Effect of Exercise on Biomarkers, Fatigue, Sleep Disturbances, and Depressive Symptoms in Older Women With Breast Cancer Receiving Hormonal Therapy

Judith K. Payne, PhD, RN, AOCN®, Joanne Held, BSN, RN, Josh Thorpe, PhD, and Heather Shaw, MD

Purpose/Objectives: To compare the effectiveness of a prescribed home-based walking exercise intervention with usual care in older women receiving hormonal treatment for breast cancer, and to examine relationships among levels of the cortisol, serotonin, interleukin-6, and bilirubin biomarkers and fatigue, sleep disturbances, and depressive symptoms.

Design: Longitudinal randomized clinical trial.

Setting: A National Cancer Institute–designated cancer center in the southeastern United States.

Sample: 20 women (aged 55 years or older) with breast cancer receiving hormonal treatment.

Methods: Participants were randomized to a walking exercise intervention or usual care. Laboratory samples and the Pittsburgh Sleep Quality Index (PSQI), the Piper Revised Fatigue Scale, and the Center for Epidemiological Studies–Depression Scale were collected at the initial clinic visit and at 12 weeks from the groups. Questionnaires also were collected at weeks 2 and 14.

Main Research Variables: Fatigue, sleep disturbances, depressive symptoms, biomarkers, and exercise.

Findings: Effect of the exercise intervention on sleep scores was highly significant between groups. Exercise group scores on the PSQI decreased significantly over time (indicating improved sleep quality), although scores did not change significantly within the control group. Sleep actigraphy also showed significantly shorter actual wake time and less movement in the exercise group. Serotonin levels also were significantly affected by the intervention.

Conclusions: Data suggest that a walking exercise intervention improves sleep in older women receiving hormonal treatment for their breast cancer. Serotonin levels may be a useful biomarker when assessing sleep disturbances in this group.

Implications for Nursing: Clinicians need to be aware that older women receiving hormonal treatment for their breast cancer may experience fatigue, sleep disturbances, and depressive symptoms. Home-based walking activity may reduce symptom severity in this group.

Key Points...

- Minimal research exists concerning symptoms experienced by older women with breast cancer receiving hormonal therapy.
- A prescribed home-based walking intervention may improve sleep in older women receiving hormonal treatment for their breast cancer.
- Select hypothalamic-pituitary-adrenal biomarkers were different between the exercise group and the usual care group.

Breast cancer is the most common type of cancer in women, accounting for about 30% of all cancers in women in the United States (Jemal et al., 2007). The risk for breast cancer increases significantly with age and is a major health concern. Although treatment varies according to disease stage and presence of other comorbidities, women aged 55 years and older are likely to require additional treatment following surgery, including chemotherapy or hormonal therapy, and to experience treatment-related side effects. Despite reports that fatigue, sleep disturbances, and depressive symptoms are common side effects experienced by women receiving chemotherapy (Byar, Berger, Bakken, & Cetak, 2006), minimal research has been conducted on older women receiving hormonal therapy (Crivellari et al., 2007; Payne, Thorpe, Held, & Shaw, 2007; Wyatt & Friedman, 1996). Symptoms experienced by women with breast cancer, including older women, have been well-described in the literature; however, few investigations have singularly focused on older women receiving hormonal therapy for breast cancer.

Relatively little information is available about what interventions may help alleviate the symptoms or the extent to which select physiologic factors, such as biomarkers, may influence the distressing symptoms. Although exercise has

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been shown to be effective in reducing cancer treatment-related symptoms in women aged 55 years and younger with breast cancer receiving chemotherapy (Mock et al., 2005; Stricker, Drake, Hoyer, & Mock, 2004), no research has focused on interventions to manage symptoms in older women receiving hormonal therapy. The purpose of this pilot study is to explore the efficacy of a prescribed home-based walking intervention in reducing fatigue, sleep disturbances, and depressive symptoms in older women receiving hormonal therapy for their breast cancer and to examine relationships among select biomarkers and fatigue, sleep disturbances, and depressive symptoms in the women. Specific aims include examining older women with breast cancer receiving hormonal therapy with tamoxifen, anastrozole, or letrozole to determine whether a prescribed home-based walking exercise intervention is more effective than usual care in reducing cancer treatment-related fatigue, sleep disturbances, and depressive symptoms; determine the extent to which fatigue, sleep, depressive symptoms, and biomarkers (cortisol, serotonin, interleukin-6 [IL-6], and bilirubin) change over time; and examine what relationships exist among cortisol, serotonin, IL-6, and bilirubin biomarkers and fatigue, sleep disturbances, and depressive symptoms.

