finally, patients in the third class, the Decreasing class, (5.3%), had high GSDS scores prior to surgery (63.9±12.7) that decreased during months 1 through 3 and then stabilized during months 4 through 6.

Differences in Demographic and Clinical Characteristics among the Three Predicted Classes

No differences were found among the three predicted classes in education, BMI, ethnicity, marital status, or living alone. Statistically significant differences were found among the three predicted classes in age, KPS score, SCQ score, and percent experiencing hot flashes (Table 1). Post hoc contrasts demonstrated that patients in the High Sustained class were significantly younger than those in the Low class. In terms of KPS scores, patients in the High Sustained class reported significantly lower KPS scores

than those in the Low class. Patients in the High Sustained class reported significantly higher mean SCQ scores compared to the Low class. While 32% of the sample reported hot flashes, post hoc contrasts revealed that a significantly higher proportion of women with hot flashes were in the High Sustained class compared to the Low class (p=0.002).

The only clinical characteristics that were different among the classes, in omnibus tests, were type of surgery (i.e., breast-conserving, mastectomy) and having undergone breast reconstruction at the time of surgery. Post hoc contrasts revealed that a significantly higher proportion of women who underwent a mastectomy were in the Decreasing class compared to both the High Sustained and Low classes (p=0.001). Similarly, a significantly higher proportion of women who underwent breast reconstruction at the time of surgery were in the Decreasing class compared to both the High Sustained and the Low classes (p=0.002).

For both having undergone adjuvant CTX and RT, the omnibus tests found significant differences among the predicted classes (p<0.02 and p<0.05, respectively). However, post hoc contrasts only revealed a significant difference for adjuvant CTX. A significantly higher proportion of women who underwent adjuvant CTX were in the High Sustained class compared to the Low class (p=0.016).

Differences in Subscale and Total Sleep Disturbance Scores Prior to Surgery Among the Three Predicted Classes

The differences in subscale and total sleep disturbance scores (GSDS) among the three predicted classes prior to surgery are shown in Figure 2. Differences among the predicted classes were found for the GSDS subscale scores of sleep quality (F(2, 382)=82.94), sleep quantity (F(2, 377)=53.24), sleep onset latency (F(2, 385)=68.01),

mid-sleep wakes ($F_{(2, 384)}$=24.04), early awakenings ($F_{(2, 383)}$=53.84), medication for sleep ($F_{(2, 382)}$=19.67), and excessive daytime sleepiness ($F_{(2, 382)}$=64.51) scores, as well as for the total sleep disturbance score ($F_{(2, 381)}$=142.80; all $p \leq 0.0001$). Post hoc contrasts demonstrated that the Decreasing and High Sustained classes had significantly higher sleep quality (4.5±1.7 and 4.2±1.7, respectively), sleep quantity (5.5±1.6 and 5.4±1.4, respectively), mid-sleep wakes (5.2±1.5 and 4.8±2.1, respectively), early awakenings (4.4±2.5 and 4.2±2.4, respectively), and excessive daytime sleepiness (2.8±1.2 and 2.6±1.2, respectively) scores compared to the Low class (2.0±1.6, 3.9±1.3, 3.2±2.5, 1.8±2.0, 1.3±0.9, respectively; all $p \leq 0.001$). Sleep onset latency demonstrated a similar pattern of relationships, the Decreasing and High Sustained classes had significantly higher scores (4.7±1.7 and 3.2±2.5, respectively) than the Low class (0.9±1.3; both $p \leq 0.001$). In addition, the Decreasing class had a significantly higher sleep onset latency score (4.7±1.7) than the High Sustained class (3.2±2.5; p=0.005). The High Sustained class had higher medications for sleep scores (0.6±0.8) than the Low class (0.2±0.4; $p \leq 0.001$). Finally, the Decreasing and High Sustained classes had higher total sleep disturbance scores (63.9±12.7 and 59.3±19.2, respectively) than the Low class (30.8±11.9; both $p \leq 0.001$).

Differences in Fatigue and Energy Scores Prior to Surgery Among the Three Predicted Classes

Significant differences in physical fatigue (LFS; $F_{(2, 375)}$=26.68; $p \leq 0.0001$) and energy (LFS; $F_{(2, 379)}$=8.67; p=0.0002) scores among the three predicted classes are shown in Figure 3. The Decreasing and High Sustained classes had higher mean fatigue scores prior to surgery (3.7±2.1 and 3.8±2.3, respectively) compared to the Low class

(2.1±2.1; both p≤0.01). The High Sustained class had lower mean energy scores prior to surgery (4.5±2.1) compared to the Low class (5.5±2.8; p≤0.001).

