Factors Associated with Sleep Disturbances in Women Undergoing Treatment for Early-Stage Breast Cancer

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Abstract

Purpose

The purpose of this study was to examine factors associated with sleep disturbance in women receiving adjuvant therapy for breast cancer.

Methods

This study employed a cross-sectional design using data collected at 3-months post-surgery from an ongoing longitudinal parent study. Adjuvant treatment groups included chemotherapy, radiation, aromatase inhibitor, and no adjuvant treatment. Symptoms were measured using the patient self-report measures.

Results

The sample included 156 women diagnosed with early-stage breast cancer. There were significant differences in levels of reported sleep disturbance between treatment groups (p=0.049), with significantly higher levels of sleep disturbances in those receiving radiation compared to those receiving no adjuvant treatment (p=0.038) and in those receiving chemotherapy and those receiving no adjuvant treatment (p=0.027). Increased sleep disturbance was found to be a significant predictor for increased pain severity, nausea severity, anxiety, depressive symptoms, fatigue, decreased physical function, and decreased ability to participate in social roles and activities. Co-occurring symptoms with sleep disturbance differed between adjuvant treatment groups. Sleep disturbance was also associated with younger age (p=0.008).

Conclusions

Patients undergoing chemotherapy or radiation for breast cancer report higher levels of sleep disturbance than those not receiving adjuvant therapy. Sleep disturbance is associated with other symptoms experienced by patients with cancer and thus requires continual assessment and future research into effective interventions.

Background

Sleep disturbance is a common complaint among women undergoing treatment for early-stage breast cancer. More than 70 percent of patients with breast cancer undergoing chemotherapy report sleep disturbances [1], and over 85 percent of patients undergoing radiation for breast cancer have abnormally frequent nighttime awakenings [2]. Sleep disturbance can persist beyond the course of treatment, with a recent meta-analysis finding a pooled prevalence of 0.40 in breast cancer survivors [3].

Sleep disturbance has been identified as part of a symptom cluster with pain and fatigue, which emerges in women receiving chemotherapy for breast cancer and can continue after the cessation of treatment [4]. A symptom cluster has been defined as “three or more concurrent symptoms that are related to each

other but are not required to share the same etiology" [5]. The relationship between sleep disturbance and pain in patients with breast cancer appears to be complex and multidirectional, with decreased sleep quality prior to breast cancer surgery being associated with increased post-operative pain and increased analgesic requirements [6]. Prior to surgery, more women with presurgical breast pain reported clinically significant levels of sleep disturbance than those without presurgical breast pain [7]. Additionally, pretreatment sleep disturbance has been associated with increased pain in patients receiving radiation therapy for breast cancer [8]. The relationship between fatigue and sleep disturbance in patients with breast cancer may be multifaceted, with fatigue demonstrating significant association with subjective measures of poor sleep, but not with objective measures of sleep quality using actigraphy [9].

Associations have also been demonstrated between sleep disturbance and symptom burden in this patient population. In patients receiving chemotherapy, trait anxiety, depressive symptoms, decreased functional status, and evening fatigue have all been associated with higher levels of sleep disturbance [10]. In patients with gastrointestinal cancer, shorter sleep duration was significantly associated with fatigue, pain, anxiety, depression, and decreased quality of life [11]. Additionally, chemotherapy induced nausea and vomiting has been associated with poor sleep quality in patients with breast cancer [12]. Nausea is also a significant predictor of cancer-related fatigue, a relationship mediated by the effect of nausea on sleep disturbance [13]. Poor sleep quality has also been associated with lower functional status and decreased quality of life in individuals with a cancer diagnosis [14-15].

Suggested guidelines for the treatment in sleep disturbance in patients with cancer suggest treatment of risk factors such as pain, depression, and anxiety [16]. However, guidelines fail to clarify the best treatment methods for these risk factors in the context of sleep disturbance and cancer, highlighting the need for further understanding of these co-occurring symptoms. Furthermore, the treatment algorithm does not include nausea or poor functional status as risk factors to address in the treatment of sleep disturbance.