Conceptual Model

The conceptual model guiding this study is based on components from a biobehavioral conceptual framework developed by Payne (2004), suggesting that fatigue, sleep disturbances, and depressive symptoms may result from a dysregulation of hormones (cortisol, serotonin, IL-6, and bilirubin) produced within the neuroendocrine system. The current study’s authors hypothesized that interventions, such as walking exercise, may effect positive changes in neuroendocrine-based metabolic regulatory hormones (e.g., lower cortisol and IL-6 levels, higher serotonin and bilirubin levels), which may suggest a mechanism that contributes to fatigue, sleep disturbances, and depressive symptoms in patients with breast cancer.

Background and Significance

Breast cancer affects one in seven women over the age of 85 years, and 1 in 13 between the ages of 60–79 years (American Cancer Society, 2007). Although treatment varies according to disease stage and presence of other comorbidities, older women are as likely as younger women to require additional treatment following surgery, including hormonal therapy, and to experience treatment-related side effects. Almost all patients with cancer receiving chemotherapy treatment report fatigue as the most frequent and distressing side effect, followed by sleep disturbances and depressive symptoms (Byar et al., 2006; Mock, 2004; Payne, Piper, Rabinowitz, & Zimmerman, 2006). The literature has documented that chemotherapy frequently results in short- and long-term consequences that can affect patients’ physical, functional, and psychosocial well-being (Byar et al.); however, a significant gap exists in the literature regarding hormonal therapy side effects for older women with breast cancer (Wyatt & Friedman, 1996). Although hot flashes have been described in relation to hormonal treatments for postmenopausal women with breast cancer, the literature has not been consistent in reporting the frequency of hot flashes in relation to other symptoms, such as fatigue.

Early treatment of older patients with breast cancer has increased cure and survival rates (Kimmick & Muss, 2004). However, despite the fact that breast cancer affects older postmenopausal women at rates nearly double that of younger premenopausal women (Jemal et al., 2007), only a few studies have explored treatment-related side effects in these women (Cirrivallari et al., 2007; Wyatt & Friedman, 1996). Although extensive research has been conducted on the overall use of hormonal agents in the treatment of breast cancer, minimal research has been conducted on hormonal therapy specific to older women with breast cancer. A host of adverse side effects are possible, but common side effects of the hormonal agents tamoxifen, anastrozole, and letrozole include nausea, bone pain, and hot flashes. In addition, no research was found on management strategies for hormone-related side effects.

Fatigue, sleep disturbances, and depressive symptoms frequently occur in women with breast cancer during and following their treatment. Although the symptoms appear to occur at the same rate in younger women with breast cancer (Payne et al., 2006), this symptom cluster has not been well-studied in older women with breast cancer receiving hormonal therapy.

Fatigue

Although poorly documented in the literature, cancer treatment-related fatigue (CRF) has been identified as an issue for women receiving hormonal treatment (Hamm & Allegra, 1991; Woo, Dibble, Piper, Keating, & Weiss, 1998). Fatigue is one of the most common and poorly understood symptoms experienced by patients with cancer (Cella, 1998; Jacobsen et al., 1999; Vogelzang et al., 1997) and is an almost universal symptom in patients receiving treatment (Berger, 1998; Byar et al., 2006). Fatigue may affect the ability of patients to tolerate various treatment modalities and is a major reason why patients with cancer discontinue or delay treatments (Dodd, Miaskowski, & Paul, 2001).

