Biomarkers, Fatigue, Sleep, and Depressive Symptoms in Women With Breast Cancer: A Pilot Study

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Purpose/Objectives: To evaluate the changes in reports of fatigue, sleep disturbances, and depressive symptoms and serum cortisol, melatonin, serotonin, and bilirubin during adjuvant chemotherapy in women with breast cancer and to determine whether any correlations exist between the symptom parameters and biomarkers.

Design: Prospective longitudinal, correlational, repeated-measures pilot study.

Setting: Large southwestern, university-based, National Cancer Institute–designated cancer center.

Sample: 22 subjects (11 women with stage II breast cancer receiving adjuvant chemotherapy and 11 cancer-free women who were matched by age, ethnicity, and menopausal status).

Methods: Questionnaires (fatigue, sleep, depressive symptoms), wrist sleep actigraphy, and laboratory analysis of serum samples. All subjects (i.e., women with breast cancer receiving chemotherapy and a comparison group of cancer-free women who were matched by age, ethnicity, and menopausal status) were admitted to a general clinical research center for two nights during cycles 1 and 4 for data collection.

Main Research Variables: Biomarkers (serum cortisol, melatonin, serotonin, and bilirubin), fatigue, sleep, and depressive symptoms.

Findings: Mean fatigue scores of the subjects with cancer were significantly higher than the healthy comparison group. Subjects with cancer had a significantly lower mean actual sleep time compared to the comparison group at cycle 1. No significant difference was found between the groups at cycle 4. Depression scores also differed significantly between the cancer group and comparison group. Select biomarkers changed over time and were associated with subjective parameters of fatigue, sleep, and depressive symptoms.

Conclusions: Findings suggest that fatigue, sleep, and depressive symptoms are more prevalent in women with cancer than a cancer-free comparison group. Biomarkers changed over time and provide a possible explanatory mechanism for the three related symptoms.

Implications for Nursing: Data help to explain a mechanism that may underlie fatigue, sleep, and depressive symptoms and provide a theoretical framework from which to establish evidence-based interventions for symptom management.

Key Points . . .

- Fatigue, sleep disturbances, and depressive symptoms are significantly higher in women with stage II breast cancer receiving adjuvant chemotherapy compared to disease-free women.
- Select hypothalamic-pituitary-adrenal biomarkers may be related to fatigue, sleep disturbances, and depressive symptoms.
- Healthcare providers need to be aware of a possible underlying mechanism of related symptoms in an effort to establish evidence-based practice for tailored symptom management interventions.

Breast cancer frequently requires adjuvant chemotherapy to treat micrometastatic disease following surgery. Although clinical trials have demonstrated long disease-free intervals with curative intent, the treatment frequently involves significant short- and long-term side effects, including fatigue, sleep disturbances, and depressive symptoms. Fatigue continues to be described as the most common and distressing symptom associated with chemotherapy (Irvine, Vincent, Graydon, Bubela, & Thompson, 1994; Jacobsen et al., 1999; Mock, 2004; Payne, 2002; Piper, Lindsey, & Dodd, 1987; Winningham et al., 1994), but little is known about the underlying etiology of fatigue and its closely interrelated association with sleep disturbances and depressive symptoms or its association with select biomarkers (i.e., serum cortisol, melatonin, serotonin, and bilirubin). The frequency and prevalence of this symptom cluster and related sequelae identify it as a significant problem for patients with cancer receiving treatment.

The neuroendocrine system, specifically the hypothalamic-pituitary-adrenal (HPA) axis, provides regulatory functions; the changes in the production of biochemical levels produced in the axis likely exert complex interactions and influences that researchers are only beginning to understand (Cleeland et al., 2003; Payne, 2004; Vgontzas & Chrousos, 2002).
Background and Literature Review

