PATTERNS OF FATIGUE AND FACTORS INFLUENCING FATIGUE DURING ADJUVANT BREAST CANCER CHEMOTHERAPY

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TITLE

Patterns of Fatigue and Factors Influencing Fatigue

During Adjuvant Breast Cancer Chemotherapy

BY

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Women beginning adjuvant chemotherapy for breast cancer seek information from health professionals regarding fatigue, but knowledge regarding this distressing symptom is currently limited. The purposes of this study were to describe the patterns of fatigue and of factors influencing fatigue across the first three cycles of chemotherapy and to determine the extent to which health and functional status, chemotherapy protocol, physical activity behaviors, activity/rest cycles, nutrition behaviors and status, stress management behaviors, interpersonal relations behaviors, symptom distress and reaction to the diagnosis of cancer explain fatigue at each treatment and predict fatigue at the mid-point of the first three chemotherapy cycles. A model drawn from Piper's framework (1987) guided this prospective, descriptive, repeated measures design study. Data collection included: Background data, Piper Fatigue Scale, MOS-SF-36, Health-Promoting Lifestyle Profile II, wrist actigraph, hematocrit, body mass index, Modified Symptom Distress Scale and Reaction to the Diagnosis of Cancer Questionnaire. Descriptive statistics, paired t-tests, simple and repeated measures ANOVA, cosinor and path analyses were used. In this sample of 60 women, total fatigue and its 4 dimensions and severity of symptoms distress fluctuated significantly from higher levels at treatment times to lower levels at cycle mid-points, with activity/rest cycles varying in an inverse pattern. Fatigue was explained at treatment times

(R^2=.52-.71) by symptom distress (ß=.54-.62), chemotherapy protocol (ß=.32) and interpersonal relations behaviors (ß= -.40) and predicted at cycle mid-points (R^2=.45-.60) by symptom distress at the time of treatments (ß=.33-.43), physical function status (ß=-.39), general health (ß=-.32) and reaction to the diagnoses of cancer (ß=-.39). Higher perceived fatigue levels were associated with lower daytime activity indicators and high levels of night-time awakenings at various times. Women can be instructed to monitor fatigue intensity and to expect the patterns of fatigue to be similar during the first three chemotherapy cycles. These findings provide a foundation for future intervention studies aimed at modification of fatigue.

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CHAPTER 1

INTRODUCTION

Over the last 20 years, cancer diagnostic methods, treatment patterns, and mortality rates have changed dramatically (American Cancer Society, 1996). Advances in science have resulted in the development of methods for earlier detection of a variety of types of cancer, including mammography for breast cancer. There also has been increased use of multi-modal therapy in an attempt to improve long-term survival rates. One large group of long-term cancer survivors who often receive multi-modal treatment is women with stage I or II breast cancer. However, combined treatment modalities (surgery, radiation and chemotherapy) exert a substantial multidimensional toll on the women who receive them (Institute of Medicine, 1993). In response to more intensive treatments, there has been increased emphasis by health-care providers and health economists on determining the change in the behavioral functioning or well-being of individuals from prior to diagnosis through treatment and beyond the traditional disease end-points.

With approximately half of the over one million persons diagnosed with cancer each year now living for 5 years or more (Mayer & O'Connor, 1989), a major component of survivorship is rehabilitation of the individual with cancer, beginning at the time of diagnosis (Watson, 1990). Women with early stage breast cancer make up a large percentage of these survivors, with 5-year survival rates for stage I greater than 90%, and for stage II greater than 70% (American Cancer Society, 1996). However, long-term survivors from breast cancer report many physical, psychological, and social sequelae related to decreased energy (Fobair,

et al., 1986; Polinsky, 1994). These effects are being experienced by more and more women each year.

The number of cases of breast cancer is increasing in all sectors of society, with over 180,000 cases diagnosed in 1995, and projections that approximately one in eight American women will experience breast cancer during their lifetime (Miller, et al., 1994). As more women experience and survive breast cancer, discovery of the impact of the disease and treatment on women's lives is essential in order to provide rehabilitative efforts focused on improving the well-being of this group of cancer survivors. Women who have experienced treatment for breast cancer are also joining forces and speaking out in loud voices at the local, state and national level to promote research efforts to control breast cancer and its related sequelae. A managed care environment will challenge all health care professionals to provide efficient services that promote wellness and decrease use of medical professional services for chronic symptom distress.

Adjuvant chemotherapy is frequently prescribed for women with early stage breast cancer in an attempt to eradicate or arrest occult micro-metastatic disease and increase the disease-free survival figures (Goodman, 1991). Patients who have received adjuvant chemotherapy for breast cancer have reported long-term effects on general activity level and physical symptoms (Silberfarb, Maurer & Crouthamel, 1980). Assistance for breast cancer survivors who receive multi-modal treatments should expand beyond American Cancer Society's "Reach to Recovery" program and other support groups. Recent developments in scientifically-based symptom management interventions to control nausea have resulted in improved levels of health and functional status during treatment and increases in the use of

out-patient clinics for treatment. Interventions also need to be developed that assist in the management of acute fatigue, prevent the development of chronic fatigue, and promote well-being in this ever increasing population (Institute of Medicine, 1990). Identification of patterns, correlates and predictors of fatigue will assist health care team members in designing appropriate interventions to modify this distressing symptom.

Fatigue is a universal human experience that occurs on a continuum ranging from tiredness to exhaustion. Scientists have investigated the multi-dimensional concept of fatigue since the early 1900's, but theory regarding the physiological, biochemical, and behavioral mechanisms of the phenomenon still is very limited. Although fatigue is clinically significant, its complex nature and etiology have discouraged researchers who have examined the concept. The resulting lack of research, from which theories can be developed, has hampered investigators interested in the study of fatigue in patients with cancer (Tiesinga, Dassen, & Halfens, 1996; Winningham, et al., 1994).

Fatigue is the most common and disturbing symptom complaint resulting from cancer therapies: it is reported by 60-100% of patients receiving treatment (Graydon, 1994; Irvine, Vincent, Bubela, Thompson & Graydon, 1991b; Richardson, 1995). Scientists do not agree on the definition of fatigue, and it is not known how subjective perceptions may be related to physiological indicators (Winningham, et al., 1994). Much of the difficulty in defining, assessing and managing fatigue arises from lack of precision arising from its nature as a private, subjective sensation with multidimensional influences (Hegyvary, 1993; Pearce & Richardson, 1994). The development of a body of relevant knowledge related to fatigue has also been restricted by the absence of longitudinal design studies, by the use of

unidimensional measurements, and by the inability to examine and compare findings across studies. Fatigue commonly precedes, accompanies, or follows many malignancies and may limit participation of clients in research protocols, again inhibiting knowledge building (Piper, Lindsey, & Dodd, 1987). Interventions to prevent or reduce the development of chronic fatigue problems secondary to primary treatment of breast cancer are needed, but first, patterns of and factors influencing acute fatigue need to be described.

