Sleep Disruption in Breast Cancer Patients and Survivors

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Abstract
Sleep disruption is prevalent in patients and survivors of breast cancer. Most patients undergoing chemotherapy will experience transient sleep disruption, and nearly 60% will have chronic sleep problems. Numerous factors contribute to sleep disruption in women diagnosed with breast cancer. Sleep disruption is a consequence of several biological alterations, including circadian disruption and immune and metabolic deregulations. These systems also play significant roles in the control and progression of breast cancer. Sleep disruption is associated with many side effects and psychiatric and medical comorbidities. This article discusses the relationship between stress and posttraumatic stress disorder, depression and fatigue, and how sleep disturbance might be the cause or consequence of these disorders. Current evidence for management of sleep disturbance in breast cancer and high chronic use of hypnotic medication in this population is also discussed. Finally, the differences in management of sleep disturbance during acute cancer care and during the survivorship phase are discussed. More research is needed on accurate and timely assessment of sleep disturbance associated with breast cancer, and additional tailored approaches for the management of sleep problems in breast cancer should be developed. (JNCCN 2013;11:1523–1530)

Women diagnosed with breast cancer experience a high prevalence of sleep disruption during treatment and survivorship. Sleep disruption encompasses a wide range of sleep disorders (e.g., insomnia, restless legs syndrome, sleep apnea) in patients with breast cancer. Although numerous sleep disorders occur in women with breast cancer, insomnia is one of the most prevalent. Insomnia involves difficulty falling asleep or staying asleep, waking up earlier than intended, or having unrestored sleep. For clinical diagnosis, these difficulties are typically associated with daytime impairment, such as fatigue or excessive sleepiness at least 3 times a week for 30 minutes or more for at least 1 month. Nearly 80% of women undergoing chemotherapy for breast cancer will experience insomnia symptoms, and approximately half of those patients will meet full clinical criteria for insomnia.1 Before surgery, 69% of women with nonmetastatic breast cancer reported having insomnia symptoms, and although these rates declined over time, 42% of women were still experiencing insomnia symptoms at 18 months after surgery.2 In studies of women with metastatic breast cancer, 63% have reported experiencing insomnia symptoms.3,4 Insomnia also occurs in patients undergoing radiation treatment, but at lower rates than in those undergoing chemotherapy.

This article focuses on insomnia, and uses the terms sleep disruption and insomnia interchangeably as they are used in the literature. The responsible mechanisms of sleep disruption associated with breast cancer are addressed, in addition to treatment-related and behavioral factors implicated in the development of sleep disturbance. Finally, this article discusses sleep disturbance and its associated side effects in breast cancer, followed by evidence-based interventions that improve sleep among individuals with breast cancer.

Circadian Regulation of Sleep
Circadian and sleep-wake cycles are closely linked. Circadian disruption arises in patients with cancer secondary to the disease itself and its treatment, or the psychological response to the disease. Sleep disruption can be either the consequence or the cause of circadian dysregulation in people diagnosed with cancer. The
disturbance of the biological clock in those diagnosed with cancer is evidenced by the alteration of the circadian rest-activity rhythm and the sleep-wake cycle, and by the flattening of the rhythmic secretion of cortisol. Circadian disruption in cancer has been unrecognized and overlooked until recently; however, patients with breast cancer experiencing disturbed rhythms have shorter overall survival than others with robust rhythms. Recent studies have also found that the uncoupling of the circadian and sleep-wake systems results in a higher incidence of pathologies, such as accelerated aging, metabolic syndrome, and affective and cognitive impairments, and also a higher incidence of cancer.

Immunity, Metabolic Regulation, and Sleep

Strong preclinical and clinical evidence exists for the role of inflammatory processes in the development of behavioral symptoms, including sleep disruption and fatigue. Proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF-α), are immune mediators released by activated immune cells in response to pathogen invasion, tissue damage/injury, and cytotoxic factors, including chemotherapeutic agents. These soluble mediators are responsible for a large set of behavioral changes, referred to as sickness behavior. Fatigue and sleep problems represent key features of these cytokine-induced behavioral alterations. Cancer drugs can enhance proinflammatory cytokine release from healthy and/or malignant cells, and high levels of serum cytokines (TNF-α, IL-1, and IL-6) have been associated with chemotherapy-induced fatigue. Cytokines may also influence sleep-regulatory functions, and thus increased levels of cytokines could be partially responsible for the high prevalence of sleep disturbances in patients with cancer. Alternatively, sleep disruption or reduced sleep activates inflammatory pathways and proinflammatory cytokine release. This bidirectional interaction of inflammation and altered sleep may promote the development of chronic sleep disorders and subsequent psychological symptoms in patients with and survivors of cancer.