Differences in Attentional Fatigue Prior to Surgery Among the Three Predicted Classes

Significant differences in attentional fatigue among the three predicted classes are shown in Figure 3A (AFI; $F(2, 383)=29.40$; $p≤0.0001$). The Decreasing and High Sustained classes had lower mean AFI scores (i.e., higher levels of attentional fatigue) prior to surgery (6.0±1.8 and 6.0±1.9, respectively) compared to the Low class (7.4±1.6; both p≤0.01).

Differences in Depression and Anxiety Prior to Surgery Among the Three Predicted Classes

Significant differences in depressive symptoms (CES-D; $F(2, 378)=41.69$; $p≤0.0001$), as well as trait (STAI-T; $F(2, 380)=20.61$; $p≤0.0001$) and state (STAI-S; $F(2, 374)=20.91$; $p≤0.0001$) anxiety, among the three predicted classes are shown in Figure 3B. The Decreasing and High Sustained classes had higher CES-D scores prior to surgery (19.8±11.0 and 16.9±9.9, respectively) compared to the Low class (8.8±6.8). Similarly, the Decreasing and High Sustained classes had higher STAI-T scores prior to surgery (48.8±13.5 and 44.8±13.5, respectively) compared to the Low class (36.7±12.0). Only the High Sustained class had higher STAI-S scores prior to surgery (37.8±9.6) compared to the Low class (31.8±7.0).

DISCUSSION

To our knowledge, this study is the first to use GMM to identify predicted classes of breast cancer patients with distinct sleep disturbance trajectories prior to surgery through

six months after surgery. These analyses revealed three distinct predicted sleep

disturbance classes. Although, sleep disorders (e.g., insomnia, delayed sleep phase

disorder) could not be diagnosed, a large percentage of these women (i.e., High Sustained

class; 55%) self-reported total GSDS scores that were well above the clinically

meaningful cutoff score (i.e., ≥43) (18) for over six months. In addition, women in the

Decreasing class (5.3%) had a mean score above the clinically meaningful cutoff score

prior to surgery that persisted through the first month after surgery. Equally important,

approximately 40% of our sample had relatively low GSDS total scores prior to and

following surgery. If only mean GSDS scores were used to describe changes in sleep

disturbance over time in this sample (see Figure 1), these distinct phenotypes would not

have been identified. In addition, the interpretation of the data would be markedly

different – in that GSDS scores for over 50% of the sample that were above the clinically

meaningful cutoff for a period of six months would have been missed.

In terms of the mean sleep disturbance scores prior to surgery and through six months

after surgery, These scores are similar to the GSDS scores of 44.3 and 44.7 reported for

patients with breast cancer prior to the initiation of RT (19,60), as well as to those

reported by oncology patients undergoing outpatient treatment for a variety of cancer

diagnosis (i.e., 54.7 (23) and 51.2 (21)). The women in this sample had higher sleep

disturbance scores than women prior to (i.e., 42.3) and up to six weeks following a

hysterectomy (i.e., 39.1) (61). In addition, women who were pregnant (i.e., 62.8 (62)),

postpartum (i.e., 55.5 and 56.2 (25,62)), night shift workers (i.e., 60.5 (63)), or women

with HIV (i.e., 64.6 (26)) had higher mean sleep disturbance scores.

Of note, women who were younger, had lower performance status scores (i.e., KPS), higher comorbidity scores (i.e., SCQ), and reported hot flashes were more likely to have higher levels of ongoing sleep disturbance (High Sustained class). These associations are consistent with previous reports. For example, the association between age is consistent with previous studies found that younger oncology patients report higher levels of sleep disturbance (21,23), but inconsistent with one study of objective sleep in women who had completed CTX for breast cancer (64). In addition, previous studies with heterogeneous samples of cancer patients found that poorer functional status scores were associated with higher levels of sleep disturbance (23,65,66). Finally, the association between hot flashes and sleep disturbance are consistent with previous reports of breast cancer patients during (7) and after treatment (67).

An interesting finding in this study is that women who underwent a mastectomy and/or had reconstruction to the affected breast were more likely to be in the Decreasing class compared to the Low and the High Sustained classes. These findings suggest that the types of surgical procedure(s) have an influence on women's sleep patterns prior to and in the immediate postsurgical period. One possible explanation for this relationship is that this group of women were more concerned about the surgical interventions they are about to undergo. This hypothesis is supported by the finding that the Decreasing class reported significantly higher state anxiety scores than the Low GSDS class. In addition, based on an analysis of a single item from a Quality of Life inventory, women in the Decreasing class reported more difficulty coping with their disease and treatment (5.7 ± 2.9; $0 =$ not at all difficult to $10 =$ extremely difficult) than the Low class (2.3 ± 2.4) and High Sustained class (3.8 ± 2.7; both $p\leq0.006$). However, once the surgical procedure

is completed, sleep disturbance in this group of women resolves, unlike the women in the High Sustained class.