Within a model derived from the works of Piper, Lindsey and Dodd (1987), Walker, Sechrist and Pender (1987), McCorkle (1987) and Frank-Stromborg (1989), this study describes patterns of and factors influencing fatigue among women newly diagnosed with Stage I or II breast cancer during adjuvant chemotherapy. Development and evaluation of this model will provide direction for future studies that examine factors influencing fatigue.

Conceptual Framework

The conceptual model for this study, shown in Figure 1, is drawn heavily from Piper's integrated fatigue model (IFM) for the conceptualization of fatigue in healthy and clinical populations (1987). While various theories have been proposed to explain fatigue's etiology, the actual factors that produce fatigue are unknown and merit examination (Piper et al, 1987). Piper's IFM, which appears in Appendix A, synthesizes the fatigue literature in healthy and clinical populations to generate nursing theory about fatigue in cancer patients. It includes 13 biochemical, physiologic, and psychosocial patterns believed to be the factors most likely to influence fatigue. Disease, treatment, symptom, activity/rest, energy and energy substrate, psychological, and social patterns from the model were selected for

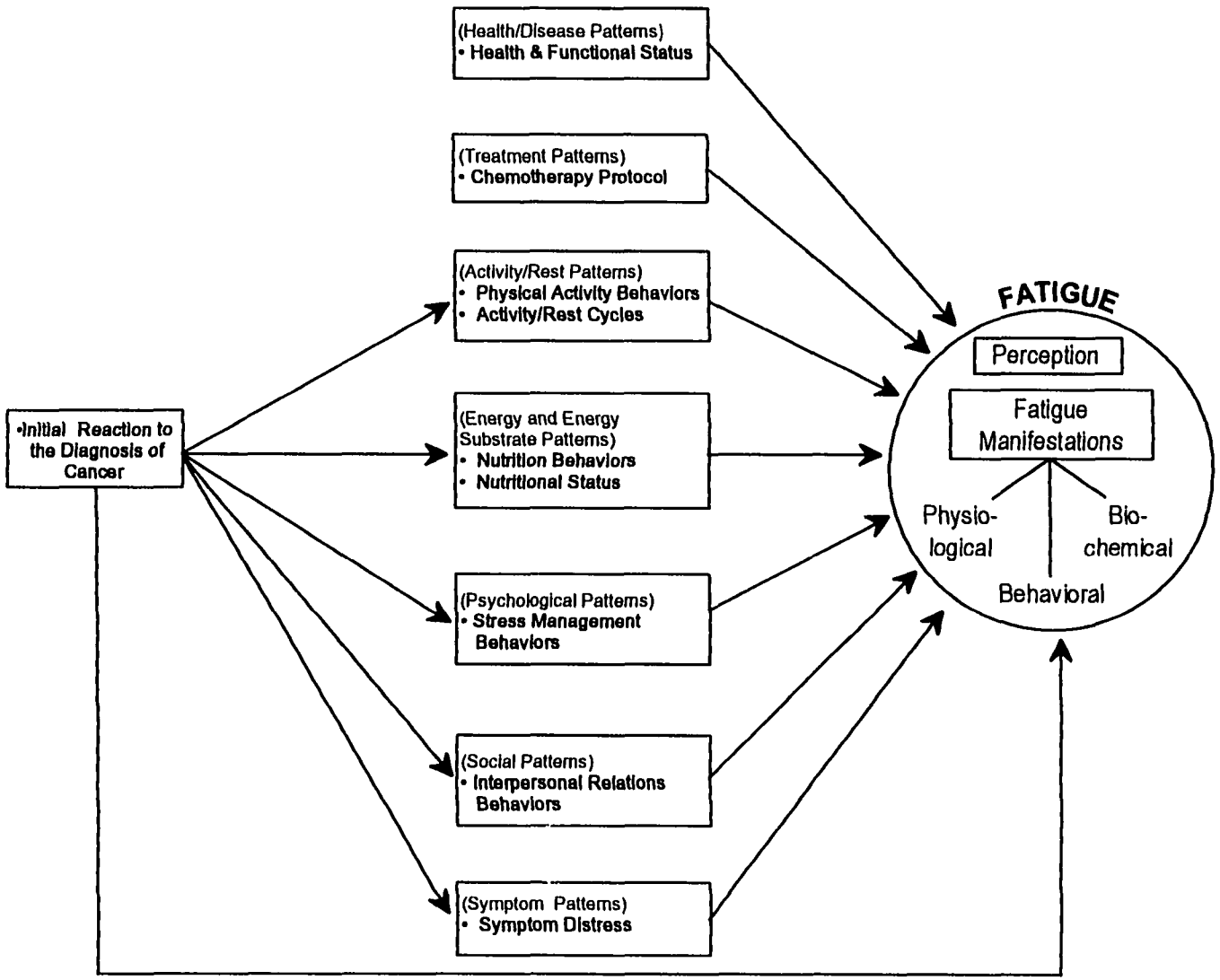


Figure 1. Conceptual model for the study of factors influencing fatigue experienced by Stage I or II breast cancer patients receiving chemotherapy.

examination in this study. A strength of the IFM framework is its utility to researchers in guiding investigations that examine factors related to fatigue (Winningham et al, 1994).

Figure 1 displays the temporal sequence of variables examined. Initial reaction to the diagnosis of cancer as well as seven patterns drawn from Piper's IFM (shown in parentheses) are proposed to directly influence fatigue among women newly diagnosed with stage I or II breast cancer. Initial reaction to the diagnosis also is proposed to influence fatigue indirectly through its influence on selected health-promoting lifestyle behaviors, activity/rest cycles, nutritional status and symptom distress. The seven factors drawn from Piper's IFM are represented in this study by the variables shown in bold print in the center column on the model. The disease pattern from the Piper IFM has been renamed the health/disease pattern for this study to reflect a broader scope of perceived overall health and functional status rather than a particular stage or pattern of disease as described by Piper, et al., (1987). Treatment patterns are represented by the chemotherapy protocols [those with and without intravenous Adriamycin (doxorubicin) and Cytoxan (cyclophosphamide)]. Symptom patterns are represented by the perceived severity of symptoms previously identified as most distressing to women receiving adjuvant breast cancer chemotherapy treatments. The remaining four factors (physical activity behavior, nutrition behavior, stress management behavior and interpersonal relations behavior) are dimensions of a health-promoting lifestyle (Walker, et al., 1987; Walker & Hill-Polerecky, 1996).