Dodd et al. (2001) investigated the effects of symptom clusters, such as pain, fatigue, and insufficient sleep, on the

<table>
<thead>
<tr>
<th>Patients on hormonal therapy* (N = 20)</th>
<th>Usual Care (N = 10)</th>
<th>Intervention Exercise (N = 10)</th>
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</thead>
<tbody>
<tr>
<td><strong>Biomarkers</strong></td>
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<tr>
<td>Cortisol</td>
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<td>Serotonin</td>
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<td>Interleukin-6</td>
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<tr>
<td>Bilirubin</td>
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</tbody>
</table>

*58 patients met demographic, biobehavioral, physiologic, and psychological eligibility criteria; 20 agreed to participate.

Note. Solid lines indicate direct relationship or effect whereas dotted lines indicate indirect relationship or effect.

Figure 1. Study Design Schema
functional status of 23 outpatients receiving chemotherapy and found that, along with age and pain, fatigue predicted adverse changes in functional status, a particular concern for older women who, even without CRF, are at risk for age-related functional decline.

Sleep Disturbances

The relationship between CRF and objective measures of quality and quantity of sleep is not fully understood. Whether CRF experienced during the day relates to sleep patterns or to the quality and quantity of sleep obtained at night has not been determined (Ancoli-Israel, Moore, & Jones, 2001; Berger et al., 2005). However, research does suggest that fatigue, sleep disturbances, and depression positively correlate with one another (Patrick et al., 2003; Redecker, Lev, & Ruggiero, 2000; Roscoe et al., 2002; Taylor, Lichstein, Durrence, Reidel, & Bush, 2005).

Depressive Symptoms

Depression is characterized by feelings of sadness, despair, and discouragement. Depressive symptoms are a frequently experienced side effect following cancer diagnosis and treatment, with an incidence ranging from 20%–30% (Lovejoy, Tabor, Matteis, & Lilis, 2000; Vena, Parker, Cunningham, Clark, & McMillan, 2004). Other studies suggest that rates of depressive states for patients with cancer are comparable to similarly ill patients with other diagnoses, with about one-third of patients reporting mild to moderate symptoms of depression (McDaniel, Musselman, Porter, Reed, & Nemeroff, 1995; Spiegel & Giese-Davis, 2003). Prior research demonstrates relationships between depressive symptoms, fatigue, and sleep disturbances (Patrick et al., 2003) and emerging research suggests a relationship with hormonal biomarkers (Payne et al., 2006; Redecker et al., 2000).

Biomarkers

Cortisol, serotonin, IL-6, and bilirubin biomarkers have hypothalamic-pituitary-adrenal (HPA) axis neuroendocrine-based regulatory functions. Previous research has shown that cortisol, melatonin, and bilirubin changed over time in women with breast cancer receiving chemotherapy (Payne, 2002; Sephton, Sapolsky, Kraemer, & Spiegel, 2000). The authors of this study analyzed serotonin radioimmunoassay levels for several reasons, including that in looking at the symptom of depression, serotonin seemed more enticing than melatonin. In addition, because the pineal gland produces melatonin (which is a precursor to serotonin) at night, it is necessary to draw serum samples between midnight and 4 am to obtain the peak level of melatonin production. Because the authors did not have access to the patient population during that time of day, serotonin was evaluated as a potential biomarker for fatigue, sleep disturbances, and depressive symptoms.

Symptom Management

Adherence to prescribed cancer treatment protocols is extremely important. Decreased dosages or interruptions in treatment protocols may reduce the generalizability of study results and diminish the chances for long-term remission or cure. Therefore, developing strategies that enable older patients with cancer to better tolerate treatments and for clinicians and researchers to track adherence to treatments and symptoms experienced by those patients is critical.