As would be expected, women with higher levels of sleep disturbance had problematic sleep disturbance parameters at baseline compared to women with lower levels of sleep disturbance. Women in the High Sustained class had significantly worse sleep quantity, quality, onset latency, mid sleep awakenings, early awakenings, and excessive daytime sleepiness, as well as used significantly more sleep medications than women in the Low class. These findings suggest that women in the High Sustained class had problems with sleep initiation, as well as maintenance. The reports of increases in sleep onset latency and mid sleep wakes are similar to findings reported by women undergoing CTX for breast cancer (10,11,13). In addition, women with very high levels of sleep disturbance prior to surgery that decreased throughout the study (i.e., Decreasing class) had worse sleep quality, quantity, onset latency, mid sleep wakes, early awakenings, excessive daytime sleepiness, and overall disturbance than women in the Low class. Interestingly, women with high preoperative levels of sleep disturbance that decreased over the next six months (i.e., Decreasing class) had worse baseline sleep onset latency than women in the High Sustained class. This finding suggests that in this cohort these women had a particularly difficult time with the initiation of sleep.

Women with high levels of sleep disturbance that presented for six months (i.e., High Sustained class) as well as those with high levels of sleep disturbance prior to surgery that decreased over time (i.e., Decreasing class), reported higher fatigue, less energy, more attentional fatigue, worse depressive symptoms, as well as higher levels of state and trait anxiety, than women in the Low class. Of note, the severity scores for the majority

of the associated symptoms were above the cutoff scores for clinically meaningful levels of depressive symptoms, anxiety, decreased levels of energy, and moderate levels of attentional fatigue. These findings are consistent with previous reports. For example, the positive relationship between physical fatigue and sleep disturbance was substantiated in prior studies of breast cancer patients before CTX (7,10,68-70) and RT (7). In addition, in a study of breast cancer patients at the initiation of RT, higher levels of attentional fatigue was associated with higher levels of sleep disturbance (71). The relationship between depressive symptoms and sleep disturbance is consistent with previous reports of breast cancer patients before (72), during (7,8) and after adjuvant treatment (8,73). Finally, in one of the few studies that evaluated anxiety and sleep disturbance in women prior to surgery for breast cancer (6) a positive association was found between these two symptoms. Findings from this study suggest that high levels of sleep disturbance co-occur with a number of symptoms in over 60% of women who are about to undergo surgical treatment for breast cancer. These women may represent a particularly vulnerable group of women who require interventions to deal with these symptoms before and following their initial treatment. Additional research is warranted to determine how these various symptoms co-occur across the treatment trajectory and whether sleep disturbance influences the trajectories of these other common symptoms over the course of the women's treatment for breast cancer.

This study has several limitations that should be acknowledged. Although a valid and reliable self-report measure was used to evaluate sleep disturbance, no objective evaluation was done to corroborate the self-reported sleep disturbance. Although this study had an ample sample size to obtain meaningful, reliable estimates of the predicted

classes (52,53), one of the distinct predicted classes (Decreasing class) was quite small (n=21). The small sample size of this class may have led to an under-estimation of the differences between the Decreasing class and the other two classes. However, significant differences were found for some of the variables between the Decreasing class and the other two classes. Of note, it is possible that the three distinct predicted classes found in this study may be a sign of some unique characteristics of this sample. Finally, caution should be used when interpreting these findings, until they are replicated in future studies.

Despite these limitations, findings from this study have implication for both clinical practice and research. Clinicians need to be aware that a relatively high percentage of women with sleep disturbance prior to surgery for breast cancer will continue to have sleep problems during subsequent treatments. In addition, women who will undergo a mastectomy, undergo reconstruction, are younger, and are experiencing hot flashes may represent a particularly high risk group of women who require a sleep intervention prior to surgery. Clinicians need to perform routine assessments of sleep disturbance prior to surgery.

Future research needs to attempt to replicate these predicted classes in other samples of breast cancer patients, as well as the demographic and clinical characteristics that distinguish among these predicted classes. In addition, research is warranted to determine the mechanisms that underlie these high levels of sleep disturbance. Finally, interventions should be developed and tested to alleviate sleep disturbance and its associated symptoms.

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Figure Legends

Figure 1. General Sleep Disturbance Scale (GSDS) trajectories for observed (actual) scores and estimated (predicted) scores for patients in each of the three predicted classes, as well as the mean GSDS scores for the total sample.

