

The Trajectory of Fatigue in Adult Patients With Breast and Ovarian Cancer Receiving Chemotherapy

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Purpose/Objectives: To describe the trajectory of fatigue and determine the feasibility of exploring physiologic mechanisms of fatigue in adult patients receiving chemotherapy for breast and ovarian cancer.

Design: Descriptive, longitudinal, repeated measures.

Setting: Outpatient ambulatory cancer centers within two large, academic, teaching hospitals with overnight hospital stays in general clinical research centers.

Sample: Seventeen adult participants with either early-stage breast or ovarian cancer receiving chemotherapy for the first time.

Methods: Demographic questionnaire; Piper Fatigue Scale (PFS); hemoglobin, bilirubin, melatonin, and weight change were measured at baseline, three months, and approximately six months. PFS also was collected at three additional two-week nadir, post-treatment, measurement points. Descriptive statistics and repeated analysis of variance measures were used to analyze data.

Main Research Variables: Fatigue, hemoglobin, bilirubin, melatonin, and presence of other comorbid disease.

Findings: Subjective fatigue was experienced by the majority of patients receiving chemotherapy. It was irregular over time, intensified at three months, and continued after treatment ended. The physiologic trajectory of fatigue from baseline to three months indicated a significant change over time in hemoglobin in the breast cancer group ($p = 0.02$) and in nighttime melatonin levels for both breast and ovarian cancer groups ($p = 0.03$). Although not significant, daytime melatonin levels changed over time from baseline to six months.

Conclusions: Fatigue fluctuates during the course of chemotherapy treatment and does not cease after treatment ends. Preliminary findings suggest that fatigue mechanisms may have an undetermined physiologic basis.

Implications for Nursing: Assessment of cancer treatment-related fatigue must be ongoing, even after treatment ends. Findings suggest an awareness of the importance of understanding fatigue mechanisms to enable future testing of research-based interventions.

Fatigue is the most frequently reported side effect of cancer treatment, and some estimates report its occurrence in up to 100% of patients (Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Jacobsen et al., 1999). Interest in fatigue experienced by patients receiving cancer treatment has increased substantially in recent years. This heightened interest is consistent with literature reporting that fatigue remains the most common and distressing symptom

Key Points . . .

- ▶ Although early treatment of patients with breast and ovarian cancer has demonstrated increased cure and survival rates, therapy frequently results in short- and long-term effects, such as fatigue.
- ▶ Fatigue is experienced by the majority of patients receiving chemotherapy, intensifies during the course of treatment, and does not necessarily cease immediately after treatment ends.
- ▶ Patients with ovarian cancer experienced greater levels of fatigue than patients with breast cancer.
- ▶ Findings suggest that fatigue mechanisms may have an as yet undetermined physiologic basis.

experienced by patients with cancer receiving chemotherapy (Atkinson et al., 2000; Jacobsen et al.). Cancer treatment-related fatigue (CRF) is disruptive and can adversely affect quality of life and the optimal recovery course of patients receiving treatment (Broeckel et al.; Richardson, Ream, & Wilson-Barnett, 1998).

Although CRF occurs frequently, minimal research has been conducted to understand its mechanisms. Most studies of fatigue related to cancer treatment have focused on patients' subjective self-reported experiences, with a few studies measuring changes in fatigue over a course of repeated treatments (Jacobsen et al., 1999). The current study was designed to determine whether fatigue levels and select physiologic measures would change over time while subjects were receiving chemotherapy treatment and to examine fatigue mechanisms on a yet undetermined biophysiologic basis. Specifically, the purposes of this pilot study were to evaluate changes in levels of subjective fatigue in patients with early-stage breast and ovarian

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cancer receiving adjuvant chemotherapy over an approximate six-month period, examine changes in select physiologic variables, investigate the relationship between subjective fatigue and three posited physiologic variables (i.e., hemoglobin, bilirubin, and melatonin) over time, and determine whether the presence of comorbid disease affects the fatigue experience.