Management of treatment side effects is a priority for oncology nurses and an important focus for oncology nursing research (Ropka et al., 2002). Despite the fact that nearly all patients receiving treatment report fatigue and sleep disturbances, a lack of understanding about the etiology of these symptoms has made effective interventions difficult to devise. Interventions to manage side effects of cancer treatment can improve patients’ quality of life and functional status. Aerobic exercise is an evidenced-based intervention that has been used to reduce CRF, improve mood, and increase functional ability of patients with cancer receiving treatment (Mock et al., 2005; National Comprehensive Cancer Network, 2007; Schwartz, 1998). Biomarkers, such as cortisol, serotonin, IL-6, and bilirubin, and adherence to an aerobic walking program, may provide the conceptual linkages necessary for understanding mechanisms that may modulate symptoms, such as CRF and sleep disturbances, and to determine who is at risk for fatigue (Payne, 2002; Payne et al., 2006), sleep disturbances (Byar et al., 2006), and depressive symptoms (Vena et al., 2004). The purpose of the current study, therefore, was to compare the effectiveness of a prescribed home-based walking exercise intervention with usual care in older women with breast cancer receiving hormonal therapy and to examine the relationships among fatigue, sleep characteristics, and depressive symptoms with levels of cortisol, serotonin, IL-6, and bilirubin biomarkers.

Table 1. Data Collection Schema

<table>
<thead>
<tr>
<th>Measure</th>
<th>Time 1</th>
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<th>Time 3</th>
<th>Time 4</th>
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<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Center for Epidemiological Studies–Depression Scale</td>
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<tr>
<td>Bilirubin</td>
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</table>

Methods

A longitudinal, repeated measures clinical trial design was used in this pilot study to determine the feasibility of a prescribed walking exercise program for older women with breast cancer receiving hormonal therapy and to examine what relationships exist among cortisol, serotonin, IL-6, and bilirubin biomarkers and fatigue, sleep disturbances, and depressive symptoms. Participants were randomized to either a walking exercise intervention (n = 10) or to usual care (n = 10), defined as standard interaction with nurses, physicians, and staff (see Figure 1). Participants in the exercise group were compensated by receiving a pedometer. Patients in the usual care group received a $10 gift card. The study was approved by the university institutional review board and scientific advisory committee.

Sample and Setting

Potential participants were recruited from breast cancer clinics of a university National Institutes of Health
Comprehensive Cancer Center in the southeastern United States. Eligibility criteria included postmenopausal women who were diagnosed with breast cancer and receiving hormonal therapy with tamoxifen, anastrozole, or letrozole (the three most frequently prescribed hormonal medications during the period of recruitment and study enrollment); aged 55 years and older and with complaints of fatigue; had a Karnofsky Performance Scale score of 80 or higher; spoke English; had no documented history of neurologic deficits or mental illness such as psychotic depression within the past year; and had no neuromuscular deficits that would contraindicate a walking exercise intervention.

Patients meeting study criteria were referred by their oncologist or advanced practice nurse for possible recruitment. To include only patients who were experiencing fatigue, potential participants who met all other criteria were pre-screened by the principal investigator or study coordinator for fatigue by asking them three questions to assess their fatigue level and its affect on daily activities: (a) On a scale of 0–10, with 0 indicating no fatigue and 10 indicating extreme fatigue, how do you rate your usual rate of fatigue? (b) Thinking about the answer you just provided, how frequently do you feel that level of fatigue (on a scale of 0–10)? (c) To what extent does your fatigue interfere with your usual activities of daily living (on a scale of 0–10)? The purpose of the three questions was to confirm that the patients were experiencing fatigue; however, the questions have not been validated. Women were invited to participate in the study if their answers to each of these three questions were a

### Table 2. Demographic Characteristics

<table>
<thead>
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<th>Characteristic</th>
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<th>SD</th>
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<tbody>
<tr>
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<table>
<thead>
<tr>
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<tr>
<td>20,001–40,000</td>
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<td>25</td>
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<td>20</td>
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<tr>
<td>&gt; 60,000</td>
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<tr>
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</tr>
<tr>
<td>College degree or higher</td>
<td>8</td>
<td>40</td>
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\(N = 20\)
Andrykowski, 1998). Seven component scores are summed to produce a global PSQI score that ranges from 0–21; higher total scores on the global index indicate more sleep complaints and lower sleep quality. Sleep watch actigraphs were used to measure actual sleep time, actual wake time, movement during sleep, and sleep efficiency.