Figure 2. Differences in total and subscale scores on the General Sleep Disturbance Scale (GSDS), prior to surgery, among the three predicted classes. All values are plotted as means ± standard deviations. For the quality, quantity, mid sleep awakenings, early awakenings, and excessive daytime sleepiness subscales scores, as well as the total GSDS scores post hoc contrasts demonstrated that Low GSDS < Decreasing GSDS and High Sustained GSDS classes (all p≤0.001). For sleep medication subscale scores, post hoc contrasts demonstrated that Low GSDS class < High Sustained GSDS class (p<0.001). For sleep onset latency subscale scores, post hoc contrasts demonstrated that Low GSDS < High Sustained GSDS < Decreasing GSDS classes (both p≤0.005).

Figure 3A. Differences in physical fatigue, energy, and attentional fatigue scores, prior to surgery, among the three predicted classes. All values are plotted as means ± standard deviations. For physical fatigue, post hoc contrasts demonstrated that Low GSDS < decreasing GSDS and High Sustained GSDS classes (both p<0.007). For energy, post hoc contrasts demonstrated that Low GSDS > High Sustained GSDS class (p≤0.001). For attentional fatigue, post hoc contrasts demonstrated that Low GSDS > Decreasing and High Sustained GSDS classes (i.e., higher Attentional Function scores indicate lower levels of attentional fatigue, p≤0.002).

Figure 3B. Differences trait anxiety, state anxiety, and depressive symptoms, prior to surgery, among the three predicted classes. All values are plotted as means ± standard

118

deviations. For trait anxiety, post hoc contrasts demonstrated that Low GSDS < High

Sustained GSDS ($p<0.001$). For state anxiety and depression, post hoc contrasts

demonstrated that Low GSDS < Decreasing GSDS and High Sustained GSDS classes (all

$p<0.001$).

Table 1. Baseline Demographic and Clinical Characteristics of the Total Sample (n=398) and of the Three Latent Classesnnnnnnnnnn

Characteristic	Total Sample (n=398)	Low GSDS (1) n=158 (39.7%)	Decreasing GSDS (2) n=21 (5.3%)	High Sustained GSDS (3) n=219 (55.0%)	Omnibus Statistics and Post hoc Comparisons
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	54.9 (11.6)	57.7 (12.1)	53.8 (9.8)	53.0 (10.9)	$F_{(2, 395)}=7.95$; $p=0.0004$ 1>3
Education (years)	15.7 (2.7)	15.5 (2.6)	15.5 (2.1)	15.9 (2.7)	$F_{(2, 390)}=0.98$; $p=0.38$
KPS score	93.2 (10.3)	96.5 (6.8)	92.9 (10.1)	90.9 (11.7)	$F_{(2, 388)}=14.20$; $p\leq0.0001$ 1>3
SCQ score	4.3 (2.8)	3.7 (2.4)	3.9 (2.7)	4.8 (3.1)	$F_{(2, 394)}=7.11$; $p=0.001$ 3>1
Body mass index (kg/m^2)	26.8 (6.2)	26.5 (5.8)	24.5 (4.6)	27.2 (6.5)	$F_{(2, 389)}=2.15$; $p=0.12$
	n (%)	n (%)	n (%)	n (%)	
White	255 (64.1)	102 (65.0)	17 (81.0)	136 (62.4)	$\chi^2=2.92$; $p=0.23$
Married/partnered	165 (41.5)	62 (39.5)	11 (52.4)	92 (42.6)	$\chi^2=1.37$; $p=0.51$
Work for pay	189 (47.5)	86 (54.4)	10 (47.6)	93 (43.1)	$\chi^2=4.73$; $p=0.09$
Lives alone	95 (23.9)	37 (23.7)	8 (38.1)	50 (23.1)	$\chi^2=2.36$; $p=0.31$
Gone through menopause	248 (62.3)	104 (68.0)	14 (66.7)	130 (61.0)	$\chi^2=1.93$; $p=0.38$
Experiencing hot flashes	127 (31.9)	37 (23.4)	4 (19.0)	86 (39.3)	$\chi^2=12.30$; $p=0.002$ 3>1
Stage of disease					
0	73 (18.3)	25 (15.8)	8 (38.1)	40 (18.3)	$\chi^2=11.83$; $p=0.07$
I	151 (37.9)	72 (45.6)	5 (23.8)	74 (33.8)	
IIA, IIB	141 (35.4)	50 (31.6)	7 (33.3)	84 (38.4)	
IIIA, IIIB, IIIC, IV	33 (8.3)	11 (7.0)	1 (4.8)	21 (9.6)	
Surgical treatment					