Numerous studies have attempted to identify the physiologic mechanisms of cancer treatments that cause side effects such as fatigue (Haylock & Hart, 1979; Jones, Wadler, & Hupart, 1998; Payne, 2002; Payne, Piper, Rabinowitz, & Zimmerman, 2003; Raab et al., 1999; Sephton, Sapolsky, Kraemer, & Spiegel, 2000; Toutou, Bogdan, Levi, Benavides, & Auzeby, 1996). In addition, various theories have been proposed to explain how fatigue occurs (Aistars, 1987; Cleeland, 2001; Grandjean, 1970; Gutstein, 2001; Irvine et al., 1994; Norris, 1982; Payne, 2004; Pickard-Holley, 1991; Piper et al., 1987; Winningham et al., 1994). Fatigue has been attributed to various factors, including stress (Aistars), endocrine imbalances (Cleeland, Payne, 2002, 2004), sleep disturbances (Ancoli-Israel, Moore, & Jones, 2001; Berger, 1998; Berger & Higgirbotham, 2000; Carpenter et al., 2004), biochemical changes secondary to disease and treatment, weight change, and internal and external environmental conditions (Payne, 2002, 2004; Piper, 2003; Winningham & Barton-Burke, 2000; Winningham et al., 1994). Sleep disturbances have been associated with endocrine imbalances, fatigue, depression, renal problems, and other sequelae (Berger et al., 2005). Similarly, depression occurs with many of the same disease and treatment antecedents as fatigue and sleep disturbances. However, few studies have investigated the actual mechanisms leading to fatigue or the suspected correlates of sleep disturbances and depressive symptoms.

Most studies of fatigue have focused on patients’ self-reported experiences, but few have measured changes in fatigue and related symptoms (sleep and depressive symptoms) over a course of treatment (Carpenter et al., 2004; Jacobsen et al., 1999). In an early study of patients with cancer receiving radiation therapy, investigators attempted to identify possible mechanisms of fatigue but were unable to do so (Haylock & Hart, 1979). In a more recent study, posited biomarkers were measured in patients with early-stage breast and ovarian cancer who were receiving chemotherapy for the first time and found changes over time in two biomarkers: melatonin and hemoglobin (Payne, 2002). Nighttime melatonin and hemoglobin levels decreased at the three-month measurement point during chemotherapy, whereas daytime melatonin levels increased over time. Although the change was not statistically significant, the upward trend in daytime melatonin levels suggested a plausible explanation for the increased fatigue intensity experienced by women with breast cancer receiving adjuvant chemotherapy. The findings suggested a possible physiologic basis for cancer treatment-related fatigue.

Clinically, sleep disturbances and depressive symptoms frequently occur in concert with cancer-related fatigue. Sleep disturbances, which are common among patients with cancer, also are likely related to fatigue (Ancoli-Israel et al., 2001; Berger, 1998; Berger et al., 2002; Savard & Morin, 2001; Silberfarb, Hauri, Oxman, & Schnurr, 1993). In their research, Savard and Morin have shown that sleep is a highly structured and well-organized activity that follows a circadian periodicity regulated by the interplay of biologic processes such as melatonin production and environmental factors. The researchers postulated that fatigue and mood disturbances are among the possible consequences of sleep disturbances experienced by patients with cancer. However, data are limited regarding the association between sleep disturbances and fatigue related to cancer treatment.

The dysregulation of HPA-related biomarkers may be among the mechanisms underlying fatigue, sleep disturbances, and depressive symptoms (Redwine, Hauger, Gillin, & Irwin, 2000). Few studies have examined bilirubin as a possible marker of cancer-related fatigue. Measurement of serum bilirubin can help to evaluate the hepatobiliary and erythropoietic function of red blood cells associated with cancer treatments and, thus, is considered a potential marker in the study of fatigue (Payne, 2002).

Serotonin and melatonin are the major secretory products of the pineal gland and are important regulators of the 24-hour sleep and wake cycles that all individuals experience (Birdsall, 1996; Claustrat, Brun, & Chazot, 2005; Cupp, 1997). Melatonin production is inhibited by light and increases sharply with darkness; therefore, an individual’s natural wake and sleep cycle corresponds with melatonin production (Cupp). The link among sleep, melatonin, and serotonin is important to consider because serotonin is a precursor to melatonin and may be an indicator of depression. Furthermore, depressive symptoms and fatigue are believed to be connected via a neuroendocrine transmitter pathway (Cleeland, 2001; Payne, 2002, 2004; Vgontzas & Chrousou, 2002). Fatigue may be affected by the body’s production of melatonin and serotonin (Payne, 2002, 2004).