Chemotherapy treatment has been implicated in the development of sleep disturbance. One study found that breast cancer survivors reporting sleep duration changes were 2.64 times more likely to have received chemotherapy than survivors with no change in sleep duration [17]. Women who received chemotherapy for breast cancer also reported higher levels of sleep disturbance, fatigue, and depression than women who did not receive chemotherapy [18]. Studies of sleep-disturbance trajectories show that a subset of patients experience increasing sleep disturbance during chemotherapy treatment for breast cancer [1]. Additionally, many of the referenced studies investigating sleep disturbance and its relation to other symptoms were completed in patients receiving chemotherapy; literature examining sleep disturbance in the context of radiation therapy is comparatively sparse. In one study among men with prostate cancer, however, self-reported sleep disturbance was found to increase during radiation treatment [19].

Though there is limited information on the relationship between sleep disturbance and radiation therapy, particularly among patients with breast cancer, studies have shown that symptom clusters emerging at

the end of radiation treatment included decreased wellbeing, depression and anxiety; nausea and decreased appetite; drowsiness and dyspnea [20]. Previous studies suggest that sleep disturbance co-occurs with these symptoms, supporting the examination of sleep disturbance in the population of patients with breast cancer who are receiving radiation therapy. Aromatase inhibitor (AI) therapy for breast cancer has also been implicated in development of sleep disturbance, with insomnia complaints exceeding 50% in women taking an AI [21]. However, review of the literature revealed a lack of research investigating how sleep disturbance may differ among women receiving chemotherapy, radiation, AI therapy, or no adjuvant therapy.

Patient characteristics may also be associated with sleep disturbance in patients with cancer. Younger age has been associated with increased sleep disturbance [15, 22-24], although other studies have found no association between age and sleep disturbance in patients with breast cancer [1]. Additionally, a large (n=12,098) longitudinal study found that breast cancer diagnosis was not significantly related to decreased sleep quality compared to pre-diagnosis, although sleep quality continued to decrease over time [25]. This would indicate that study participants would report poorer sleep quality as they aged. Higher body mass index (BMI) has also been found to be associated with increased subjective and objective sleep disturbance [2,10].

The primary aim of this secondary analysis was to investigate differences in self-reported sleep disturbance between patients currently receiving chemotherapy, AI therapy, radiation, or no adjuvant treatment for breast cancer. We hypothesize that patients receiving radiation or chemotherapy at the time of analysis will report higher levels of sleep disturbance than those receiving no current adjuvant treatment. Our secondary aim was to investigate the association of sleep disturbance severity with the severity other self-reported symptoms, including pain, nausea, fatigue, anxiety, depressive symptoms and physical and social functioning in patients with early-stage breast cancer by adjuvant treatment modality. The tertiary aim of this study was to investigate the association of sleep disturbance with patient and cancer characteristics such as age and BMI. We hypothesize that increased reports of sleep disturbance will be associated with higher BMI and lower age.

Methods

Design

This study employed a cross-sectional design using data collected at three months after initial surgical treatment during a longitudinal parent study investigating treatment induced nausea and vomiting and its genetic underpinnings in women with early-stage breast cancer. Study participants were recruited in the preoperative holding area of a teaching hospital in western Pennsylvania by trained members of the research team between April 2018 and March 2020.

Inclusion and Exclusion Criteria

Participants were eligible for recruitment to the parent study if they were female; between the ages of 18 and 90 years; diagnosed with early-stage breast cancer; classified as stage I, II, or IIIa; and scheduled for breast cancer surgery. Exclusion criteria for the parent study included a history of neurologic conditions such as stroke, head injury, spinal cord injury, or intracerebral hemorrhage. A total of 156 participants are included in this analysis, as this represented all participants who had responded to the 3-month survey as of March 2020. Surveys collected after this were not included due to the potential confounding effects of the Covid-19 pandemic response on symptom burden in this population.

Data Collection

Qualtrics © 2020 software was used for all data collection and entry. Participants were recruited in the preoperative holding area following protocols approved by the University of Pittsburgh institutional review board. Data collected from the participant in the preoperative holding area included (1) age; (2) race; (3) smoking status; and (4) type of surgery. Age and BMI were obtained from participant's electronic medical record.