Health-promoting lifestyle has been defined as "a multi-dimensional pattern of self-initiated actions and perceptions that serve to maintain or enhance the level of wellness, self-actualization, and fulfillment of the individual" (Walker, et al., 1987, p. 77). Health-

promoting behavior is directed toward sustaining or increasing an individual's level of well-being as opposed to decreasing the probability of disease (Pender, 1982). This positive approach to living may assist individuals in maintaining and improving health status during and after treatment for breast cancer. Involvement in health-promoting behaviors such as physical activity, nutrition, stress management, and positive interpersonal relations offer strong potential for well-being in ambulatory cancer patients; these dimensions are similar to the dimensions of high level wellness described by Travis and Ryan (1988) and Ardell (1986).

A health-promoting lifestyle has been identified as an important component of living with a chronic disease (Miller, 1982). Health-promoting strategies have been found to be vitally important to reducing the risk of secondary disabilities, promoting reintegration into the community, and maintaining quality of life of disabled persons, and were more likely to occur among females (Lusk, Kerr, & Ronis, 1995; Marge, 1988; Stuifbergen & Becker, 1994). Frank-Stromborg, Pender, Walker, and Sechrist (1990) have drawn attention to the importance of health-promoting lifestyle behaviors as major self-care components among ambulatory cancer patients. Women with cancer who have control over their lifestyle behaviors may be able to use them to control symptoms such as fatigue and to improve their quality of life.

A series of studies on the activity patterns of cancer patients provide a model for research demonstrating the influence of one dimension of the health-promoting lifestyle behavior profile on symptom distress (MacVicar & Winningham, 1986; Winningham & MacVicar, 1988; MacVicar, Winningham & Nickel 1989; and Winningham, MacVicar,

Bondac, Anderson & Minton, 1989). The investigators reported improvement in functional capacity and mood, and reduction in nausea and weight gain associated with a 10-week, three times a week, moderate intensity aerobic exercise program during treatment for early stage breast cancer. Fatigue was not examined in those studies. The limited number of studies suggest the need for further examination of the health-promoting lifestyle behaviors as factors influencing fatigue in women with breast cancer.

Fatigue has been proposed as the common denominator of symptom distress in cancer patients (McCorkle, 1987, Morris, 1982). Fatigue appears to present not only as a primary symptom, but as a secondary symptom accompanying other distressing sensations such as nausea, insomnia, negative mood, and pain (Blesch et al. 1991; Ehlke, 1988; McCorkle and Young, 1978; & Winningham, 1992). Further study of the relationship between patterns and severity of distressing symptoms and fatigue is needed to identify and modify correlates of fatigue in early stage breast cancer.

Frank-Stromborg (1989) has suggested that the initial reaction to the diagnosis of cancer may be helpful or detrimental to adaptation during treatment and beyond. In a long term study of women with early stage breast cancer, Pettingale, Morris, Greer and Haybittle (1985) found significant differences in survival at 5 and 10 years when the women were compared by their recall of (3 months post-operative) impressions of their reaction to the diagnosis of cancer. Women with a reaction of denial or a fighting spirit also had a more favorable outcome than did those who showed a stoic acceptance or helpless/hopeless response.

Frank-Stromborg, et al. (1990) reported that the confronting dimension of the reaction to the diagnosis of cancer emerged as a strong predictor of a health-promoting lifestyle, and suggested that a health-promoting lifestyle might be an intervening variable between reaction to the diagnosis of cancer and adjustment to cancer and survival. This result supports the importance of a cancer specific cognitive/perceptual variable in explaining the occurrence of health enhancing behaviors among ambulatory cancer patients. The relationship of reaction to the diagnosis of cancer to fatigue directly or indirectly through its influence on health-promoting lifestyle has not been examined. The style of reaction to a diagnosis of cancer may also influence perceptions of the presence and severity of distressing symptoms, and this relationship warrants examination.

With an increasing number of cancer survivors and emphasis on health promotion at all points along the wellness-illness continuum, examination of the value of a health-promoting lifestyle in modifying fatigue experienced by individuals being treated for early breast cancer is warranted from both the quality of life and cost containment perspectives. Study results can identify behaviors of most influence on fatigue, and assist in targeting areas for intervention that are both effective and cost efficient.

Purpose

The purpose of this study was to describe patterns of and factors influencing fatigue among women newly diagnosed with stage I or II breast cancer during adjuvant chemotherapy. The following research questions were addressed:

1. What are the patterns of fatigue and of selected factors influencing fatigue among women with stage I or II breast cancer across the first three cycles of chemotherapy?

2. To what extent do health and functional status, chemotherapy protocols, physical activity behaviors, activity/rest cycles, nutrition behaviors and status, stress management behaviors, interpersonal relations behaviors, symptom distress patterns and reaction to the diagnosis of cancer explain fatigue 48 hours after each of three chemotherapy treatments?
3. To what extent do health and functional status, chemotherapy protocols, physical activity behaviors, activity/rest cycles, nutrition behaviors and status, stress management behaviors, interpersonal relations behaviors, symptom distress patterns and reaction to the diagnosis of cancer predict fatigue at the midpoints of each of three chemotherapy treatment cycles?

Significance

Cancer is a catastrophic disease causing physical and psychological changes over time that increasingly challenge the person's ability to function as a normal social being (McCorkle & Quint-Benoliel, 1983). The experience of breast cancer involves receiving prescribed therapies, symptom management, and challenges to body image. A woman's experience with breast cancer and its treatment is believed to influence many aspects of her daily life in terms of health habits, attitudes, and feelings about herself. The breast cancer experience may change a woman's future behaviors, her self-image, and the way she views the world (Nelson, 1991). Frank-Stromborg (1986) defined health as the realization of fullest human potential, a condition which is not negated by cancer. Having cancer and being healthy can be compatible. Ardell (1986) states that there is a healthy way to experience a disease as well as a constantly challenging way to remain healthy.

Women with breast cancer and their families seek the assistance and expertise of oncology nurses and the multi-disciplinary team to survive this challenge and maintain health and functional status during and after treatment. Brief out-patient chemotherapy treatments limit the interaction time between nurses and patients, and management of symptoms with pharmacologic interventions often dominate patient education and discussions. Women currently need to seek out information on management of fatigue. Nurses currently lack scientifically based instructions regarding strategies, and therefore use folklore as a basis to manage this distressing symptom.