Literature Review

Early treatment of patients with cancer clearly has demonstrated increased cure and survival rates; however, therapy frequently results in short- and long-term consequences that affect patients' physical and psychosocial well-being. Fatigue is one such side effect. Despite 40%–100% of all patients with cancer reporting fatigue (Broeckel et al., 1998; Irvine, Vincent, Graydon, Bubela, & Thompson, 1994; Vogelzang et al., 1997), the lack of a clear definition or understanding of the fatigue phenomena has made investigation difficult. Nursing literature suggests that CRF is multifaceted and multidimensional (Nail, 1996; Piper, Lindsey, & Dodd, 1987; Richardson, 1995; Richardson et al., 1998). A variety of definitions have been described by researchers who characterize fatigue as a subjective feeling of increased discomfort with decreased functional status related to a decrease in energy (Irvine, Vincent, Bubela, Thompson, & Graydon, 1991; Pickard-Holley, 1991; Piper et al., 1987). More recently, Richardson and Ream (1997) defined fatigue as an unrelenting overall condition that interferes with individuals' ability to function in their normal capacity. According to Richardson et al., definitions of fatigue developed by other disciplines include physiology, which describes fatigue's affect on human muscle (Edwards, 1981); psychology, which defines fatigue through stress and emotions (Bartley, 1976); ergonomics, which views fatigue from a work performance perspective (Grandjean, 1970); and medicine, which focuses on the signs and symptoms of fatigue (Barofsky & Legro, 1991).

Etiology

Fatigue in people with cancer has been attributed to several possible mechanisms or etiologies, including sleep disturbances, biochemical changes secondary to disease and treatment, weight change, and internal and external environmental conditions (Piper et al., 1987; Winningham & Barton-Burke, 2000; Winningham et al., 1994). Accumulation of various metabolites has been proposed as one of the possible causes of fatigue. In patients with cancer, the accumulation of lactate

(Norris, 1982), hydrogen ions (Karlsson, Sjodin, Jacobs, & Kaiser, 1981), and cell destruction end-products (Haylock & Hart, 1979) has been suggested to be a likely mechanism for fatigue. These changes in energy production and substrates can profoundly influence human performance and the development of fatigue. Changes may result from abnormalities in energy expenditure (Ryden, 1977; St. Pierre, Kasper, & Lindsey, 1992); cancer cachexia by producing alterations in glucose, lipid, and protein pathways (Spiekerman, 1993; Tisdale, 1997); anorexia (Atkinson, 1985; Wilkes, 2000); infection (Straus et al., 1985; Valdin, Steinhardt, & Feldman, 1989); fever (Edwards et al., 1972; Puccio & Nathanson, 1997); and imbalances in thyroid hormones (Axelrod et al., 1983).

Other factors that may contribute to fatigue include oxygenation patterns, changes in regulation or transmission patterns, fluid and electrolyte imbalances affecting muscular strength, psychological patterns, and environmental, social, and life event patterns (Winningham & Barton-Burke, 2000). Oxygen available at the mitochondria level commonly can be affected by anemia. Anemia is defined as a blood hemoglobin concentration below 12 g/dl in women or below 13 g/dl in men (Beare & Myers, 1998). These normal values may vary slightly among individuals and depend on other factors such as altitude and hydration status of the individual. Although studies have not consistently demonstrated a positive correlation between anemia and fatigue, the level of oxygenation in the body remains a strong potential predictor of the occurrence of fatigue (Cella, 1998). Haylock and Hart (1979) suggested that a relationship exists between anemia and fatigue in patients receiving radiation therapy treatments. Several quality-of-life studies that examined anemia and fatigue have determined that the use of epoetin alfa can improve quality-of-life measures slightly (Del Mastro et al., 1997; Demetri, Kris, Wade, Degos, & Cella, 1998; Glaspy et al., 1997). Clinical observation and laboratory analysis provided data to hypothesize that bilirubin levels may be an additional, and potentially more accurate, indicator of fatigue than hemoglobin. Measurement of serum bilirubin can help to evaluate hepatobiliary and erythropoietic function of red blood cells associated with cancer treatment (Beare & Myers; Holmes, 2001). Thus, measurement of bilirubin must be considered a possible marker in the study of fatigue.