Breast-conserving	318 (79.9)	131 (82.9)	10 (47.6)	χ^2=14.63; p=0.001 2>1,3
Mastectomy	80 (20.1)	27 (17.1)	11 (52.4)	
Sentinel node biopsy	328 (82.4)	138 (87.3)	16 (76.2)	χ^2=4.53; p=0.10
Axillary lymph node dissection	149 (37.4)	52 (32.9)	5 (23.8)	χ^2==5.15; p=0.08
Breast reconstruction at the time of surgery	86 (21.6)	30 (19.1)	11 (52.4)	χ^2=12.44; p=0.002 2>1,3
Neoadjuvant chemotherapy	79 (19.8)	27 (17.1)	4 (19.0)	χ^2=1.41; p=0.50
Adjuvant chemotherapy	133 (33.4)	43 (27.2)	4 (19.0)	χ^2=8.05; p<0.02 3>1
Adjuvant radiation therapy	224 (56.3)	99 (62.7)	8 (38.1)	χ^2=6.16; p<0.05

KPS- Karnofsky Performance Status
SCQ-Self-Administered Comorbidity Questionnaire

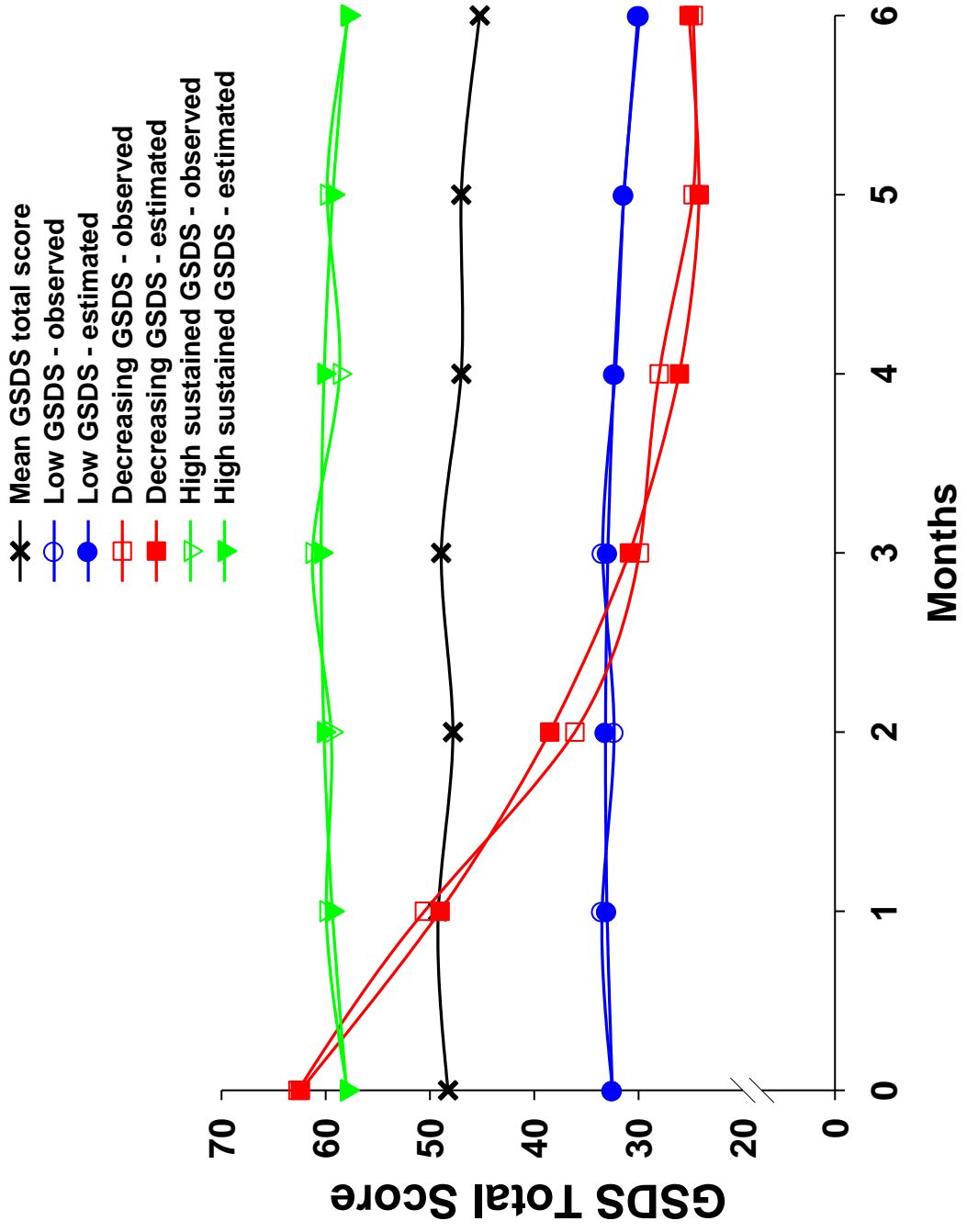Table 2: Fit Indices for the GMM Class Solutions for 398 Breast Cancer Patients