In 1991, the Oncology Nursing Society (ONS) conducted a survey of research priorities, and respondents consistently identified symptom management and quality of life (QOL) as the highest priority areas for research to be conducted (Mooney, Ferrell, Nail, Benedict & Haberman, 1991). Research to improve symptom management was also among the priority psychosocial areas identified in 1993 by a survey sponsored by the Institute of Medicine (IOM). Efforts directed toward further understanding of fatigue will contribute to meeting objectives identified by both ONS and the IOM, and improve patient-focused outcomes.

Fatigue is the most common symptom complaint resulting from cancer therapies. If not successfully managed, fatigue may become chronic and have long lasting negative effects on many aspects of survivors' lives (Irvine, et al, 1991b). Despite the frequency of this disturbing complaint, the health care team currently lacks effective interventions to reduce fatigue's impact on the individual (Winningham et al, 1994). Clinical research is needed that will expand the knowledge base regarding the patterns of and factors influencing fatigue.

Modification of acute fatigue may reduce interferences with role functioning during and after treatment in an ever increasing number of cancer survivors.

Health-promoting lifestyle behaviors theoretically offer promise in reducing perceived fatigue and increasing well-being from the onset of cancer treatment, but research on this aspect of survivorship has not yet been reported (Berger, 1995g). Research in the 1970's focused on improving survival rates from cancer and in the 1980's began to examine the quality of life of survivors. Researchers in the 1990's have also focused attention on modification of symptom distress related to treatment. Results from this study may guide future investigations focused on adoption and maintenance of health-promoting lifestyle behaviors as interventions aimed to modify fatigue experienced by women with breast cancer during and after chemotherapy in order to reach desired clinical outcomes.

The American Cancer Society recommends a variety of health-promoting behaviors to prevent cancer (Reardon and Aydin, 1993). However, little is known about the health-promoting lifestyle behaviors of patients with cancer who are treated with the intent of cure. Reardon and Aydin explored factors that might influence cancer patients to make health-promoting changes in their own behavior. They found that coping strategies are significant predictors of changes in stress level, diet, and mental outlook, and that patient attitudes concerning responsibility for recovery contribute to positive changes in exercise. Simmons (1993) examined health-promoting lifestyle behaviors of healthy Navy personnel and determined that all six dimensions, plus overall health-promoting lifestyle, were strongly associated with a more positively perceived health state. Adoption of health-promoting

lifestyle behaviors offers potential benefit to improve adaptation and promote a more positive perception of health-status among women with breast cancer.

Assumptions

The following assumptions were made as a basis for this study:

The first assumption is that the subjects receiving intravenous chemotherapy were capable of quantifying the intensity of subjective fatigue on paper and pencil tests. Piper, Lindsey, Dodd, Ferketich, Paul, & Weller, (1989a) found that the Piper Fatigue Scale generated a full range of scores from participants.

The second assumption is that fatigue experienced after chemotherapy treatments has temporal characteristics. Some evidence is available to support this assumption. Berger found fluctuating levels of fatigue reported by women with breast cancer throughout the day for several days after receiving chemotherapy (1995b). Piper et al, (1987) included the temporal dimension in their definition of fatigue after an extensive review of the literature. In the current study, instruments were completed during the same 4-hour block of time each day. Data were collected approximately 12 hours after the mid-point of the previous night's sleep on the same day of each chemotherapy cycle in an attempt to control for extraneous temporal variability in fatigue perception measurements.

The third assumption is that individuals may under-report symptoms such as fatigue over time. Breetvelt & Van Dam (1991) reported that cancer patients may unconsciously under-report the intensity of symptoms as a result of shifting their set-point. Subjects were instructed to compare their current status at all time points to their baseline (recall of prior to diagnosis) status in order to decrease the likelihood of a response-shift over time. The

fourth, and related assumption, is that individuals can validly compare present status to baseline values.

Limitations

Limitations of this study included sampling bias, response set bias, and issues related to actigraphs. There were several sources of sampling bias. In recruiting subjects to participate in a longitudinal research study that began approximately 4 weeks after breast cancer surgery, those who were more likely to experience a higher intensity of fatigue may have declined to participate or dropped out during the study. Feelings of being overwhelmed by the diagnosis and treatment may have carried over during the treatment period and led to emotional exhaustion, but data from such women who declined or dropped out were not captured. There also may have been a self-selective drop out rate among those with higher levels of fatigue and lower levels of support.

Response set bias was another potential limitation of this study, since self-report instruments were utilized. Respondents may have underestimated or overestimated responses for a variety of reasons. Some individuals may have misrepresented their attitudes by giving responses that were consistent with prevailing social mores (Polit & Hungler, 1987). In an attempt to minimize this limitation, subjects were advised that there were no right or wrong answers, and that their honest evaluation was requested. Data also were examined for outliers that may reflect underestimates or overestimates of true responses.

Operation of the actigraphs was another potential limitation to the study, since pilot study experiences revealed certain limitations of the instrument. Actigraphs are devices worn on the wrist that monitor and record body movement over time. Some actigraphs fail to

activate, despite routine procedures. Batteries may not last until the actigraph has been downloaded. Women may decide to take the actigraph off at any point during the monitoring, limiting the amount of data retrieved. Women may have behaved differently with the actigraph on than they would have if it was not monitoring their activity.

Definitions

For the purposes of this study, variables were conceptually and operationally defined as follows:

Fatigue

Fatigue was defined as "a subjective feeling of tiredness that is influenced by circadian rhythm and can vary in unpleasantness, duration, and intensity" (Piper, et al, 1987, pg. 19). In contrast to tiredness, "subjective fatigue is perceived as unusual, abnormal, or excessive whole-body tiredness disproportionate to or unrelated to activity or exertion" (Piper, 1993a, pg. 286). Fatigue may be acute or chronic, is not dispelled easily by sleep or rest; and may have a profound negative effect on the person's well-being and quality of life. Fatigue was measured by the Piper Fatigue Scale (Piper, Dibble, & Dodd, 1996), which appears in Appendix B.

Health and Functional Status

Health and functional status was defined as the subjective assessment or evaluation of one's current state of well-being and ability to perform customary or expected roles. Health and functional status was measured by the physical functioning, role-physical, general health, social functioning, role-emotional, and mental health scales of the Medical Outcomes Study

Short-Form Health Survey (MOS-SF-36) (Ware & Sherbourne, 1992) which appears in Appendix C.