Participants were contacted after surgery on either a weekly or monthly basis either by telephone or email to respond to a survey administered by trained study staff. Patient reported outcomes at three months post-surgery were used in this study, as this time point represents the period in which participants were likely to be receiving their first course of adjuvant therapy.

Measures

Information on adjuvant treatment modality at the time of the survey was collected from the medical record. Participants receiving radiation or chemotherapy were classified as such being their primary adjuvant treatment. Participants receiving AI therapy not in conjunction with chemotherapy or radiation were placed in the AI group. Participants who had not begun adjuvant treatment yet or would not be receiving any adjuvant treatment were grouped into the no adjuvant treatment group.

Patient reported outcomes were used for symptom measurement in this analysis. Pain and nausea severity were each measured on an 11-point numerical rating scale (NRS), with "0" indicating no pain or nausea and "10" indicating the worst pain or nausea ever experienced. Co-occuring symptoms were assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS®-29 Profile v2.0). The PROMIS® is a National Institute of Health initiative to develop standardized items that measure feelings, function, and perceptions. PROMIS®-29 includes brief, valid assessments for sleep disturbance, anxiety, depressive symptoms, fatigue, and pain interference as well as functional status and ability to participate in social roles and activities [26]. Norm based T-scores have been developed, with a score of 50 representing the mean of the general population. T-scores for symptoms were calculated from participant responses to the PROMIS® subscales according to validated protocols for the PROMIS® reporting tool. For sleep disturbance, anxiety, depressive symptoms, fatigue, and pain interference, a score above 50 indicates a worse outcome as compared to the general population. A score

below 50 indicates a worse outcome for functional status and ability to participate in social roles and activities [27].

Statistical Analysis

Data were analyzed using IBM® SPSS® Statistics for Windows (version 25, IBM Corp., Armonk, NY). An alpha level of 0.05 was used for all statistical tests. Comparative procedures were used to compare patient demographics across treatment groups. There were no outliers in sleep disturbance T-score by adjuvant treatment group as assessed by boxplot, with an outlier being defined as falling greater than 3 box lengths from the edge of the box in the boxplot. The histogram of studentized residuals from a univariate analysis of variance of sleep disturbance t-score by treatment group indicated approximate normality. The assumption in homogeneity of variance in sleep disturbance T-scores by adjuvant treatment group was met, as assessed by Levene's test (p=0.41). Levene's test showed homogeneity of variance in age (p=0.16) and BMI (p=0.28) among treatment groups, and there were no significant differences in age (p=0.13) or BMI (p=0.67) among treatment groups. Fischer's exact test showed no significant differences in race by treatment group (p=0.39).

Analysis of variance (ANOVA) was used to determine differences in mean sleep disturbance T-scores between the radiation, chemotherapy, AI, and no adjuvant treatment groups. A post-hoc multiple comparison procedure using Dunnett's t-test was used to compare sleep disturbance between each treatment group and the no adjuvant treatment group.

Linear regression was performed to assess the effect of sleep disturbance on the other reported symptoms within each adjuvant treatment group. Visual inspection of a histogram showed normality of the residuals for each symptom T-score pairing. The Pearson's correlation coefficient was also calculated to determine the relationship between BMI, age, and sleep disturbance T-score.

Results

Demographic and Clinical Characteristics

The sample for this study included 156 participants who completed the three months assessment following surgery for early-stage breast cancer. The average age of participants was 59.10 years, with an average BMI of 29.56 kg/m^2. A description of participant demographic and clinical characteristics by adjuvant treatment group can be found in Table I.