GMM Solution	LL	AIC	BIC	Entropy	BLRT (df)	VLMR (df)
1-Class[a]	-4522.03	9076.05	9139.84	N/A	N/A	N/A
2-Class	-4488.48	9018.95	9102.67	0.56	67.10** (5)	67.10 (5)
3-Class[b]	**-4473.49**	**8998.99**	**9102.63**	**0.71**	**29.97† (5)**	**29.97** (5)**
4-Class	-4471.97	9007.93	9135.50	0.56	5.63^{ns} (5)	5.63^{ns} (5)

^{ns} = not significant; * $p \geq .05$; ** $p \geq .01$; *** $p \geq .001$; **** $p \geq .0001$; † $p < .00005$

^{a} Latent growth curve model with linear and quadratic components; $Chi^2 = 43.72$, 19 df, $p < .001$, CFI = .99, RMSEA = .057.

Note that entropy, BLRT, & VLMR are not relevant for the latent growth model.

^{b} 3-class model was selected.

Abbreviations: GMM = Growth mixture model; LL = loglikelihood; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; BLRT = parametric bootstrapped likelihood ratio test for K-1 (H0) vs K classes; VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test for K-1 (H0) vs K classes.
Note that these models were estimated from GSDS scores that were linearly transformed into 10-point intervals (y / 10) to reduce the size of variance components and improve estimation.

Table 3. Parameter Estimates for Predicted Growth Mixture Model Latent Classes from 7 Assessments of the General Sleep Disturbance Scale (GSDS)[a]

| Parameter Estimates[b]	Low GSDS N = 158	Decreasing N = 21	High Sustained N = 219
	Means (S.E.)	Means (S.E.)	Means (S.E.)
Intercept	32.5 (3.6)	62.4 (4.2)	58.0 (2.7)
Linear Slope	0.70 (0.8)	-14.8 (2.2)	1.6 (0.7)
Quadratic Slope	-0.19 (0.1)	1.4 (.3)	-0.28 (0.1)
Variances[c]			
Intercept	104.4 (47.8)	28.9 (13.3)	318.4 (42.9)
Linear Slope	0[c]	0[c]	47.7 (18.4)
I with S Covariance	0[c]	0[c]	1.4 (0.5)

Abbreviations: S.E. = Standard Error
[a] Trajectory group sizes are for classification of individuals based on their most likely latent class probabilities.
[b] Growth mixture model estimates were obtained with robust maximum likelihood.
[c] Fixed at zero to aid in model convergence.