Chemotherapy Protocol

Chemotherapy protocol was defined as the selection of one of three current standard regimens of adjuvant anti-neoplastic drug treatments given to women with Stage I or II breast cancer. These included: 1) 21 or 28-day cycles of Cyclophosphamide, Methotrexate, and 5-FU (CMF); 2) 21 day cycles of Adriamycin and Cyclophosphamide (A/C); and 3) 28 day cycles of Cyclophosphamide, Adriamycin and 5-FU (CAF)). While the number of cycles of treatment varied from 4 to 6, this study was limited to the first three cycles of each regimen in order to reduce likelihood of dropouts and understand the patterns in the early stages of treatment. An index of chemotherapy protocols was developed for use after consultation with oncologists caring for women with early breast cancer. When examinations involve symptom distress and fatigue in this study, protocols were divided categorically as regimens with and without intravenous Adriamycin and Cytoxan. When examinations involve activity/rest patterns and fatigue, the categories remain the same but are reported in a manner consistent with previous reports as non-Adriamycin versus Adriamycin-based regimens. Protocols and categories appear in Appendix D.

Physical Activity Behavior

Physical activity behavior was defined as "regular participation in light, moderate and/or vigorous activity. It may occur within a planned and monitored program for the sake of fitness and health and/or incidentally as a part of daily life or leisure activities" (Walker & Hill-Polerecky, 1996). Physical activity behavior was measured by the physical activity

subscale of the Health-Promoting Lifestyle Profile II (HPLP-II), which appears in Appendix E.

Activity/Rest Cycles

Activity/rest cycles were defined as the indices that reflect motion within each 24-hour period. These cycles were measured using the wrist actigraph, from which a variety of sleep/wake cycle variables were calculated including mesor, amplitude, mesor plus amplitude on day 3 (Day high 3) and night-time awakenings (Brown, Smolensky, D'Alonzo & Redman, 1990). Mesor was defined as the rhythm-determined average value that may equal the calculated mean activity over time. Amplitude was defined as the amount of difference from the mesor at the time of the peak or the trough of the cosine curve, indicating the extent of a rhythmic change (Farr, Campbell-Grossman & Mack, 1988). Day high 3 was defined for this study as the sum of the mesor and the amplitude for a 24-hour period approximately 48-72 hours after chemotherapy treatments and at the mid-point recovery and served as a reflection of overall activity plus bursts of activity during the most active period of the day. The number of night-time awakenings was defined as the number of awakenings per night-time sleep period. Number of awakenings per night was determined by an algorithm developed by Kripke, Mullaney, Messin & Wyborney (1978) that estimates the number of arousals from activity events and their distribution per unit time. Night-time sleep period was defined as the time between the subject pressing the event mark button upon retiring and on awakening. The event marks were validated additionally by subject recorded times of retiring and awakening that were recorded on the M-SDS form.

Nutrition Behavior

Nutritional behavior was defined as "the knowledgeable selection and consumption of foods essential for sustenance, health, and well-being, consistent with the guidelines for choosing a healthful daily diet provided by the Food Guide Pyramid" (Walker & Hill-Polerecky, 1996). Nutrition behavior was measured by using the nutrition subscale of the HPLPII, which appears in Appendix E.

Nutritional Status

Nutritional status was defined as the body's oxygen carrying capacity and caloric reserve status. These biological values provide objective data regarding nutrition of the individual. Anemia decreases the blood's oxygenation and delivery of essential nutrients to the cells, decreasing the energy available to the organism (Nail, 1990; Tait & Aisner, 1989). Hematocrit levels of the blood were examined as a measurement of oxygen carrying capacity. Caloric reserve stored as body fat was determined using the body mass index (BMI). BMI has been described as being useful in determining the amount of body fat and nutritional risk (Zeman & Ney, 1988). BMI was calculated as total body weight in kilograms divided by height in meters squared.

Stress Management Behavior

Stress management behavior was defined as the capability of identifying and mobilizing psychological and physical resources effectively to control or reduce tension (Antonofsky, 1987; Ardell, 1986; USDHHS, 1991). Stress management behavior was measured by the stress management subscale of the HPLPII, which appears in Appendix E.

Interpersonal Relations Behavior

Interpersonal relations behavior was defined as the use of communication to achieve a sense of intimacy and closeness within meaningful, rather than casual, relationships with others. Communication involves the sharing of thoughts and feelings through verbal and non-verbal messages (Travis & Ryan, 1988; Walker, et al., 1987). Interpersonal relations behavior was measured with the interpersonal relations subscale of the HPLPII, which appears in Appendix E.

Symptom Distress

Symptom distress was defined as the severity of three symptoms (nausea, mood, and sleep disturbance) previously identified as distressing to women receiving adjuvant breast cancer chemotherapy and was measured by a scale modified from the Symptom Distress Scale (SDS) developed by McCorkle and Young (1978). Scale items were modified to reflect more severity than distress of symptoms experienced during cancer treatments. The modified Symptom Distress Scale (M-SDS) appears in Appendix F.

Initial Reaction to the Diagnosis of Cancer

Initial reaction to the diagnosis of cancer was defined as confronting reactions and distress reactions. Confronting responses to the initial cancer diagnosis are represented by expressions of fighting spirit and stoic acceptance, while distress reactions include helpless/hopeless, denial, fatalism and future uncertainty responses (Frank-Stromborg, 1989). This was measured by the Reaction to the Diagnosis of Cancer Questionnaire (Frank-Stromborg, 1989) which appears in Appendix G.

CHAPTER 2

REVIEW OF THE LITERATURE

The literature review includes studies examining patterns of fatigue and of selected factors influencing fatigue in patients seen by primary care physicians and in patients with cancer receiving treatment. The review demonstrates what is known in regard to variables that were selected for this study because they were proposed to influence fatigue. The relationship between health/disease patterns and fatigue is described, followed by the relationship between cancer treatment patterns and fatigue. Four patterns from the Piper Integrated Fatigue Model (activity/rest, energy and energy substrate, psychological and social) that have been shown to be conceptually linked with four dimensions of health-promoting lifestyle behaviors then are discussed in regard to their relationships to fatigue. Next, the relationship of symptom patterns to fatigue is described. Finally, the linkage between initial reaction to the diagnosis of cancer and the outcomes of treatment, which may include fatigue, is presented. Sections of the review are organized according to the patterns described by Piper as factors influencing fatigue associated with cancer chemotherapy. Each pattern is represented in this study by at least one measurable variable, and these variables are underlined in each section of the literature review.

Fatigue

Fatigue has been recognized as an almost universal side effect of cancer and cancer treatment and has been included in many studies for the past 15 years as a single item on a symptom distress index. Numerous studies found that fatigue was the most frequent symptom complaint resulting from radiation therapy (RT), chemotherapy (CT), and biological modifier (BRM) response therapy for cancer (Haylock & Hart, 1979; Irvine et al.,

1991b; Piper, et al., 1989c; Richardson, 1995). Despite the reported prevalence of this symptom, there is no generally agreed upon definition of fatigue.