Table I: Sample Characteristics for 156 Women with Early-Stage Breast Cancer

Characteristic	*No adjuvant treatment*	*Chemotherapy*	*Radiation*	*Aromatase Inhibitor*	*Test Statistic*	
n (%)	59 (37.8)	24 (15.4)	47 (30.1)	26 (16.7)		
Sociodemographic characteristics, mean (SD)					***F***	***p***
Age (years)	58.51 (13.70)	56.67 (12.26)	57.48 (11.60)	63.60 (9.42)	1.89	0.13
BMI (kg/m^2)	28.83 (6.98)	29.51 (5.68)	29.56 (9.47)	30.45 (7.36)	0.52	0.67
Race, n (column %)					***p***	
Caucasian	49 (84.5)	19 (79.2)	44 (95.7)	23 (88.5)	0.39	
African American	9 (15.5)	3 (12.5)	1 (2.2)	3 (11.5)		
Asian	0 (0)	2 (8.3)	1 (2.2)	0 (0)		

Sleep Disturbance Across Treatments

Mean sleep disturbance T-scores for each treatment group can be found in Table II. At three months post-surgery, there was a significant difference in mean sleep disturbance T-scores among treatment groups (p=0.049). Specifically, there were significant differences in mean sleep disturbance T-scores between the chemotherapy group and no adjuvant treatment groups (p=0.027) and the radiation group and no adjuvant treatment group (p=0.038). No significant difference was observed between the AI group and the no adjuvant treatment group (p=0.147).

Table II: Sleep Disturbance Across Treatments

Mean T-score by Treatment	n	Mean T-score	Standard Deviation	95% Confidence Intervals
Chemotherapy	24	50.39	9.15	46.52-51.89
Radiation	47	49.21	9.13	46.53-54.24
Aromatase Inhibitor	26	48.72	7.34	45.68-51.75
No adjuvant treatment	59	45.50	8.21	43.36-47.64
Total sample	156	47.90	8.66	46.53-49.28

Association between Sleep Disturbance and Other Symptoms

In the group with no adjuvant treatment, linear regression established that sleep disturbance was significantly associated with (β=0.358, p=0.005) as well as nausea severity (β=0.348, p=0.007). Sleep

disturbance was also significantly associated with pain interference (β=0.403, p=0.002) and fatigue (β=0.484, p<0.001)

In the radiation group, linear regression established that sleep disturbance was significantly associated with anxiety (β=0.508, p<0.001), depressive symptoms (β=0.422, p=0.003), fatigue (β=0.444, p=0.002), pain interference (β=0.548, p<0.001), as well as pain severity (β=0.524, p<0.001), and nausea severity (β=0.405, p=0.005). Sleep disturbance was also a significant negatively associated with physical function (β=-0.497, p<0.001), and ability to participate in social roles and activities (β=-0.533, p<0.001).

In the chemotherapy group, linear regression established that sleep disturbance was significantly associated with anxiety (β=0.608, p=0.002) and depressive symptoms (β=0.630, p=0.001). Ability to participate in social roles and activities (β=-0.492, p=0.015) was significantly negatively associated with sleep disturbance in this group.

In the AI group, sleep disturbance was associated with fatigue (β=0.575, p=0.003). Sleep disturbance was not associated with any other symptoms in this group.

Sleep Disturbance with Participant Demographics

An assessment of the total sample, age was significantly negatively correlated with sleep disturbance (r=-0.204, p=0.008). No significant association was found between sleep disturbance and BMI.

Discussion

Consistent with prior research, our findings supported the hypothesis that patients with breast cancer undergoing chemotherapy report higher levels of sleep disturbance than those not undergoing treatment. We also concluded that patients with breast cancer undergoing radiation report higher levels of sleep disturbance than those not undergoing treatment, although the level of subjective sleep disturbance is similar between those undergoing chemotherapy and radiation. While a prior study found that insomnia was more likely to be discussed with patients at appointments with a transplant team or medical oncologists, when compared to other provider teams [28], this finding highlights the need for all providers, including radiation oncologists, to assess sleep disturbance in their patients, as it may be associated with a variety of treatments.

Other studies have suggested that sleep disturbance may occur in a symptom cluster along with fatigue and pain [4], as well as in conjunction with a variety of other symptoms including the severity of depressive symptoms, anxiety, and nausea, and decreased quality of life [10-13]. For women receiving radiation, sleep disturbance was associated with pain, pain interference, nausea, anxiety, depressive symptoms, fatigue, decreased physical function and decreased ability to participate in social roles, indicating a central role for sleep disturbance in symptom burden for this population. The large number of co-occurring symptoms for the women in the radiation group highlights the need for overall symptom control.