Cortisol, which impacts metabolism, response to stress, immune function, and emotional stability, has a permissive effect in that it must be present for other physiologic processes, such as catecholamine action, to occur (Payne, 2004). Because cortisol production (like melatonin) also is affected by a diurnal rhythm, it may be linked to other markers associated with cancer treatment-related fatigue, sleep disturbances, and depressive symptoms.

The biobehavioral conceptual framework guiding the current study postulates that physiologic and psychological factors, including the neuroendocrine components of the HPA axis, are associated with fatigue, sleep, and depressive symptoms. This pilot study examined fatigue, the related correlates of sleep and depressive symptoms, and select biomarkers (serum cortisol, melatonin, serotonin, and bilirubin) over time in women with early-stage breast cancer receiving adjuvant chemotherapy. Specifically, the aims of the pilot study were to (a) evaluate changes in subjective reports of fatigue and the correlates of sleep and depressive symptoms with serum cortisol, melatonin, serotonin, and bilirubin from cycles 1–4 of adjuvant chemotherapy in women diagnosed with early-stage breast cancer compared to a healthy comparison group that was matched by age, ethnicity, and menopausal status and (b) determine whether any correlations exist between the subjective parameters and biomarkers in the subjects studied.

Research questions addressed in the study were (a) To what extent do fatigue, sleep disturbances, depressive symptoms, and select biomarkers (serum cortisol, melatonin, serotonin, and bilirubin) change over time? and (b) To what extent do...
changes in select biomarkers correlate with subjective measures of fatigue, sleep disturbances, and depressive symptoms?

**Methods**

Setting and Sample

A prospective, repeated-measures pilot study was conducted over a 12-month period. Twenty-two subjects were enrolled in the study; 11 were women diagnosed with stage II breast cancer and were receiving doxorubicin and cyclophosphamide chemotherapy every three weeks, and 11 were cancer-free women. Each patient with cancer was matched to a healthy control by age, ethnicity, and menopausal status. Patients with cancer were recruited from a large southwestern university health science center. Healthy controls were recruited from a nearby university, school of nursing, and local community. Approval was obtained from the university’s investigational review board. Potential patient subjects were prescreened at the cancer center’s scheduling center and the medical oncology clinics by medical oncologists and trained research nurses. All study personnel had completed and were current with institutional and federal investigational review board training requirements.

The 11 women with breast cancer were scheduled to receive adjuvant chemotherapy for the first time. They either had had a mastectomy (n = 6) or lumpectomy (n = 5) and axillary lymph node dissection. A routine metastatic workup, including laboratory tests, a chest x-ray, and a bone scan as deemed appropriate by the treating physician, had been performed on the patients. Before the administration of chemotherapy, all patients received a standard antiemetic regimen consisting of ondansetron and prochlorperazine as needed.

Only one subject with breast cancer who was approached declined to participate in the study. All subjects were 21 years or older and were cognitively intact with no documented neurologic deficits or mental illness within the prior year. A signed consent form was obtained from each subject prior to data collection. How patients experienced fatigue, sleep disturbances, and depressive symptoms at critical points around the administration of chemotherapy was important to determine; therefore, data were collected at four measurement points (i.e., during cycles 1 and 4 on days 1–3 and at the two-week nadir points). The measurement points pre- and postadministration of chemotherapy were selected to determine whether any immediate changes occurred related to chemotherapy administration. Although complete blood counts were not obtained because subjects were not able to return to the clinic at the two-week nadir, this point was chosen for return of the completed subjective questionnaires via self-addressed, postage-paid envelopes. Research suggests that the time point corresponds with maximal bone marrow suppression and possibly a peak in fatigue for patients receiving chemotherapy (Jacobsen et al., 1999; Payne et al., 2003). The time points during cycle 1 and cycle 4 were chosen to determine whether any cumulative effect was present on the variables after successive rounds of chemotherapy. Measurements were performed for the control group on the same time schedule.