There is agreement that fatigue related to cancer therapy is a multi-faceted, subjectively measured phenomenon, but no physiological measurement that quantifies this concept has been accepted. Decreases in both physical and mental functioning and in energy efficiency are identified as attributes of fatigue. Fatigue interferes with daily living by creating a decreased capacity for physical and mental work (Aistars, 1987; Barofsky & Legro, 1991; Blesch et al., 1991; Cimprich, 1990; Pickard-Holley, 1991). Both acute and chronic fatigue are undesirable symptoms for patients who are survivors of cancer. Studies of cancer survivors conducted years after treatment found that decreased physical endurance was the most frequent after-effect of treatment, and it interfered with work and leisure activities (Fobair, et al, 1986). For most, but certainly not all cancer patients, pervasive tiredness and weakness along with certain treatment side effects constitute the greatest obstacles to independence in daily living (Kurtzman, Gardner, & Keller, 1988).

Consistent weaknesses of methodology and reliability and validity of measurements of fatigue have been identified in studies conducted thus far in patients with cancer (Irvine et al. (1991b). Investigations are needed that accurately elucidate the subjective and objective dimensions of the concept and precisely measure fatigue in healthy and clinical populations (Piper, 1986). A strength of Irvine, Vincent, Bubela, Thompson & Graydon's 1994 study was its use of a comparison group (Smets, Garssen, Schuster-Uitterhoeve & de Haes, 1993). Studies that build on groundwork laid by Piper and others that examine the etiology, patterns, characteristics and correlates of fatigue are needed so that interventions can be developed.

Health/Disease Patterns

Health and disease patterns are believed to influence the fatigue experienced with cancer treatments. The wide variation in reported baseline fatigue levels among healthy individuals supports the multi-dimensional etiologies of this symptom, and suggests that fatigue associated with cancer treatments could be modified by manipulating the key bio-psycho-social-spiritual factors that are effective in modifying fatigue in health.

A convenience sample of 155 adult women who described themselves as persistently fatigued, but otherwise well, completed the Piper Fatigue Self-Report Scale (PFS), the Beck Depression Inventory (BDI), and an investigator-designed questionnaire that collected behavioral and socio-demographic data (Libbus, Baker, Osgood, Phillips & Valentine, 1995). Statistically significant relationships were noted between depression scores and fatigue, as well as, between sleep patterns, rest quality, perceived stress and fatigue. A multiple regression model revealed an adjusted R^2 of .43 with depression serving as the major predictor variable for fatigue in this sample (ß=0.29, p=0.001).

Cathebras, Robbins, Kirmayer and Hayton (1992) examined the prevalence, psychiatric co-morbidity and outcome of patients with a presenting complaint of fatigue in a primary care setting. Fatigue was the major complaint in 6.7% (42), of the 686 patients. A determination of fatigue was made based on the patient's response to a question regarding the reason for the office visit and the physician's response to a questionnaire at the end of the patient interview. Patients with fatigue were more likely than other clinic patients (45.2% versus 28.2%) to have received a lifetime diagnosis of depression or anxiety disorder, and 16 (17.2%) fatigue patients were currently diagnosed with major depression. Only those

fatigued patients who had coexisting depressive symptoms reporting significantly more unexplained physical symptoms and greater perceived stress than did non-fatigued patients. One-half to two-thirds of fatigued patients continued to be fatigued one year later.

Kirk et al.'s 1990 prospective investigation of fatigue as a presenting complaint in the primary care setting revealed that patients with fatigue, while demographically similar to patients without fatigue, had significantly worse physical and mental health at study intake. Kirk's comprehensive literature review concerning fatigue in the general population revealed a very limited number of studies, all with serious methodologic flaws. Results revealed that 63% of physicians and 52% of patients rated the origin of fatigue as primarily physical (γ=0.48, $p<0.05$); but in 41% of cases, physicians indicated there was substantial interaction between physical and psychological factors. Only two discriminators (anxiety and depression) separated fatigue of physical versus psychological origin. Retention of subjects was a significant problem in the study, and 46% of the sample was lost to follow-up.

A retrospective chart review describing the rates of occurrence, methods of evaluation, and diagnoses of patients complaining of fatigue in a university family medicine practice setting was conducted by Sugarman and Berg (1984). After excluding patients in whom a definite etiology for the fatigue was identified at the first visit, 118 patients aged 15 and over with unexplained fatigue were identified during a two-year study in a practice of 6,000 active adult patients (9.9/1,000 patients/year). Laboratory tests such as hematocrit helped provide diagnoses in only 9 of the 118 patients and were not considered cost effective. The researchers concluded by commenting that what is known about fatigue is far less than what is not known.

A prospective study of 1000 consecutive patients in a primary care clinic in an urban general medicine practice setting was conducted by Bates et al., (1993) to determine the prevalence of unusual, debilitating fatigue and its association with chronic fatigue syndrome (CFS). Fatigue of at least 6 months duration without apparent cause was reported by 85 (8.5%) of the patients, and of these, 48 refused further evaluation, 11 were unavailable, and 26 remained as participants in the study. Only three patients met the Center for Disease Control and Prevention criteria for CFS. Further study of the incidence rates and patterns of fatigue and CFS in the general population is needed.

This series of studies consistently reported a relationship between fatigue and depression in patients seen in primary care settings. Mood, especially depression, has also been reported to influence perceptions of fatigue and other symptoms in the cancer patient (Piper, 1993b; Spiegel, 1990). Perkins, et al., (1995) reported that complaints of fatigue and insomnia in otherwise asymptomatic HIV-infected individuals are likely to be related to psychological disturbances and possibly major depression, which can be treated. No studies were found that linked fatigue with other variables in individuals without acute or chronic illness. Examination of patterns of fatigue in the above populations is needed to provide baseline values from which to compare values from clinical populations. Lack of instruments to measure fatigue in healthy populations in order to discriminate fatigue from depression and to identify its characteristics, patterns and severity has challenged practitioners making a differential diagnosis and planning treatment. The relationship between psychiatric morbidity and fatigue needs to be considered in this, and future studies.