Sleep plays an important role in metabolic regulation, and sleep disruption has been linked with weight gain. Overweight is associated with a chronic low-grade inflammatory state characterized by increased levels of inflammatory markers, including C-reactive protein and proinflammatory cytokines. Moreover, obesity is prevalent among women with breast cancer and has been associated with an increased prevalence of sleep problems, including daytime sleepiness and sleep apnea. Obesity is associated with a greater risk of experiencing fatigue, which may lead to sleep-related alterations, such as daytime napping, in patients and survivors of breast cancer.

Behavioral Factors Associated With Sleep Disturbance

The development of sleep disturbance in patients with breast cancer can be understood by using a well-known behavioral model of sleep disturbance, which was originally proposed by Spielman et al and later refined by Morin. The model formed the foundation for the cognitive behavioral treatment of insomnia in the general population, and more recently for patients and survivors of cancer. In women with breast cancer, sleep disturbance might occur as a result of having a predisposition for sleep disturbance. Factors that can predispose someone to sleep disturbance include female sex, trait anxiety, and a family history of sleep problems. When women are diagnosed with breast cancer, sleep disturbance might occur as a result of having a predisposition for sleep disturbance. Factors that can predispose someone to sleep disturbance include female sex, trait anxiety, and a family history of sleep problems. When women are diagnosed with breast cancer, they experience a myriad of precipitating factors for sleep disturbance. These factors may involve the stress related to the diagnosis of breast cancer, cancer treatments and the associated side effects, and psychiatric and physical factors, such as anxiety, depression, pain, and frequent urination. Patients might respond to their sleep disturbance by spending more time in bed to compensate for lost sleep, shifting their sleep phase by either delaying sleep or wake time, and taking naps. These behaviors, although initially adaptive for acute short-term illness, are maladaptive for patients who have chronic illness and chronic sleep disruption. These maladaptive behaviors are called perpetuating factors because they can maintain sleep disturbance long after the cancer treatment is completed.

Factors Contributing to Sleep Disruption

Age

Although the data available in the cancer literature with regard to sleep and aging are limited, evidence
suggests that sleep disturbances are associated with breast cancer treatment type (eg, endocrine therapy), menopausal status, and older age. Other studies found that younger age was associated with significant sleep disturbance. Overall, the findings are mixed with regard to aging and sleep disturbance among women with breast cancer. However, mounting evidence shows that younger patients might have higher rates and potentially more serious forms of sleep disturbance, possibly because of the greater severity of the breast cancer in younger women, greater psychosocial burden, and potentially reduced opportunity for sleep regulation because of employment and childcare. However, more research is needed to fully elucidate the relationship between sleep and age in patients and survivors diagnosed with breast cancer.

Cancer Treatments

Lorizio et al reported that women with higher levels of endoxifen, the most active metabolite of tamoxifen, were more likely to experience sleep disruption. In addition, 64% of women who were taking tamoxifen also experienced hot flashes, which may independently contribute to disturbed sleep. Recently, Savard and Ivers reported that both chemotherapy and hormonal treatment were associated with increased sleep disruption and that the relationship between chemotherapy and disrupted sleep was mediated by the presence of nausea, hot flashes, and pain. Interestingly, radiation treatment did not lead to increased sleep disturbance in their study. Synthetic glucocorticoids used in supportive care may disrupt circadian rhythm. Newer agents, such as single- or multi-target tyrosine kinase inhibitors, can also affect sleep. Stress and Posttraumatic Stress Disorder

Being diagnosed with breast cancer results in a series of stressors, including the possibility of foreshortened future, invasive testing, anticipated and unanticipated side effects, financial burdens, and fear of cancer recurrence. Psychological stress can have a significant impact on sleep and is a precipitating factor for the development of insomnia. Recent research suggests that a significant minority of women diagnosed with breast cancer experience persistent posttraumatic stress disorder (PTSD), with African American, Asian, and younger women disproportionally and negatively affected. A strong link also seems to exist between the experience of perceived discrimination or unfair treatment and both subjective and objective sleep disturbance. One study showed that racial minority breast cancer survivors were at higher risk for sleep-wake disturbances. However, the effects of unfair treatment and discrimination are universally related to sleep disruption, regardless of racial/ethnic differences. A paucity of research exists investigating these mechanisms in patients and survivors of breast cancer.