Factors Affecting Sleep Quality

Melatonin is an important regulator of the wake and sleep cycles and is the major secretory product of the pineal gland (Cupp, 1997). Because the circadian rhythm is regulated by

Table 1. Data Collection Schedule

Measurements	Prior to Receiving Chemotherapy (Initial Treatment)	Two-Week Chemotherapy Nadir	Three Months	Two-Week Chemotherapy Nadir	Six Months	Two-Week Chemotherapy Nadir
Piper Fatigue Scale (about 11 am)	X	X	X	X	X	X
Demographics and health history	X	–	–	–	–	–
Weight	X	–	X	–	X	–
Hemoglobin	X	–	X	–	X	–
Bilirubin	X	–	X	–	X	–
Melatonin 2 pm	X	–	X	–	X	–
Melatonin 2 am	X	–	X	–	X	–

Table 2. Demographic Characteristics of Sample

Characteristic	Frequency	
	n	%
Marital status		
Never married	2	12
Married	9	53
Divorced	4	23
Widowed	2	12
Education		
Completed grade school	4	23
Some high school	3	18
Completed high school	2	12
Some college	3	18
Completed college	3	18
Graduate school	2	12
Yearly income		
Less than \$10,000	5	29
\$10,000–\$19,999	2	12
\$20,000–\$29,999	2	12
\$30,000–\$39,999	2	12
\$40,000–\$49,999	2	12
\$50,000–\$59,999	1	6
\$60,000 or more	2	12
No answer	1	6
Ethnic heritage		
Caucasian	12	71
African American	–	–
Hispanic	4	23
Asian	–	–
Native American	1	6

N = 17

Note. Because of rounding, not all percentages total 100.

the normal production of melatonin and relates to the 24-hour rest and activity cycle that all individuals experience (Birdsell, 1996), fatigue may be adversely affected by the body’s production of melatonin. Melatonin production increases with darkness and decreases sharply with light; therefore, the natural wake and sleep cycles correspond with melatonin production and diminish with the onset of daylight and awakening. As a result, as melatonin production increases with darkness, sleep typically occurs. Reiter (1995) reported that although melatonin serum levels fluctuate throughout the nocturnal cycle, peak production occurs between 1–4 am.

Changes in sleep quality and timing associated with chemotherapy have been explored. Piper (1997) noted that women with breast cancer receiving adjuvant chemotherapy reported that they were sleeping and napping more by the third treatment. Berger (1998) investigated the relationship between fatigue and circadian rhythms of activity and rest in women with breast cancer during the first week of chemotherapy and confirmed that women who were less active during the day had more intense fatigue. Glaus (1993) found that potential differences exist between the circadian rhythm of fatigue in patients with cancer versus in healthy volunteers. Study findings revealed that healthy controls felt fit in the morning and tired in the evening, with increasing levels of fatigue over the course of the day. The profile was different in patients with cancer; fatigue was reported constantly, but it decreased in the evening (Glaus).

An abundance of literature exists exploring correlates of fatigue during and following various cancer treatment modalities. However, research focusing on mechanisms of CRF and understanding what effect potential physiologic markers may exert on fatigue has not been conducted. Furthermore, whether a correlation exists between physiologic and psychological markers of CRF has not been studied adequately. This pilot study was designed to explore areas of fatigue research that have not been studied adequately and to determine the feasibility of generating data supporting evolving knowledge that will help in understanding mechanisms of fatigue.

Methods

Design

A prospective, longitudinal, repeated-measures design was used to evaluate changes in levels of CRF, explore the relationship between subjective fatigue and three posited physiologic markers (i.e., hemoglobin, bilirubin, and melatonin) over time, and determine whether the presence of comorbid disease influenced the fatigue experience.