Health/disease patterns were represented in this study by the variable health and functional status, and measured by the Medical Outcomes Study-Short Form (MOS-SF36) health survey (Ware & Sherbourne, 1992). The MOS instrument has been used in two nursing studies involving adult oncology patients, but neither examined fatigue in relation to health and functional status. Sarna (1993) used the MOS physical functioning subscale to obtain the subject's view of his/her limitations in physical activities owing to health problems in adults currently receiving or not receiving treatment for non-small cell lung cancer. The 10-item scale measures the concepts of self-care, mobility, ambulation and varying degrees of physical activity. There were no differences between the mean scores on the physical functioning subscale for the CT group as compared with the untreated cohort. A single cycle of CT did not seriously alter physical activities for the majority of treated patients. The scale was sensitive to changes over time.

Hughes (1993) used the 20-item MOS-SF instrument to measure physical, social and role functioning, mental health, health perceptions, and pain in a sample of 71 early stage breast cancer patients from diagnosis to 8 weeks post-operatively. Reliability and validity for this instrument have been established in large populations (N= 8,294). Decreases in physical [F (1,51)=27.09, p=0.001] and role functioning [F (1,51)=14.82), p= 0.001], and social functioning [F (1,51)=4.55, p= 0.05] occurred over time in this sample. However, pre- and post-treatment mean scores for the mental health, pain, and overall health perceptions subscales were not significantly different ($p>0.05$). The type of surgical intervention (mastectomy versus lumpectomy and radiation) was reported to be unrelated to functional status.

The dimensions of functional status undergo changes during the treatment and recovery periods after the diagnosis of breast cancer. Self-care abilities are affected at the time of surgery, during adjuvant treatment, and potentially for a long time afterwards (Tulman & Fawcett, 1990). Roles assumed by women include employment outside the home as well as major responsibility for household management and social activities. Northhouse (1989) and Northhouse and Swain (1987) found that although husbands adjust their role activities after their wives are diagnosed with breast cancer, the wives experience more adjustment problems in the areas of domestic, social, and vocational activity roles. Additional research is needed to further understanding of the influence of breast cancer patients' health and functional status on perceptions of fatigue over time.

Treatment Patterns

Fatigue can be a prevalent and serious problem for patients being treated for cancer, and yet little is known about its prevalence, patterns, and impact on quality of life (Irvine, et al., 1994). Most research that has focused on fatigue and cancer treatment patterns has examined responses to chemotherapy protocols, which is the focus of this review. The area was first explored without identification of a conceptual model. McCorkle and Young (1978), using a Symptom Distress Scale (SDS) developed for the study, found that fatigue was significantly correlated to mood ($r=0.60$), appetite ($r=0.61$), and insomnia ($r=0.55$) in 60 outpatients with cancer. McCorkle and Quint-Benoliel (1983) also utilized the SDS to measure fatigue and the Profile of Mood States (POMS) (McNair, Lorr & Droppleman, 1971) to measure mood in both lung cancer and myocardial infarction patients. Both groups identified fatigue as their most distressing symptom, with mood disturbance significantly

greater for cancer than cardiac patients. Additional studies by Blesch et al., (1991); Cassileth et al., (1985); Fernsler (1986); Nerenz, Levanthal, and Love, (1986); Pickard-Holley (1991); and Rhodes, Watson, and Hanson (1988) have examined the relationship between CT treatments and fatigue. Mock, et al. (1994) reported high prevalence and intensity of fatigue in women receiving chemotherapy for breast cancer. Irvine et al. (1994) reported equivalent baseline fatigue levels between controls and patients with cancer prior to treatment, but significant increases in fatigue levels in the cancer patients 14 days after treatment with chemotherapy as compared to controls. The Pearson Byars Fatigue Feeling Checklist (Pearson & Byars, 1956) was used to measure fatigue, and the reliability ranged from alpha= 0.82-0.97 in this sample. Both symptom distress and fatigue intensity were predictors of impairment in functional activities related to illness ($p=0.001$).

The studies described above used a variety of designs and an assortment of unidimensional measurement tools, many of which were without established reliability or validity. Studies did not control for time of day of tool administration or collection time of samples for laboratory analysis, important considerations in fatigue research. Consequently, generalizability of results is difficult.

A limited number of studies have focused on the examination of fatigue and other symptoms in women receiving adjuvant chemotherapy specifically for breast cancer. Four were recall, one time interview studies (Bruera et al, 1989; Knobf, 1986; Meyerowitz, Sparks, & Spears, 1979; Meyerowitz, Watkins, & Sparks, 1983) and several others were prospective, repeated measure design studies (Berger, 1995a; Cimprich, 1990, 1993; Greene,

Nail, Fieler, Dudgeon & Jones, 1994; Mock et al, 1994; Piper, Dibble, & Dodd, 1991; Piper, et al., 1989b; and Piper, 1993b).

Meyerowitz, et al. (1979), and Meyerowitz, et al. (1983) were the pioneers in investigating the impact of adjuvant CT on women with breast cancer. Fifty women post-mastectomy were interviewed once about perceptions regarding psychosocial effects of CT, one to 30 months into their adjuvant CT regimen (mean time of treatment prior to interview was 11.4 months). Patients were receiving intravenous CT for over a year, followed by BCG administered weekly or every other week for 2 years. Fatigue was experienced by 96% of the subjects, and interfered with social and work-related activities. Fatigue appeared to be related to CT since energy levels were reported to improve between treatment cycles. Every woman reported adverse changes in her life as a result of CT. Weaknesses of the study include use of measurement tools without established reliability and the cross-sectional design.

Knobf (1986) studied physical and psychological distress and lifestyle changes in 78 women with stage II breast cancer receiving adjuvant therapy. The majority were treated with cyclophosphamide, methotrexate and 5-fluorouracil/5-FU (CMF) regimen with or without vincristine and prednisone, a regimen of moderate intensity. A single interview also included a modified Symptom Distress Scale (McCorkle & Young, 1978) and the Psychiatric Status Schedule (Spitzer, Endicott, Fleiss & Cohen, 1970). Fatigue caused the most distress in these women, followed by insomnia. Average ratings for fatigue intensity were low (<3 on a 1-5 scale), perhaps because approximately one third of subjects had completed CT 2 months to 5 years before the interview. The limitations of this study included the cross-sectional design,

the widely variable amount of time between cancer treatment and the interview, and the lack of control of co-morbid conditions.

Bruera et al. (1989) studied aesthesia, the combination of physical and mental fatigue, in 64 Canadian women with recurrent breast cancer and age-matched controls. Approximately 3/4 of the women were being treated with CT, while the remaining 1/4 of the subjects were receiving Tamoxifen. Results included significantly more patients than controls reporting substantial increases in their physical fatigue during the last year, and 41% were considered aesthetic based on results from Visual Analog Scales (VAS) rating energy and ability to perform activities of daily living. Asthesia did not significantly correlate with type of treatment ($p>0.05$). Weaknesses of the study include the cross sectional design and sample mix. The strengths of the study include the use of a control group and use of a VAS measurement which has demonstrated reliability and efficiency in measurement.