Depression and Fatigue

Sleep disturbance in breast cancer is often related to psychological sequelae that include depression and fatigue. With more than 20% to 30% of women with breast cancer reporting depression, and depression worsening with more-advanced breast cancer, the combination of cancer and depression acts synergistically to hamper sleep. For example, one study showed that worsening depression predicted progressive sleep problems.

In addition, several studies have shown a significant relationship between fatigue and sleep disturbance in women with breast cancer. In a large study of patients with cancer (N=823), those with insomnia had significantly more fatigue and depression than those who reported some or no sleep disturbance. Research investigating these relationships in patients with breast cancer prior to adjuvant treatment suggests that poor sleep is associated with worse functional well-being and increased fatigue. In contrast, greater physical and psychological well-being has been linked with better sleep quality among patients with cancer. These findings show that sleep disturbance negatively impacts a constellation of psychological and physical health indices. Furthermore, targeting interventions to improve sleep among women with breast cancer may reduce the impact of depression or fatigue. Further clarifying these mechanisms and identifying temporal precedence of sleep disturbance, depression, or fatigue in breast cancer will better inform providers as to where to intervene.

Sleep Architecture

Relatively few studies have used polysomnography (PSG; a gold standard for diagnosing sleep disorders) to measure objective sleep disturbance among women with breast cancer. Of those studies that used PSG,
dysregulation of sleep architecture in patients with cancer was evidenced by lower sleep efficiency, more time in lighter sleep, and less time in deep or slow-wave sleep, and less rapid eye movement sleep than experienced by the general population. However, one small study found little change in PSG-assessed sleep before and after completion of chemotherapy. Although the evidence is mixed, these studies suggest that either breast cancer and/or treatment might have an adverse objectively measurable effect on sleep architecture. Although some evidence shows that survival and objective sleep disturbance are related in advanced breast cancer, further research is needed to determine their mutual interaction.

Management of Sleep Disturbance

Psychological
Several evidence-based interventions are recommended by the American Academy of Sleep Science, including stimulus control therapy, sleep restriction therapy, and relaxation. Cognitive behavioral therapy for insomnia (CBT-I) is based on the behavioral sleep model proposed by Spielman et al and encompasses the components mentioned. CBT-I is an evidence-based treatment for managing insomnia in the general population. CBT-I typically consists of 4 to 7 individual sessions led by a licensed clinical psychologist who has additional training and certification in behavioral sleep medicine. Modified CBT-I has been successfully used with breast cancer survivors and has resulted in improvements in sleep, with these improvements occasionally sustained at 12-month follow-up. Although research suggests that patients undergoing chemotherapy have more sleep problems than those receiving other treatments or survivors, the authors identified only 2 randomized controlled trials using behavioral interventions to treat patients undergoing chemotherapy. The first trial used a nonspecific sleep intervention and found no effect on sleep problems. The second trial in patients undergoing chemotherapy showed that those who participated in the behavioral treatment had significantly better sleep quality than controls. Overall, these findings suggest that patients with breast cancer may derive significant benefit from interventions targeting sleep disruption throughout the cancer treatment and recovery process.

Pharmacologic
Lorazepam (31.4%) and zolpidem (29.4%) are commonly prescribed for management of sleep disturbance in patients with breast cancer undergoing neoadjuvant and adjuvant chemotherapy. Patients with and survivors of breast cancer seem to use the sleep medication for prolonged periods. A recent large study of 1984 patients with cancer found that 22.6% were taking hypnotic medication for sleep problems, and half of those were taking medication every night for periods longer than 6 months. The chronic use of sleep medication has limited value for long-term treatment, and poses risks of habituation. The effects of using sleep aid medications during cancer treatment are unknown, but their use can lead to potentially harmful pharmacologic interactions. However, no randomized controlled trial to date has evaluated the efficacy or safety of hypnotics in patients with cancer undergoing chemotherapy. Only one randomized controlled trial examined their effect on women diagnosed with breast cancer scheduled to undergo surgery. Although this was a randomized controlled trial, the medication was used only for 3 nights and showed no adverse events.