The study required participants to be admitted to a general clinical research center (GCRC) for two nights during chemotherapy cycles 1 and 4 for a total of four nights. GCRCs are research units staffed with personnel trained in the research process. Saline-locked peripheral IVs were inserted into subjects’ lower forearms during the first evening of their hospitalization and removed prior to discharge on the morning of day 3. The melatonin radioassay procedure protocol had been developed in collaboration with the GCRC laboratory supervisor and staff nurses during a previous preliminary study (Payne, 2002). Staff nurses were instructed to carry a small penlight to use only when necessary and to leave the doors to subjects’ rooms open no more than three inches to ensure that light did not affect melatonin levels. As an incentive, all participating subjects were offered a prorated $50 per night or a total of $200.

Patients with breast cancer were admitted the night before they were scheduled to receive chemotherapy treatment. Laboratory blood work was collected the night before chemotherapy and repeated the night following chemotherapy. Cortisol samples were collected on the morning of days 2 and 3. Sleep wrist actigraphs were placed on the subjects’ nondominant wrists and worn from the night of admission through discharge on the morning of day 3; other select questionnaire instruments were completed during hospitalization. Healthy comparison subjects were hospitalized concurrently with the subjects with cancer.

Measures

The valid and reliable self-report measures used in the current study were the Piper Fatigue Scale (PFS) (Piper et al., 1998) and the Center for Epidemiological Studies–Depression (CES-D) Scale (Radloff, 1977). Subjects also completed a demographic questionnaire to provide information on their age, ethnicity, education, marital status, employment, household income, sleep disturbances, use of sleeping medications, menstruation status, and presence of other diseases.

The PFS is a 22-item instrument that measures subjective fatigue and has been used extensively in cancer populations (Piper, 2003). The instrument has four subscales or dimensions of subjective fatigue: affective meaning, sensory, behavioral or severity, and cognitive or mood. Cronbach alphas for the total and all subscales range from 0.91–0.98 (Berger & Higginbotham, 2000; Piper et al., 1998; Schneider, Prince-Paul, Allen, Silverman, & Talaba, 2004).

Depressive symptoms were measured by using the 20-item CES-D scale, which measures the depressive symptoms experienced in the past week. The CES-D scale has demonstrated high internal consistency in patients and caregivers, with Cronbach alphas ranging from 0.86–0.91 (Given et al., 1993; Radloff, 1977).

Physiologic measures were serum cortisol, melatonin, serotonin, and bilirubin levels. Daytime melatonin samples were drawn at 2 pm, and nighttime melatonin levels were drawn hourly from 12–7 am. Serum serotonin samples were drawn at 8 am on the day of chemotherapy and again on the morning after chemotherapy. Cortisol samples were collected at 4 am and 7 am on days 2 and 3 after chemotherapy. A complete blood count and bilirubin samples were drawn in the clinic prior to admission. Because of the subjects’ inability to manage additional travel to the clinic, a complete blood count was not obtained at two-week nadir points for cycle 1 or 4. All blood samples were taken to the GCRC laboratory immediately after they were drawn; melatonin and serotonin samples were spun and aliquoted into plastic vials and frozen at −70°C. The samples were batched, and analysis was completed at the end of the study. A Buhlmann melatonin radioimmunoassay test kit was used by trained GCRC core laboratory personnel to measure melatonin levels in the extracted serum specimens by a double-antibody radioimmunoassay based on
the Kennaway G280 antimelatonin antibody (Vaughan, 1993). The complete blood count, cortisol, and bilirubin specimens were coordinated through the core GCRC laboratory and analyzed by Tri-Core Laboratories per Clinical Laboratories Improvement Amendments (CLIA) standard analyses. The Centers for Medicare and Medicaid Services regulate all laboratories, except research, performed on humans in the United States through CLIA. The objective of CLIA is to ensure quality laboratory clinical operations; however, CLIA has no direct Medicare or Medicaid responsibilities. Its purpose is in regulatory and certifying tasks.