124
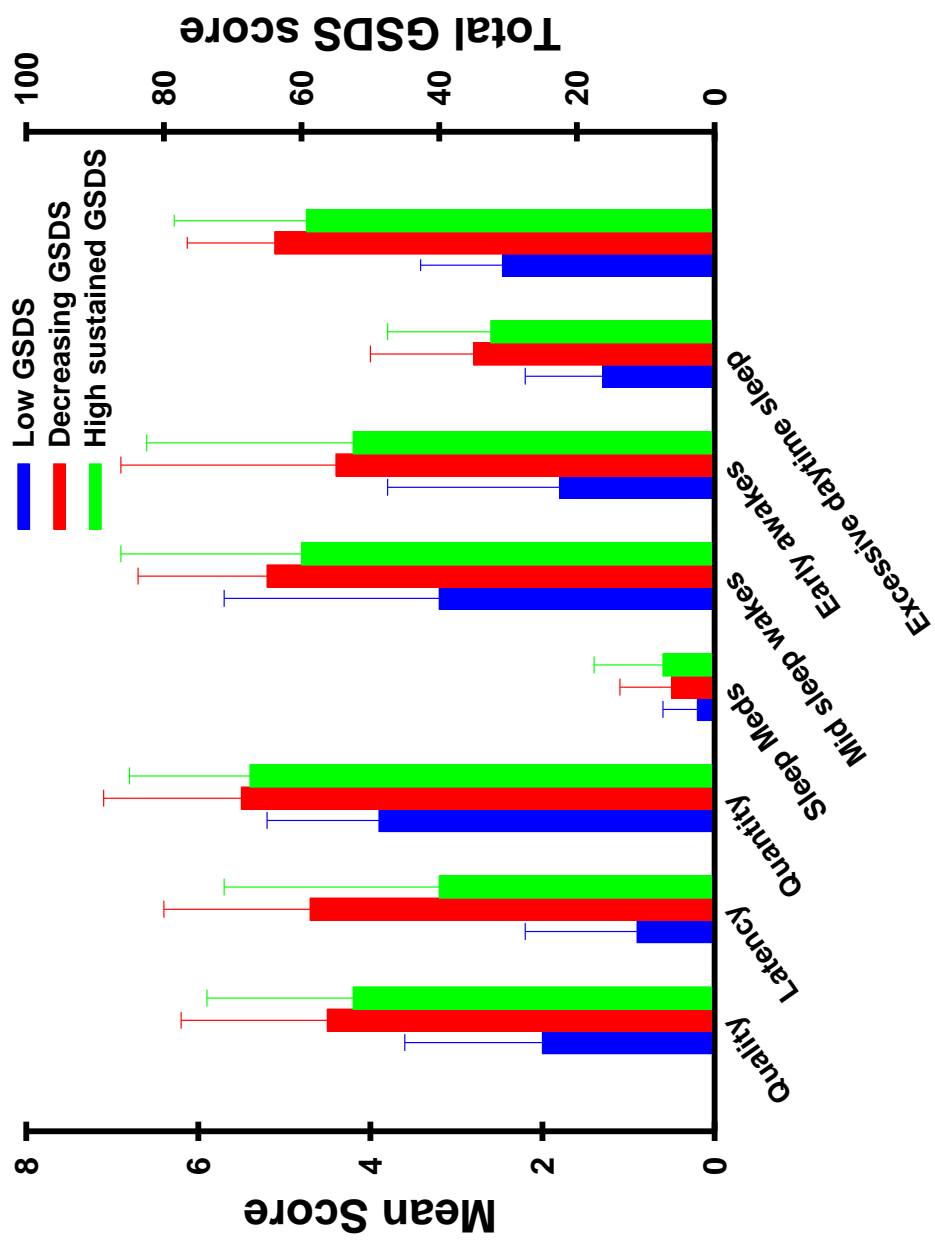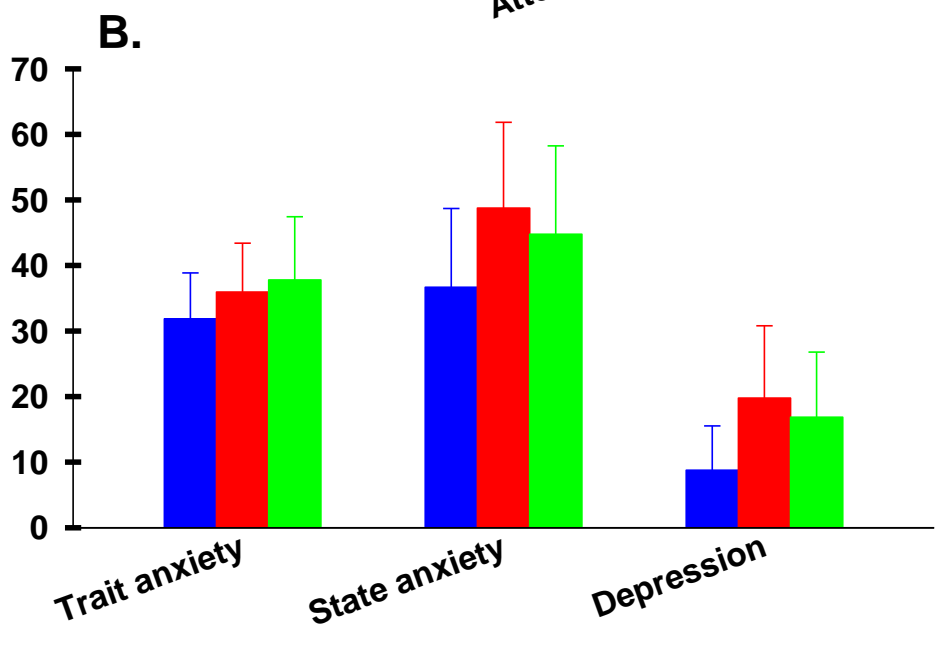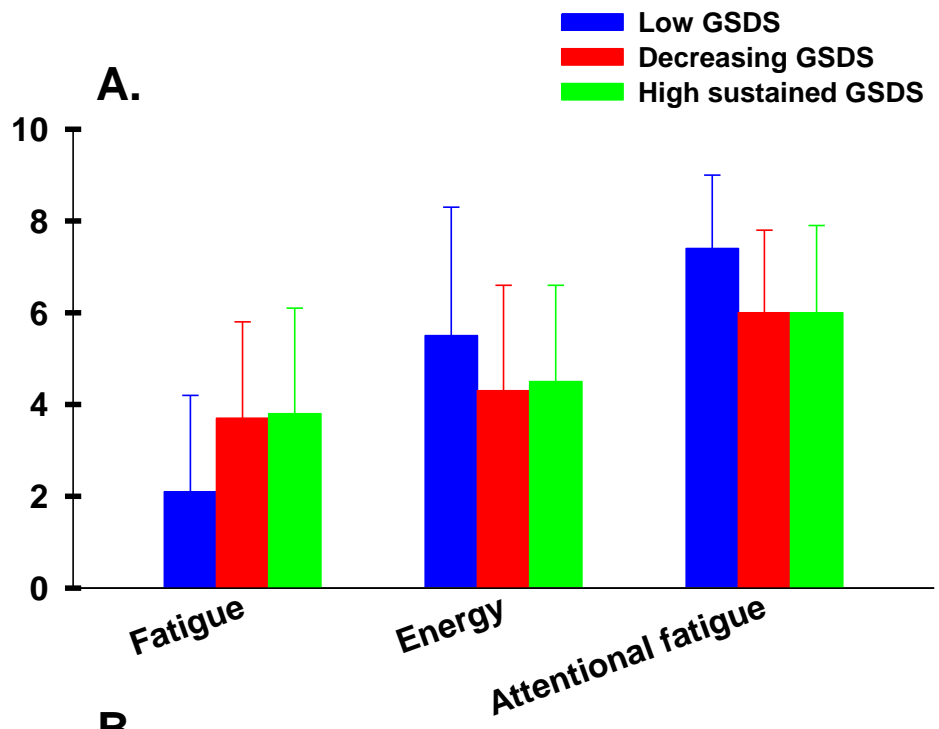
Conclusions and Implications for Clinical Practice and Research