In the women undergoing adjuvant chemotherapy, sleep disturbance was only associated with higher levels of anxiety and depressive symptoms as well as lower ability to participate in social roles. This indicates the possibility for a different underlying mechanism of sleep disturbance in women receiving chemotherapy, and the potential need to focus on the impact of psychological and social factors associated with chemotherapy treatment as they affect symptom development.

In women undergoing AI therapy, sleep disturbance was only associated with fatigue. Given that AI therapy is associated with menopausal symptoms such as hot flashes [29], it is possible that co-occurring symptoms in this group were not captured by this study. In participants receiving no adjuvant therapy, sleep disturbance was associated with pain, pain interference, nausea, fatigue.

The difference in symptoms co-occurring with sleep disturbance among treatment groups suggests that etiology of sleep disturbance may differ across treatment groups, and interventions for sleep disturbance may need to be tailored to both treatment modality and associated symptoms.

These associations between sleep disturbance and other symptoms including pain, nausea, depression, anxiety, decreased physical function and difficulty participating in social roles and activities, especially in the radiation group, suggest the need for investigation regarding how symptom burden may be treated in a holistic manner. While some research indicates that there is no clear evidence that treatment of one facet in the fatigue-depression-sleep disturbance symptom cluster is effective in mitigating other symptoms [30], other research suggests that therapy intended to relieve a single symptom, such as anxiety or depression, may be useful in relieving sleep disturbance [31]. However, recent clinical practice guidelines on the use of integrative relief for symptom burden in cancer using review of recent literature lists yoga as the only integrative therapy recommended for sleep disturbance [32]. The results of our analysis linking sleep disturbance to other symptoms suggests that the treatment of sleep disturbance may be a step towards a holistic approach to relieving symptom burden.

Our analysis supported the finding that sleep disturbance in patients with breast cancer is associated with younger age. However, in contrast to former literature, no association was found between BMI and reported sleep disturbance.

A limitation of this study was the relatively low number of minorities included in the analysis. Given the evidence on disparities in treatment for sleep disturbance in this population, care should be taken to describe the symptom experiences of minorities going forward.

Another limitation of this study was the lack of objective sleep data. Prior research using both objective and subjective sleep data in this population has found discrepancies in the two sources of sleep data [33-34], with one study finding no differences in electroencephalogram parameters between breast cancer patients who reported insomnia and those who did not [35]. Given the discrepancies between objective and subjective data on sleep disturbance in this population, caution must be used when applying the results of this analysis to objective sleep quality. The focus of the results of this study is on the patient reported outcomes regarding sleep disturbance symptoms.

Given the cross-sectional design of this analysis, future research should measure changes in sleep disturbance over time in this population, and how it may be confounded by treatment factors. Investigation into how sleep disturbance may change over the course of treatment in this population would be informative given recent research suggesting that patients with relatively low or high sleep disturbance severity before chemotherapy treatment tend to remain in the same severity group at the end of treatment [36].

Patients undergoing breast cancer treatment should be thoroughly evaluated for sleep disturbance. The association of sleep disturbance with other symptoms, including pain, nausea, anxiety, depression, decreased physical function, and difficulty participating in social roles, indicates sleep disturbance's role as an integral player in the symptom burden associated with breast cancer diagnosis. Treatment of sleep disturbance should be considered as a method to alleviate symptom burden in this population.

Declarations

Funding

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Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

All primary data are housed at the University of Pittsburgh School of Nursing and are available on request.

Code Availability

Data were analyzed using IBM® SPSS® Statistics for Windows (version 25, IBM Corp., Armonk, NY).

Authors' Contributions

N/A

Ethics Approval

The methodology for this study was approved by the Human Research Protection Office of the University of Pittsburgh (The University of Pittsburgh IRB, Protocol number 19030259).

Consent to Participate

Participants were recruited following protocols approved by the University of Pittsburgh institutional review board.

Consent for Publication

N/A

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