Sleep disturbances were measured by sleep wrist actigraphy (Berger et al., 2005; Silberfarb et al., 1993). Sleep wrist actigraphs were placed on the nondominant wrists at approximately 10 pm on the first night of admission and worn continuously until discharge on day 3 at 8 am. Self-reports of sleep disturbances were obtained from the demographic questionnaire and the PFS.

Statistical Analyses

Demographic variables were compared between the cancer and control groups using t test for the continuous variables and Fisher’s exact test for the categorical variables.

The linear mixed-model analysis for repeated measures was used to test for changes in biomarkers, fatigue, depression, and sleep variables in the cancer and control groups over time, as well as to compare the mean and mean change in the variables at each time point between the two groups. The fixed effects in the model were group (cancer versus control), which is the between-subject effect, and two within-subject repeated-measures effects that were cycle (1 versus 4) and day (admission before chemotherapy versus after chemotherapy, at day 2 or 3 or two weeks). The model also included two-factor interactions and a three-factor interaction. For each set of inter- and intragroup comparisons, Bonferroni’s method was used to adjust the p values to account for the number of tests performed, with the Bonferroni adjustment applied separately to each factor effect being tested. For the comparison of cancer and control group means at each time point, the Bonferroni adjustment accounted for four tests for the variables measured at four time points and for eight tests for the variables measured at eight time points (melatonin and cortisol). A Bonferroni adjusted p value less than 0.05 was considered statistically significant. However, because the sample size of the pilot study was small, statistical tests with a p value less than 0.10 also are reported and noted as suggestive of a possible effect.

Pearson correlation coefficients were computed to assess the linear relationship of the biomarker levels with fatigue and depression in the cancer and control groups at each cycle. The linear mixed-model analysis also was used to examine the linear association of the biomarker levels with fatigue, depression, and the sleep variables. By using a method of analysis that accounts for the correlation of the measurements at two cycles from the same subject, the researchers were able to fit a single model using the data to test for linear association. For each of the scores as the dependent variable, a model was fitted with biomarker, subject group, and cycle as the independent variables. Age was considered for inclusion as a covariate in the model but was kept in the final model only if an association was found with the dependent variable (p < 0.1).

The relationship between the biomarkers and the dependent variables of interest was measured by the slope estimate. If the slope did not significantly differ between cycles 1 and 4, a common slope was estimated from the observed values for the two cycles.

Results

Sample Description

Demographic and clinical characteristics of the patients with cancer and the control subjects are presented and compared in Table 1. The mean age of the patients with cancer and the control subjects was 47.4 ± 10.4 and 47.6 ± 10.7 years, respectively, with the majority being single or divorced (82% of patients and 55% of controls, p = 0.36). Twelve subjects were Caucasian, eight were Hispanic, and two were Native American; the patients with cancer and the control subjects were matched by age, ethnicity, and menopausal status. All subjects had a high school education, and the majority had some college; 91% were gainfully employed outside of the home. However, the patients with cancer reported a significantly lower income than the controls (p = 0.009). Even at the start of the study, 59% (n = 13) of all participants reported trouble sleeping at night: 10 subjects (91%) in the cancer group compared to 3 subjects (27%) in the control group (p = 0.008). Only 18% (three in the cancer group and one in control group, p = 0.59) took sleeping pills on occasion.

With the exception of the bilirubin and complete blood count measures, the researchers were able to obtain the biomarker measures and fatigue and depression scores for all but a few of the subjects. As a result of some miscommunication with the

<table>
<thead>
<tr>
<th>Table 1. Demographic and Clinical Characteristics</th>
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<tr>
<td>Cancer Group (N = 11)</td>
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<tr>
<td><strong>Characteristic</strong></td>
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<td>Age (years)</td>
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<td><strong>Characteristic</strong></td>
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<tr>
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<tr>
<td>Postmenopausal</td>
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<tr>
<td>Insomnia*</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Not reported</td>
</tr>
<tr>
<td>Used sleeping pills*</td>
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</tbody>
</table>

* Defined as having trouble sleeping at night
* Subjects responded to the following question: Do you take sleeping pills to help you sleep?