Sample

Seventeen female volunteers were recruited from two large academic tertiary cancer centers to participate in the study. They were 21 years of age and older, diagnosed with early-stage (stage II) breast or ovarian cancer, receiving chemotherapy for the first time, and without any documented cognitive impairment. The principal investigator obtained informed consent by discussing the necessity of being admitted to the hospital overnight to enable serum blood draws of the 2 am melatonin level following chemotherapy. National Institutes of Health (NIH) funding enabled utilization of the general clinical research centers (GCRCs) at both institutions to house the subjects overnight without cost to the subjects or their insurance companies. GCRCs are NIH-funded inpatient and outpatient nursing units with trained nursing, dietary, and laboratory staff to accommodate research studies requiring a controlled environment without cost to patients.

Instruments and Data Collection Procedure

The **Piper Fatigue Scale (PFS)** was used in this study and is comprised of 22 numerically scaled 0–10 items that measure four dimensions of subjective fatigue (i.e., behavioral/severity, affective meaning, sensory, and cognitive/mood). The standardized Cronbach’s alpha for the total and all subscale scores ranges from 0.91–0.98 (Berger & Higginbotham, 2000; Piper, 1997), indicating good reliability (Meek

Table 3. Chemotherapy Treatment Protocol

Cancer Type	n	Treatment Group	Average Length of Treatment (Months)
Breast	12	Doxorubicin/cyclophosphamide	4.25
Breast	1	Cytosol, methotrexate, 5-fluorouracil	6.5
Ovarian	4	Cisplatin based	7.5

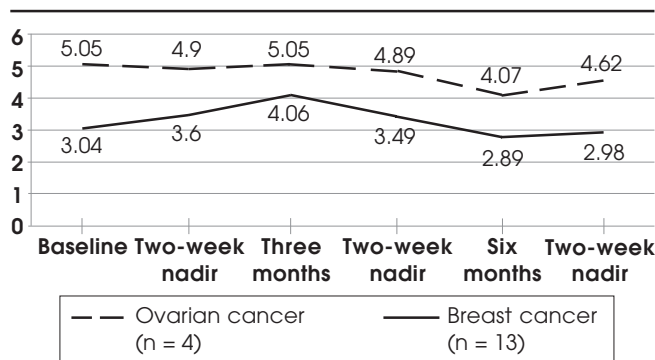


Figure 1. Total Fatigue Score Change Over Time

et al., 2000). A factor analysis with patients with breast cancer was performed to establish the instrument's validity (Piper et al., 1998). Data were collected at baseline, three months, approximately six months or the end of treatment (whichever came first), and three additional two-week nadir points. The PFS was completed by subjects between 11 am–1 pm at each subjective measurement point to ensure consistent timing of reported fatigue measures.

Hemoglobin and bilirubin values were obtained by routine hospital-approved laboratory methods prior to subjects receiving chemotherapy at baseline, three months, and approximately six months. Normal hemoglobin and bilirubin ranges in adult women are 12–15.5 g/dl and 0.1–1.2 mg/dl, respectively. Daytime melatonin serum levels were drawn by trained GCRC personnel, spun, aliquoted into labeled plastic vials, and frozen at -70°C per protocol established by the principal investigator in collaboration with GCRC scientific research and laboratory personnel. Nighttime melatonin serum samples were drawn and processed according to daytime procedure by GCRC RNs at 2 am during the night of hospitalization to capture the anticipated lowest level of melatonin production (Reiter, 1995). Table 1 provides an overall schematic data collection diagram.

Results

Sample

Patient demographics are described in Table 2. The majority of subjects with breast cancer received four cycles of doxorubicin and cyclophosphamide, and all subjects with ovarian cancer received a cisplatin-based chemotherapy regime. Table 3 summarizes the type and average length of treatment. Although four cycles of doxorubicin and cyclophosphamide typically end at three months, on several occasions low blood counts and transportation problems delayed treatment; thus, the average length of treatment for both groups was four to six months.

