Original Article

A Longitudinal Study of Depression, Fatigue, and Sleep Disturbances as a Symptom Cluster in Women With Breast Cancer

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Abstract

Context. Depression, fatigue, and sleep disturbances have been identified as a symptom cluster among breast cancer patients. However, few longitudinal studies have examined the temporal relations between these symptoms surrounding diagnosis and treatment.

Objectives. The present study investigated the co-occurrence of and interrelations between nonsomatic depressive symptoms, fatigue, and sleep disturbances in breast cancer patients at three time points: before, after, and six to eight months following adjuvant chemotherapy treatment.

Methods. Separate samples of premenopausal ($n = 67$) and postmenopausal ($n = 67$) breast cancer patients completed self-report measures of depression, fatigue, and sleep disturbances at all three time points. Path analysis was used to explore within- and cross-symptom paths across time.

Results. Depression, fatigue, and sleep disturbances were correlated within each time point. Continuity paths, whereby prior levels of symptom severity tended to predict subsequent severity of the same symptom at the subsequent time point, were significant in both samples, except for depression in the premenopausal sample. Instead, significant cross-symptom paths emerged whereby baseline fatigue predicted postchemotherapy depression, and postchemotherapy fatigue predicted depression at follow-up in the premenopausal patients. No significant cross-symptom paths emerged for the postmenopausal sample.

Conclusion. Findings supported the notion that depression, fatigue, and sleep disturbances manifest as a symptom cluster. Fatigue may precede nonsomatic symptoms of depression among premenopausal breast cancer patients and represents a potential intervention target. J Pain Symptom Manage 2015;49:707–715. © *2015 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words
Cancer, oncology, fatigue, depression, sleep disturbance, symptom cluster

Introduction

Receiving a breast cancer diagnosis and undergoing cancer treatment are commonly associated with depression, fatigue, and sleep disturbances.[1–3] These distressing symptoms not only affect patients at diagnosis and during cancer treatment but also persist years beyond the end of treatment.[4,5] Given the growing number of breast cancer survivors[6] and the impact of receiving a cancer diagnosis and undergoing treatment on mood and quality of life, it is important to understand cancer-related mental health symptoms to inform treatment and prevention efforts.

Considerable research has examined individual symptoms of depression, fatigue, and sleep disturbances in cancer populations;[7–9] however, a growing body of literature indicates that certain symptoms tend to co-occur as symptom clusters in cancer patients. A symptom cluster consists of three or more concurrent symptoms that are correlated to each other.[10] Extant literature supports the notion that

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depression, fatigue, and insomnia are a symptom cluster across cancer types, as indicated by moderate, positive correlations between all pairings of these symptoms when measured concurrently.[11,12]

Recent longitudinal studies have reported mixed findings in the investigation of temporal relationships between cancer-related symptoms. Brown et al.[13] failed to find a directional relationship between depression and fatigue in a heterogeneous sample of cancer patients. However, in a recent study that examined anxiety, depression, insomnia, fatigue, and pain over an 18 month period in mixed cancer patients, fatigue predicted depression, insomnia, and pain at subsequent time points, indicating that fatigue was the most contributive predictor over time.[14] In another heterogeneous sample of cancer patients, fatigue at baseline prospectively predicted depressive mood after treatment, rather than the opposite relation.[15] Current research implicates biological and behavioral mechanisms in the development of depression, fatigue, and sleep disturbances. Some evidence indicates that elevated inflammatory processes contribute to fatigue but not sleep disturbances or depression.[16] However, further research is needed to support the notion that fatigue may be a primary or "core" symptom in depression. Moreover, it remains to be demonstrated whether this pattern generalizes to a homogeneous breast cancer sample. Further investigation also is needed around the extent to which these symptoms occur alone vs. in combination to better delineate directionality and to aid the development of effective interventions.

The present project makes a unique contribution to the literature as the first longitudinal study that uses path analysis to examine symptom interrelations in a purported symptom cluster in breast cancer patients. The present project had three major aims: 1) to test a purported symptom cluster in the cancer literature; 2) to explore the individual course of depression, fatigue, and sleep disturbances; and 3) to explore the predictive nature of each symptom on the other two symptoms. We examined the co-occurrence, course, and interrelations between depression, fatigue, and sleep disturbances at three important time points surrounding adjuvant chemotherapy (CT) for early-stage breast cancer (i.e., before, after, and six to eight months following treatment). Because this was a secondary analysis of data from two separate studies that examined the effects of CT on cognitive functioning, we explored these symptom relations in two different samples of breast cancer patients: older, postmenopausal women (Study 1) and younger, premenopausal women (Study 2).

We proposed to test an exploratory model of all possible associations between depressive symptoms, fatigue, and sleep disturbances. In accordance with Aim 1, we expected to find correlations similar in value to those previously reported in support of the assertion that depression, fatigue, and sleep disturbances co-occur as a symptom cluster. To address Aim 2, we hypothesized that the severity of each symptom would predict severity of the same symptom at later time points. We anticipated that this pattern would be maintained even after adjusting for concurrent and previous levels of the other two symptoms. Last, in accordance with Aim 3, we hypothesized that baseline severity of each symptom would predict subsequent levels of the other two symptoms. Given that past studies have indicated that fatigue is an important predictor of other symptoms in cancer patients,[14,15] we expected that fatigue would be a stronger predictor of the other two symptoms at later time points, compared with depression and sleep disturbances.

Methods

Participants

Participants were recruited for one of two studies from the patient pool of collaborating breast surgeons and oncologists affiliated with Columbia University Medical Center in New York City. Study 1 was conducted between 2001 and 2007, whereas Study 2 was conducted between 2005 and 2011. Patients across both studies were women, newly diagnosed with Stage I–IIIa breast cancer. Possible adjuvant treatments included CT, radiation, and endocrine therapy. Exclusion criteria included prior breast cancer diagnosis; prior exposure to CT or radiation; neoadjuvant CT; and neurologic, psychological, or medical comorbidities that might affect cognitive functioning.

Eligibility criteria across the two studies differed primarily in patient age, menopausal status, and use of CT. Study 1 included postmenopausal women aged 45–70 years with postmenopausal status defined as no menstrual cycles for at least 12 months or surgical menopause. From a total of 129 patients who were approached, 81 patients completed a screen for eligibility, of which 67 eligible patients were enrolled in Study 1. Approximately half of the patients in Study 1 received adjuvant CT ($n = 36$), whereas the others were treated with surgery but no CT ($n = 31$). CT was decided between the patients and their oncologists before study enrollment. Study 2 included younger, premenopausal women aged 21–50 years, who reported regular menstrual cycles in the past year. From a total of 272 patients who were approached for Study 2, 156 patients completed a screen for eligibility, of which 67 eligible patients participated in Study 2. All patients in Study 2 received CT ($n = 67$).