Note. Because of rounding, not all percentages total 100.
phlebotomists, bilirubin samples were not obtained from six subjects (four in the control group and two in the cancer group) in cycle 1 and five control subjects in cycle 4. Complete blood count data were missing for five control subjects in cycle 1 and four subjects (two in the control group and two in the cancer group) in cycle 4; therefore, those data are not reported in this article. For the other measures, baseline melatonin was not measured at cycle 1 in three subjects (one in the control group and two in the cancer group) or at cycle 4 in two subjects (one in the control group and one in the cancer group). The other biomarker measures had minimal missing measures.

**Fatigue Group Differences**

**Group interactions:** The mean change in the subjective fatigue score from admission to the two-week nadir differed significantly between the cancer and control groups (p = 0.03). The mean changes in total fatigue scores did not differ significantly between cycle 1 and 4 (p = 0.85). The mean fatigue score for the patients with cancer was significantly higher than for the healthy controls at admission and the two-week nadir (p < 0.0001). As noted in Figure 1, the fatigue score for the control group remained fairly constant over time (p = 0.29), whereas the cancer group showed a significant mean increase in the fatigue score at the two-week nadir compared to admission (p = 0.043; mean increase of 0.8 ± 0.4 averaged over cycles 1 and 4). The finding may correlate with the patients’ hematologic nadir. Interestingly, no progressive increase in fatigue score was found over the course of the four cycles of chemotherapy; the respective admission and nadir fatigue scores did not differ significantly between cycles 1 and 4 (p = 0.65).

**Sleep Group Differences**

Mean sleep disturbances and sleep time at each of the two nights for cycle 1 and cycle 4 are shown in Figure 2. No significant three-factor and two-factor interactions of group, cycle,
cancer group had a significantly shorter mean actual sleep time (Bonferroni adjusted \( p = 0.024 \)) at cycle 1, night 2, compared to the healthy comparison group, with no significant difference between the groups at the other three periods (Bonferroni adjusted \( p = 1.0 \)). This was the night after the first cycle of chemotherapy and may reflect anxiety after the first treatment or some side effects related to the treatment that interfered with sleep. Subjects’ self-reports of sleep were congruent with wrist actigraph data indicating that they had not slept well. In the subjects with cancer, an inverse relationship existed between nighttime melatonin levels and sleep disturbances (data not shown, \( p = 0.08 \)).

**Depression Group Differences**

Depressive symptom scores from the CES-D scale differed significantly between the cancer and control groups, with a higher mean depression score among the patients with cancer (23.0 ± 2.9 versus 9.7 ± 2.8; \( p = 0.006 \) group main effect) (see Figure 3). The group differences did not vary in magnitude between cycles 1 and 4, between admission, and at the two-week follow-up (group-cycle-day interaction \( p = 0.22 \); group-cycle interaction \( p = 0.94 \); group-day interaction \( p = 0.78 \)). The variable did not change significantly over time in either of the groups (main effect: cycle \( p = 0.71 \), day \( p = 0.21 \)).

When compared to the previous scores in patients with cancer, the depression score appears to be increased at the two-week point of cycle 4, but this was not statistically significant (Bonferroni adjusted \( p = 0.47 \)).