The purpose of this dissertation research was to examine the relationships between sleep disturbance, fatigue, and breast pain in women prior to and after surgery for breast cancer. Although sleep disturbance was evaluated in patients undergoing adjuvant treatment for breast cancer (Berger & Farr, 1999; Berger & Higginbotham, 2000; Kim, Barsevick, Tulman, & McDermott, 2008; Payne, Piper, Rabinowitz, & Zimmerman, 2006; Savard, et al., 2009; Savard, Simard, Blanchet, Ivers, & Morin, 2001; Thomas, Bower, Hoyt, & Sepah, 2009), very little research has evaluated sleep disturbance prior to surgery and even less has evaluated sleep disturbance in the immediate postoperative period and for up to six months after surgery.

The results of this study demonstrate that sleep disturbance is a significant problem for a large percentage of women prior to surgery for breast cancer. In addition, fatigue, diminished energy, and breast pain are common symptoms in these patients prior to surgery for breast cancer. Hot flash severity, attentional fatigue, and physical fatigue were significantly associated with sleep disturbance prior to surgery for breast cancer. Depressive symptoms were associated with sleep disturbance prior to and after surgery for breast cancer. In addition, the severity of sleep disturbance remains at clinically meaningful levels for up to six months after surgery for breast cancer.

Implications for Clinical Practice

This study has several implications for clinical practice. Clinicians should be aware that sleep disturbance, fatigue, and decreased energy levels are common problems in women prior to surgery that need evaluation. Although sleep disturbance is often evaluated during adjuvant treatment for breast cancer, findings from this study suggest

127

that evaluation of sleep disturbance is necessary even before surgery. Clinicians should be aware that a relatively high percentage of women with sleep disturbance prior to surgery will continue to have sleep problems during adjuvant treatment for breast cancer. A higher index of suspicion for sleep disturbance is necessary for women who will undergo a mastectomy, reconstruction, and are younger. Clinicians should regularly assess performance status, the severity of hot flashes, depression, physical fatigue, and attentional fatigue in order to identify particularly high risk women that require evaluation and subsequent treatment for sleep disturbance. In addition, treatment of these associated symptoms may help to alleviate sleep disturbance.

Implications for Research

As this study is the first to evaluate for sleep disturbance prior to and for up to six months after surgery for breast cancer, the findings from this study warrant replication before definitive conclusions can be drawn. Of note, the subgroup of patients who had relatively low levels of sleep disturbance throughout the study was small and may have resulted in an underestimation of significant findings.

Future studies need to evaluate underlying mechanisms for sleep disturbance in these patients. Areas for further investigation could include genotypic evaluation, evaluation of the sleep-wake cycle using objective measures (i.e., actigraphy), and evaluation of sleep hygiene practices. In addition, longitudinal studies are needed that evaluate for sleep disturbance in these patients during subsequent treatments and into survivorship. These studies would provide information on whether or not sleep disturbance continues to worsen or improve. In addition, future studies of sleep disturbance should include the impact of demographic, clinical and symptom

characteristics such as depression, physical fatigue, attentional fatigue, severity of hot flashes, and performance status. Further studies are needed to determine if and how these symptoms influence sleep disturbance or if sleep disturbance influences these symptoms. Finally, future studies should examine interventions that can be initiated prior to surgery for breast cancer and continued during adjuvant treatment for breast cancer.

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