Subjective Fatigue

The trajectory of change over time in the subjective total fatigue scores for the entire sample, regardless of length of treatment, showed an increase in fatigue at the three-month measurement point (see Figure 1). However, total fatigue scores returned to near pretreatment scores by the six-month measurement point. Overall changes in subjective total fatigue scores were not significant. Of particular interest and documented for the first time is the finding that patients with

ovarian cancer reported greater total fatigue levels compared to patients with breast cancer.

PFS subscales were evaluated to determine whether any differences or inconsistencies were present between each of the subscales and the total fatigue score. All four subscales also demonstrated irregular patterns of fatigue over the course of treatment. Table 4 reports the means of all four subscales, reflecting the irregular and fluctuating levels of fatigue over time. The sensory subscore ($\bar{X} = 3.98$) was the most prominent dimension of fatigue that changed over time. Interestingly, the behavioral/severity subscore was the lowest ($\bar{X} = 2.53$). The affective meaning score ($\bar{X} = 3.08$) and cognitive/mood score ($\bar{X} = 3.23$) also changed over time; however, neither demonstrated statistical significance.

Physiologic Variables Associated With Fatigue

Three physiologic variables (i.e., hemoglobin, bilirubin, and melatonin) were measured at the three study points. Findings indicated changes in all three markers, with significant changes in hemoglobin and nighttime melatonin. The group of patients with breast cancer (see Figure 2) experienced a significant change in hemoglobin values from baseline to three months ($p = 0.02$). Bilirubin levels changed over time as demonstrated in Figure 3, and nighttime melatonin levels showed a significant change ($p = 0.03$) from baseline to three months for combined breast and ovarian groups (see Figure 4). Although not significant, daytime melatonin levels changed over time (see Figure 5). Because melatonin production typically is sparse during the day, the fact that daytime melatonin assay levels changed during the course of chemotherapy treatment is interesting. This research finding may hold promise as a potential mechanism and warrants further study.

The presence of other comorbid disease did not influence the fatigue experience in this patient population. However, with the exception of the diagnosis of early-stage breast or ovarian cancer, subjects had a fairly negative medical health history: One subject had glaucoma, another had diabetes mellitus, and a third had arthritis. The limited presence of comorbid disease made it difficult to draw any conclusions and remains an area that requires further study.

Discussion

In this preliminary research study, the researcher hypothesized that fatigue levels would change over time while subjects were receiving chemotherapy and that fatigue mechanisms may have a yet undetermined physiologic basis. Data results overall supported this emerging hypothesis, and preliminary information suggests that more research is needed to determine and understand fatigue mechanisms.

Table 4. Distribution of Sample on Baseline Fatigue Scores

Fatigue Scores	\bar{X} (SD)	Range
Total fatigue	3.21 (2.34)	0.45–9.4
Fatigue subscales		
Behavioral/severity	2.53 (2.71)	0–9.3
Affective meaning	3.08 (2.71)	0–8.8
Sensory	3.98 (2.68)	0–9.8
Cognitive/mood	3.23 (2.17)	1–9.6

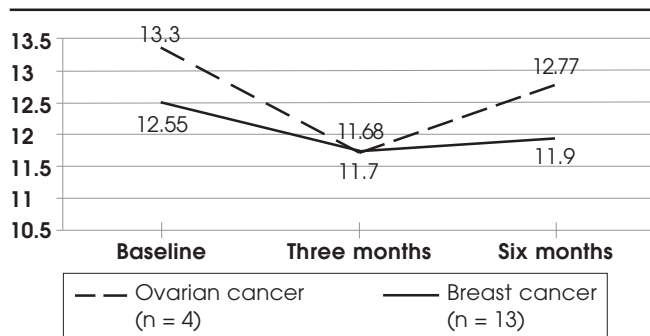


Figure 2. Hemoglobin Change Over Time

Demonstrating the highest scores, the sensory PFS subscore may provide an explanation and rationale for the terms frequently used by patients with cancer receiving chemotherapy to describe fatigue (e.g., heaviness, bushy, numb). According to Ferrell, Grant, Dean, Funk, and Ly (1996), these descriptors portray subjective feelings stemming from the senses and reflect intensity.