Exercise
Physical activity may play a significant role in promoting sleep quality, circadian synchronization, and immune function in patients with breast cancer. Increased daytime activity among these individuals has been linked to improved sleep. In general, results of physical activity interventions for adults have shown that physical activity and moderate-intensity exercise are linked to improved rest-activity cycle, better sleep efficiency, fewer nighttime awakenings, reduced sleep-onset latency, increased sleep duration, and improved sleep quality. Proposed mechanisms suggest that exercise might improve sleep through synchronizing rest and activity rhythms, and that increasing exposure to bright light during the day may also promote sleep and related neuroendocrine functioning.
Studies that have examined the relationship of exercise as it relates to sleep are small, especially in cancer populations.72,73 Furthermore, limited investigations relating physical activity and sleep quality, both subjective and objective, have been conducted in women with breast cancer.47,72 Thus, the authors suggest that this is a ripe area for developing interventions aimed at not only increasing physical activity but also examining the underlying mechanisms that improve daytime activity rhythms.

Complementary and Alternative Interventions
Complementary and alternative interventions also have been successfully used to manage sleep problems in patients with breast cancer. Chronoenhancement therapies, such as controlled bright light exposure, targeting the resynchronization of the biological clock of patients with breast cancer have shown a positive effect on fatigue and sleep74 and on the normalization of the rest-activity pattern.75 A structured yoga program, the Yoga for Cancer Survivors (YOCAS), also has been shown to help normalize sleep, reduce medication use, and normalize circadian rhythms in cancer survivors.76,77

NCCN Clinical Practice Guidelines in Oncology
NCCN issued guidelines for screening and treatment of sleep disorders as part of the guidelines for survivorship care (to view the most recent version of these guidelines, visit NCCN.org). These guidelines highlight the importance of screening, diagnosing, and treating sleep disturbance in cancer survivors. However, the authors would like to propose the importance of matching the management of sleep disturbance to cancer-specific care (eg, surgery, chemotherapy, radiation). For example, individualized interventions for sleep disturbance, such as brief behavioral interventions or skill-building, are warranted during chemotherapy or radiation treatment. Sleep aids are typically indicated for treatment of acute versus chronic sleep disturbance, and thus medication for acute sleep disturbance during chemotherapy and radiotherapy can be very helpful to patients. In the survivorship phase, more intensive, comprehensive, and longer cognitive behavioral interventions are warranted, which could lead to amelioration of sleep disturbance.

Conclusions
Sleep disturbance is prevalent in patients with and survivors of breast cancer, and is associated with reduced quality of life and possibly shorter survival. Several mechanisms underlie sleep disturbance in breast cancer, such as the stress related to the diagnosis of cancer and its treatments, preexisting medical and psychiatric conditions, and the impact of tumor on the overall biology and regulation of sleep, which is not yet fully known. Emerging evidence also suggests that multiple biological pathways involved in sleep disturbance during cancer might accelerate breast cancer progression.7,11,35,55 The present article shows that the use of hypnotic medication for sleep is prevalent and persistent among patients with breast cancer, which raises concern, given that long-term use of hypnotics (>4 weeks) is not recommended and not well studied in breast cancer. Patients and survivors of breast cancer who participate in CBT-I or other evidence-based interventions benefit from them, although conducting behavioral interventions during acute care such as chemotherapy is clearly challenging, but not impossible. In addition, exercise interventions are showing promise for the treatment of sleep problems, although whether the interventions are potent enough to treat chronic sleep conditions is unclear.

Future Directions
More research is needed to understand the cause of sleep problems in patients and survivors of cancer in order to develop better interventions. More accurate assessments of sleep disturbance are needed, such as the new integrated variable called TAP (wrist Temperature, motor Activity, and body Position).79 This variable was validated for the proper assessment of circadian system status and is able to reliably evaluate the sleep-wake rhythm compared with sleep logs under ambulatory conditions.79 The individual assessment of circadian system status before chemotherapy administration could be a valuable tool for screening of patients with disrupted rhythms. Thus, resynchronization therapies, such as controlled bright light exposure and behavioral or pharmacologic therapies, could be applied to reduce sleep disruption. Understanding causes of sleep disruption and the establishment of efficacious therapeutic modalities are clearly burgeoning areas in breast cancer research.
References