Depressive symptoms were measured with the 20-item Center for Epidemiological Studies–Depression Scale (CES-D) (Radloff, 1977). The total score has a range from 0–60 and in all cases, except for four questions, higher scores indicate more impairment. For those four questions, the scores are reversed.

The written instruments were completed by participants at four measurement points: baseline and 2, 12, and 14 weeks after baseline. A blood sample to measure serum cortisol, serotonin, IL-6, and bilirubin biomarkers was drawn in the clinic phlebotomy area of the cancer center at baseline and at the 12-week clinic visit. Cortisol and bilirubin samples were processed and analyzed at the cancer center according to routine laboratory methods, and results were directly sent to the principal investigator’s research office. Because laboratory work analyzed by radioimmunoassay require special handling (e.g., separate plasma or serum, spin, and aliquote to plastic vials, freeze samples within 30 minutes) serotonin and IL-6 samples were hand-carried immediately to the centrifuge room located on the second floor of the cancer center, spun within 30 minutes, aliquotted to 3 ml plastic vial tubes, and transported on dry ice to an adjacent laboratory and frozen at –70°F. At the end of data collection, frozen samples were sent to the InterSci Laboratory (Inglewood, CA) for radioimmunoassay analysis.

**Intervention**

The study coordinator or principal investigator explained the prescribed home-based walking exercise intervention to eligible study participants. The intervention was described as a moderate walking activity, 20 minutes in duration, four times a week. Logs were provided to study participants to record the frequency and length of their walking activity. Participants who were randomized to the exercise group were shown how to use the pedometer that they were provided as compensation and incentive for taking part in the study, but were not required to use it or asked to log their rate of speed or distance walked.

**Data Analysis**

Descriptive statistics, frequencies, t tests, and repeated measures analysis of variance (ANOVA) were used to analyze data. A mixed model statistical approach was chosen to extend the standard repeated measures ANOVA to make better use of data when missing data were present. Categorical data were summarized as frequencies and percentages, continuous data were summarized as means and standard deviation, and pair-wise correlations were examined at baseline. Repeated measures mixed-effects models (Cnaan, Laird, & Slisor, 1997) were used to examine the intervention effects on the outcome variables (biomarkers and fatigue, sleep disturbances, and depressive symptoms), as well as bivariate associations between select independent variables and outcomes. Mixed-effects models properly accounted for autocorrelated error terms within subjects and efficiently handled missing data and unbalanced designs. Two-sided p values < 0.05 were regarded as statistically significant. All data was analyzed using STATA version 9.1.

**Results**

The mean age of the 20 participants was 65 years (range 56–78 years), and all were postmenopausal. The majority of participants were married and more than half were retired (see Table 2). Participants were receiving tamoxifen, anastrozole, or...
letrozole for their breast cancer. Two subjects (one each from the control and intervention groups) withdrew from the study at midpoint, after time 1 and time 2 data collection, because of worsening health issues. In addition, two study participants refused their second phlebotomy. Therefore data analysis was completed on 18 study participants with minimal missing data.

**Fatigue**

All study participants reported moderate fatigue as measured by the PFS at four measurement points over a three-month period (X = 4.28). Although differences between the intervention and control groups were noted, levels of fatigue between the groups and across time were not statistically significant.

**Sleep Disturbances**

Study participants from both the exercise group and the usual care group experienced sleep disturbances as measured by sleep actigraphy and scores reflected on the PSQI (see Figure 2). The effect of the exercise intervention on PSQI scores was highly significant (p = 0.007). PSQI scores for the exercise group decreased significantly over time, indicating improved sleep quality. In contrast, no significant change was noted in sleep quality within the control group receiving usual care.

Statistically significant differences between groups also were found based on actigraphy analysis. After 12 weeks (time 3), actual wake time and actual sleep time were both shorter (p = 0.02 and p = 0.05, respectively) in the exercise group. Less movement during sleep (p = 0.002) also was noted in the exercise group. However, no statistically significant differences existed between groups in sleep efficiency (the ratio of total sleep time in bed) scores (see Figure 3).