Results from this study correspond with findings of other studies of fatigue in patients with cancer (Berger, 1998; Greene, Nail, Fidler, Dudgeon, & Jones, 1994; Richardson et al., 1998) and lend further support to the belief that varying levels and patterns of fatigue occur in patients receiving chemotherapy. Richardson et al. reported various patterns of fatigue throughout the day, which occurred more frequently in the afternoon and early evening in patients receiving chemotherapy. Although these findings underscore the reported fluctuation in patterns and levels of fatigue with individual study samples, why such variation was found among groups is not clear.

The current study's results run counter to the common perception held by many healthcare providers that fatigue increases at a steady rate over the course of chemotherapy treatment and diminishes after completion of the course of treatment. The difference in reported fatigue may be attributed to the type of chemotherapy received. With the exception of one subject, patients with breast cancer received a doxorubicin and cyclophosphamide protocol, whereas all patients with ovarian cancer received a cisplatin-based protocol. However, perhaps the difference in reported fatigue was caused by a prediagnosis tumor, difference in surgical procedure, or

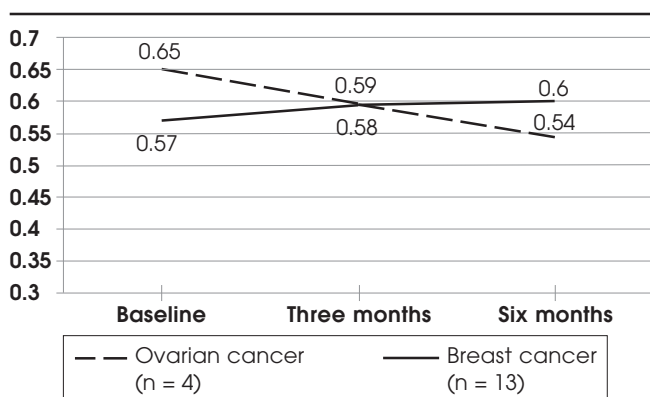


Figure 3. Bilirubin Change Over Time

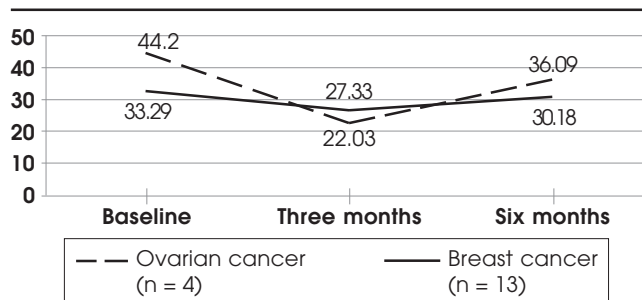


Figure 4. Nighttime Melatonin Change Over Time

other unexplained individual metabolic differences. Additional research is needed to further extrapolate and discriminate potential differences in fatigue mechanisms.

Several possible explanations exist regarding why correlations between the three physiologic variables and subjective fatigue scores were not significant. The PFS is a subjective measure of fatigue and may not capture the "moments" of fatigue experienced at any given time in this patient population. Moreover, the PFS may not be sensitive to the regulatory and metabolic changes that contribute to the fatigue experience. The possibility exists that metabolic changes may influence the fatigue phenomena that, in turn, affect subjective measurement.

The validity of the PFS to measure fatigue is considered to be good; however, other unknown factors may affect the ability of the instrument to measure changes over time in this adjuvant patient population. Interestingly, the low mean of the behavioral/severity subscore may be because the instrument is not sufficiently sensitive to determine the level of severity in this adjuvant treatment population. Subjects also may have adjusted their frame of mind, and their "set points" of fatigue may have changed over the course of diagnosis and treatment modalities. According to Berger (1998), an artificial "ceiling" may exist within the scoring of the PFS. Although the PFS has been used frequently in oncology research studies, what the total PFS score and four subscores actually mean is not consistent across the studies. In this study, many of the reported fatigue scores ranged from 3–5, yet what a "3" means has not been demonstrated. If scores typically range from 1–5, 5 may indicate a high level of fatigue, whereas in a 1–10 Likert range, a score of 5 would imply moderate fatigue. Finally, researcher-conducted studies using the PFS have not always clarified the stage of cancer and treatment protocols when describing and reporting fatigue scores. This makes it difficult to compare fatigue levels from one study to another if