**Biomarker Differences**

No significant differences were found for the serum nighttime melatonin from cycles 1 and 4 between the patients with cancer and the control group. Figure 4 shows the mean serotonin levels for days 1 and 2 in cycles 1 and 4. No significant group-cycle-day interaction existed, but a group-cycle interaction (\( p = 0.048 \)) was present. The mean serum serotonin level was significantly lower in cycle 4 compared to cycle 1 (\( p < 0.001 \)) in the patients with cancer, but no corresponding difference was observed in the control group (\( p = 0.43 \)). When comparing mean serum serotonin between cancer and control groups, the patients with cancer, on average, had a significantly lower serum serotonin than the controls at cycle 4 (\( p = 0.009 \)), with no significant difference between the groups at cycle 1 (\( p = 0.19 \)). A downward trend was observed in serotonin levels from day 1–2 during each cycle in the cancer group; however, this was not statistically significant (\( p = 0.13 \)). The possible difference in day 1 and 2 levels during each cycle in the cancer group is not believed to be a result of the antiemetic ondansetron because the half-life of the drug is about six hours and the second serotonin level was drawn approximately 20 hours after administration of the antiemetic. Cortisol levels decreased significantly the day after chemotherapy (mean decrease: 1.0 ± 0.2 at 2 am, 2.6 ± 0.1 at 7 am; both \( p < 0.0001 \)) in the cancer group (\( p < 0.0001 \)) but not in the control group (\( p > 0.61 \)). During both admissions, a significant difference was found between the cancer and control groups at the 2 am and 7 am blood draws on day 3 (i.e., the day after chemotherapy) (\( p < 0.0001 \)). This was not a result of the administration of any prechemotherapy corticosteroids.

The bilirubin level decreased significantly between cycle 1 and 4 in the breast cancer group (0.309 ± 0.041 versus 0.205 ± 0.037; \( p = 0.018 \)), with no corresponding change in the control group (0.274 ± 0.053 versus 0.294 ± 0.043; \( p = 0.69 \)). The etiology of this finding is uncertain. However, because bilirubin is a component of the HPA regulatory process and is an indicator of hepatic function, it may be a precursor to fatigue and its related sleep disturbances and depressive symptoms.
Correlations Among Measures

Tables 2 and 3 give the Pearson correlation coefficient of the biomarkers with the self-reported total fatigue and depression scores, respectively, at cycles 1 and 4 for the cancer and control groups. From the data, the researchers found a significant correlation of serotonin with self-reported fatigue and of nighttime melatonin and bilirubin with depressive symptoms. From the linear mixed-model analysis and using data from the two cycles, a significant association of serotonin with the self-reported total fatigue score and depression score was observed. In the breast cancer group, a significant positive association was seen between the self-reported total fatigue score and daytime serotonin (p = 0.013) (see Figure 5), with no significant association observed in the control group (p = 0.83). In addition, a significant, positive linear association was found between the depressive symptoms score and daytime serotonin (p = 0.015) (see Figure 6). Although the data are not shown, a positive linear association existed between the fatigue score and hematoctrit (slope: 0.155 + 0.065 increase in fatigue score per one-unit increase in hematoctrit; p = 0.025).

Discussion

The current study provides preliminary data on changes in physiologic biomarkers (i.e., serum cortisol, melatonin, serotonin, and bilirubin) that occurred during four cycles of chemotherapy. The data begin to establish links among the biomarkers and the fatigue, sleep disturbances, and depressive symptoms experienced by patients with cancer who are undergoing adjuvant chemotherapy.

The results of the study demonstrate a statistically significant difference over time in fatigue, depressive symptoms, and (at certain times) sleep disturbances between subjects with breast cancer receiving adjuvant chemotherapy and the healthy controls who were matched by age, ethnicity, and menopausal status. The longitudinal study sheds some light on the effect of chemotherapy on the variables. First, patients with cancer were more fatigued than the controls before the beginning of chemotherapy; the difference persisted throughout the duration of the study and may have been caused, in part, by their recent surgery, which, on average, occurred three to four weeks prior to beginning treatment. However, other symptom correlates, including sleep disturbances and depressive symptoms related to the recent diagnosis of a potentially life-threatening disease, cannot be excluded. Because the patients had been rendered disease-free by surgery, an underlying malignancy could not account for the differences in fatigue. Interestingly, the magnitude of the fatigue in the patients with cancer did not progress from the first to the fourth cycle. Contrary to common perception, this finding implies a lack of cumulative effect from chemotherapy on patient fatigue. However, that observation may not be generalizable because this was a pilot study and the patients received only four cycles of chemotherapy, which may be an insufficient number to yield a cumulative fatigue-producing effect. The increase in fatigue scores at the two-week nadir is consistent with a reported peak in the myelosuppressive effect of chemotherapy during each cycle. Unfortunately, in the present study, laboratory tests to confirm the increase and to establish correlations with other biomarkers were not performed.