**Biomarker Analysis**

**Cortisol:** No significant differences in cortisol levels were found between groups or across time. However, a downward trend (p = 0.19) was noted in the exercise group compared to the usual care group. Mean values for both groups at both measurement times were well within the normal range for cortisol (6–23 mcg/dl).

**Serotonin:** Significant differences in serum serotonin levels were noted between groups and across time with a significant intervention effect seen on serotonin levels (p = 0.009). Serotonin levels decreased over time in the control group. Correlations of serotonin levels with actual wake time (p = 0.06 and movement during sleep (p = 0.07) were suggestive, although not significant. Normal range for serum serotonin in women is 80–400 ng/ml.

**Interleukin-6:** No significant differences were found in IL-6 levels between groups or over time. Mean values for both groups of measurement times were within the normal range for IL-6 (2–29 ng/ml).

**Bilirubin:** Mean bilirubin values for both groups at both measurement times were at or above the upper limit of the normal range (0.01–0.3 mcg/dl). A weak intervention effect (p = 0.09) was seen for bilirubin (see Figure 4).

**Depressive Symptoms**

No significant differences in severity of depressive symptoms were noted between groups or over time (see Figure 5). Approximately 30% of study participants in each group reported some depressive symptoms on the CES-D (comparable to rates for the general population). No study participants scored at or above 18 on the CES-D (which would have triggered a report to the oncologist for further evaluation of possible depression).

**Discussion**

This pilot study provided preliminary information on the effectiveness of a prescribed home-based walking exercise intervention for fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy, and on relationships among select biomarkers that may correlate with these symptoms. Overall, walking exercise was an accepted and feasible intervention for this older patient population. When comparing the exercise group with the usual care group, serotonin levels were significantly different between the two groups (p = 0.07). Serotonin levels decreased slightly over the 14-week period in the intervention group, suggesting that exercise may exert a negative influence on the production of serotonin. Although the direction of this finding is the opposite of the authors’ previous study comparing younger women with breast cancer receiving adjuvant chemotherapy to an age- and menopausal-matched healthy control group (Payne et al., 2006), differences may be explained by the inclusion...
of a healthy control group in the previous study and that participants in this study were all older women with breast cancer, which is important to understanding the underlying etiology of these common symptoms in older patients. Although cortisol levels did not demonstrate a significant association with either the intervention or the symptoms, a downward trend in the intervention group did exist ($p = 0.19$). IL-6 levels were not significantly different between groups or over time and did not correlate with changes in other biomarker levels or with fatigue, sleep disturbances, or depressive symptoms. The significance of the bilirubin level may be an important factor related to fatigue and should be explored in future studies as a potential biomarker predictor of cancer-related fatigue.

These research findings describe the occurrence of fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy over 14 weeks. Many older women with breast cancer receiving hormonal therapy do not receive the close surveillance that women undergoing chemotherapy receive, creating a large gap in the literature describing what short- and long-term symptoms older women receiving hormonal therapy are experiencing. More descriptive studies are needed in this understudied patient population and additional intervention studies may validate these findings in a larger population.

Limitations

Limitations of this study include small sample size and subsequent limited power and that participants in the intervention group may have received more attention than those in the usual care group. In addition, the study relied on self-report measures of exercise; therefore, the authors were unable to verify actual adherence to study parameters, such as the number of times per week that subjects actually completed the 20-minute walk. Treatment fidelity tracking issues (treatment delivery, receipt, and enactment) are important in home-based intervention studies.

Conclusion

Minimal research has been conducted on the symptoms experienced by older women with breast cancer receiving hormonal therapy. Findings from this study are the first to document fatigue, sleep disturbances, and depressive symptoms in this population. In addition, the study provides preliminary data describing relationships among these symptoms and select biomarkers (cortisol, serotonin, IL-6, and bilirubin). Data from this study may contribute to the development of a better understanding of common physiologic linkages of a cluster of symptoms experienced by older women with breast cancer receiving hormonal treatment. For these women, this study’s findings indicate that a home-based walking exercise holds promise as an effective and cost-efficient intervention for reducing sleep disturbances.

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References