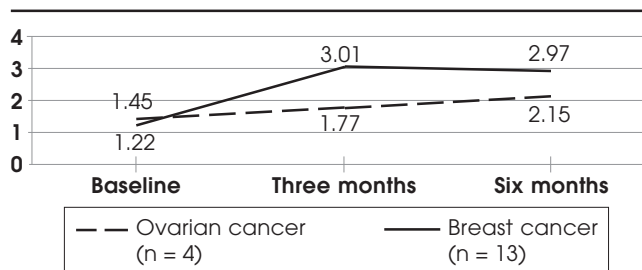


Figure 5. Daytime Melatonin Change Over Time

the stage of cancer and treatment protocols are different within the patient population being studied.

Although preliminary, these findings generate new information to support the need for continued study in the area of understanding physiologic mechanisms of CRF. Also, discriminating levels of fatigue and physiologic changes reported in one cancer group compared to fatigue in a different diagnostic group of subjects with cancer is important.

Limitations

Some limitations are present in this pilot study; for example, the study was small and lacked comparison with a volunteer group. The small sample size may have limited the ability to detect subtle changes in the fatigue scores and hemoglobin, bilirubin, and melatonin levels being studied and may have affected data analysis results.

Implications for Nursing

Preliminary data from this study have generated some implications for clinical practice. This study is the first to document increased fatigue levels in patients with early-stage ovarian cancer when compared with patients with early-stage breast cancer receiving chemotherapy. Findings support the growing body of research demonstrating that fatigue is disruptive, fluctuates during treatment, and does not necessarily cease when treatment ends. Significant changes in hemoglobin levels and nighttime serum melatonin radioimmunoassay levels at the three-month measurement in this patient population were reported for the first time. An unexpected finding documented that daytime melatonin increased from baseline over time and remained higher throughout the six-month duration of the study. Moreover, a change in total bilirubin levels over time while subjects received chemotherapy also was noted for the first time.

These data provide emerging information to support the hypotheses that fatigue levels change over time during che-

motherapy treatment and perhaps, more importantly, that fatigue mechanisms may have a yet undetermined physiologic basis. Providing clinicians with the scientific rationale to provide a possible physiologic basis for CRF offers a measure of relief and hope to healthcare providers and patients who are experiencing fatigue but do not know why or how to discriminate among possible interventions. Understanding mechanisms may empower patients and substantiate the notion that fatigue is real and not just an obscure sensation or feeling of their imagination.

Although many CRF investigations substantiate the need to determine possible mechanisms of fatigue, few studies have addressed this area of research. This knowledge gap in the fatigue literature must be resolved as clinicians increasingly seek to base interventions and care of patients with cancer on research-based evidence. Data generated from this study provide a beginning for future studies. Recommendations for future research include designing fatigue studies that correlate psychological variables, physiologic variables, and sleep quality and patterns among different oncology populations. Additional research is needed on physiologic biomarkers of fatigue that may help to explain further mechanisms of CRF. The fatigue mechanisms experienced by patients with breast and ovarian cancer may have a different mechanism than those experienced, for example, by patients with lung or colon cancer. Also, if mechanisms do differ from one patient population receiving treatment to another, perhaps optimal interventions for CRF should be tailored to fit individual populations. By studying potential physiologic mechanisms while defining the patient population being studied, knowledge will be generated regarding which future intervention studies should be developed and tested.

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For more information . . .

- Y-ME National Breast Cancer Organization
www.y-me.org
- National Breast Cancer Coalition
www.natlbcc.org
- Breast Cancer Action
www.bcaction.org

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