Similarly, depression scores differed between the two groups. The scores remained fairly constant over the course of the study; however, a trend was noted regarding an increasing

Table 2. Pearson Correlation Coefficients With the Fatigue Score

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<td></td>
<td>r</td>
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<td>r</td>
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<td>Baseline melatonin</td>
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<td>Bilirubin</td>
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<tr>
<td>Nighttime cortisol</td>
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<td>-0.54</td>
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<tr>
<td>Daytime serotonin</td>
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<td>-0.64*</td>
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* p < 0.05

Table 3. Pearson Correlation Coefficients With the Depression Score

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<td>Baseline melatonin</td>
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* p < 0.05
depression score in patients with cancer toward the end of chemotherapy. Perhaps the increased score is the result of patients who do not have to focus on the day-to-day process of “getting through chemotherapy” and instead have to contend with the rest of their lives, which can be daunting and disconcerting. The data provide an opportunity for intervention research with patients who have completed chemotherapy and may benefit from cognitive-behavioral therapy to prevent depression and the related symptoms of fatigue and sleep disturbances.

Equally important are the significant changes in biomarker levels over time and the correlations with fatigue, sleep disturbances, and depressive symptoms. Whether the correlations are causally linked is unclear. However, the preliminary results can serve as a platform for further study. Although the interest in cancer treatment-related fatigue and related symptom correlates has been great, little attention has been paid to biomarkers as possible explanations for fatigue mechanisms. This study is the first to examine select physiologic biomarkers over four cycles of adjuvant chemotherapy and explore the significance of the biomarkers with fatigue, sleep disturbances, and depressive symptoms. The preliminary findings suggest that the biomarkers change over time and may correlate with parameters of fatigue, sleep disturbances, and depressive symptoms. The findings also support previous research suggesting that fatigue is frequent and multifactorial in patients with cancer receiving chemotherapy (Cleeland, 2001; Jacobsen et al., 1999; Piper, 2003). Being described for the first time is the significant association of serotonin with self-reported total fatigue and depressive symptoms.

Implications for Practice

Although study results do not firmly establish causal relationships among all study biomarkers with fatigue, sleep disturbances, and depressive symptoms, the findings do indicate potential mechanistic actions among HPA axis biomarkers and the symptom cluster in women with stage II breast cancer. The study results are important to clinical practice because nurses and other healthcare providers can use the science of underlying HPA biomarkers in an effort to establish evidence-based practice for tailored symptom management interventions.

Selective serotonin reuptake inhibitors are the standard treatment for individuals with depression and presumably work on the premise that patients with depression have lower serotonin levels or an inability at the receptor level to maintain adequate levels. As a clinical example related to patients with cancer, if serotonin levels demonstrate a significant association with cancer treatment-related fatigue and depressive symptoms, this information provides a level of evidence that suggests that prescribed selective serotonin reuptake inhibitors may be appropriate for women experiencing fatigue, sleep disturbances, or depressive symptoms. Furthermore, if melatonin levels are positively associated with sleep disturbances, melatonin supplements or foods containing tryptophan (a precursor of melatonin and serotonin), such as turkey or bananas, may be prescribed in an effort to raise melatonin and serotonin levels. Additional research is needed in this area of symptom management.

Women with breast cancer benefit from prescribed exercise (Mock, 2004; Stricker, Drake, Hoyer, & Mock, 2004). Exercise is prescribed as an intervention for individuals with cancer-related fatigue, sleep disturbances, and mood disorders (Carlson et al., 2005). Research suggests that even mild to moderate exercise raises the levels of endorphins and serotonin (Caudell, 2000). Cortisol is a primary biomarker of the HPA axis that may mitigate stress, fatigue, and sleep disturbances (Payne, 2004; Sephton et al., 2000). The data help to explain a mechanism that may underlie the symptoms and provide a theoretical foundation from which to conduct intervention studies.

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