The prospective study conducted by Cimprich (1993) examined "attentional fatigue" which was defined for the study as "a state of reduced effectiveness and discomfort that follows intense mental efforts or excessive use of directed attention" in 32 women with early stage breast cancer. Data were collected at 4 time points during the first 3 months after surgery and during adjuvant chemotherapy. After the first observation, subjects were randomly assigned to receive an intervention designed to maintain or restore attentional capacity. Results reported include improvement in attentional capacity over the 4 time points in the intervention group, and inconsistent performance in the control group. The lack of baseline data, the lack of a stratified random sample design to control for age, surgery, and

baseline data, and the wide variations among subjects in the interval length between data collection points detracted from, but the use of a prospective design strengthened, the study.

Fatigue was examined prospectively over two CT cycles by Piper, et al., (1989b) to determine patterns of fatigue over time and the relationship between age, hemoglobin, and length of treatment regimen and perceived fatigue. Fatigue sensations were found to be most intense at time one (day 1 of the first CT cycle), and total mood disturbance and lack of vigor were greatest on the first day of the second cycle of chemotherapy for the entire group of 37 women with breast cancer. Fatigue was most intense at baseline in women under age 50. Small sample size and missing data limit the generalizability of these findings.

The first researchers to document whole body fatigue prospectively in CT patients and family members were Dodd and associates (Piper, et al., 1991). In the study, 100 CT patients (48% had breast cancer) and 126 family members were studied over a 6-month period during CT treatments for newly diagnosed or recurrent disease. Results included no significant differences in patient fatigue scores over time, measured with the POMS fatigue/inertia subscale. At the beginning of CT, perceived current health, economic status, and self-care efficacy explained 45.5% of the variance in patient fatigue scores. Fatigue was reported as the number one family member concern about the patient over time. Only at 6 months were there significant differences between groups; newly diagnosed patients (N=64) reported more fatigue than did the recurrent group (N=34). Under-reporting throughout the study may have biased results (Breetvelt & Van Dam, 1991). Another limitation was that fatigue was measured with the fatigue/inertia subscale of POMS, an instrument designed to measure mood.

Examination of fatigue patterns over the initial six cycles of adjuvant CT for newly diagnosed breast cancer by Piper (1993b) revealed that mean Piper Fatigue Scale scores (range= 0-100) at baseline were moderate ($\bar{X}$=38.9, SD=12.86), and remained relatively stable over time. The highest mean score was reported at the mid-point of the third cycle ($\bar{X}$=39.4, SD=18.77). The most significant finding of the study was that less vigor, more depression, and more mood disturbance predicted with a 47-76% degree of accuracy increased fatigue, while depression was the single most consistent predictor of chronic fatigue over time. Limitations of the study included a moderately high refusal rate and missing data.

In the only study that compared the side effects among three CT protocols, Greene et al. (1994) compared the incidence and severity of patient-reported side effects and the effect on performance of usual activities for three combination CT regimens used in the treatment of stages I-IV breast cancer. Regimens included were CMF, Cyclophosphamide, Adriamycin, and 5-FU (CAF), and Cyclophosphamide, mitoxantrone, and 5-FU (CNF). Data on side effects were collected using a self-care diary with established reliability and validity. Subjects (N=86) rated the severity of side effects on a scale ranging from 1 to 5. Disruption in usual activities was measured using a 100 millimeter VAS. Data were collected during the first and second cycles on the second and fifth days after chemotherapy. There were no differences among the groups at any time for the incidence of any side effect. The most frequently reported side effects were: fatigue, nausea, anorexia, and taste changes. Although fatigue was the most frequently reported side effect, a distinct clinical pattern was not

apparent. The limited amount of data collected from each patient is a limitation because the most intense fatigue may not have been captured.

This series of studies comprise the research to date which explored the relationship between chemotherapy protocols and fatigue experienced by patients with breast cancer during chemotherapy. Subjective assessment of mood, nausea, difficulty sleeping, depression, and difficulty concentrating were among the psychological variables where a relationship with fatigue was demonstrated in the literature. The objectively determined variables of activity level, performance status, and overall current health status have also been examined and found to have a relationship with fatigue in these patients. Patterns of fatigue intensity experienced over time were not found to be different than at baseline. Interpretation of these studies is compromised by poorly designed methodology, lack of valid and reliable instruments and the complexity of the concept. Despite these limitations, the concept is too important not to study, and should be measured while controlling for confounding variables whenever possible.

Adjuvant chemotherapy for stage I or II disease is steadily evolving and currently involves one of three regimens outside investigational protocols. These regimens include CMF (21 or 28 day cycle), AC (21-28 day cycle), and CAF (28 day cycle) for 4 to 6 months respectively, followed by 5 years of oral Tamoxifen (TAM) for women who have estrogen receptor positive tumors (Fisher, Wickerham, & Redmond, 1992). Greene et al. (1994) reported no differences in reported fatigue in women receiving CMF, CNF, or CAF on the second and fifth days after the first two cycles. Piper (1993b) examined the variables of cycle length (21-day versus 28-day) and inclusion of Adriamycin in the regimen. There were no

changes found for any of the outcome fatigue indicators by length of CT cycle, or by the inclusion of Adriamycin in the treatment regimen. No study has reported significant differences in fatigue intensity between these protocols.

Activity/Rest Patterns

One factor believed to play a significant role in the occurrence of fatigue is activity/rest patterns. Physical activity behaviors are known to influence perceptions of fatigue in health. Patterns of activity/rest cycles have been shown to be strong indicators for physical welfare and quality of life in 109 ambulatory patients with metastatic colo-rectal cancer (Mormont, et al, 1996). Both physical activity behaviors and activity/rest cycles may be associated with perceptions of fatigue experienced by patients with cancer.

A meta-analysis of 34 studies that investigated the relationship between aerobic fitness and reactivity to psychosocial stressors in 1449 healthy individuals indicated that aerobically-fit subjects had a lower stress response (mean effect size=0.48, p=0.01) compared to either a non-aerobically fit group or baseline values (Crews & Landers, 1987). Pierce and Pate (1994) determined that global mood scores on the POMS were significantly improved after a 75-minute session of aerobic line dancing among older, well participants. Tulman and Fawcett (1990) recognized that physical activity and functional status were related to psychological state and interpersonal relations of cancer patients but stated that the direction of the relationships remained unclear, may have been reciprocal, and deserved further examination. A decrease in anxiety with increased physical activity was reported by Ott, et al., (1983). Although there are few quantitative studies in patients with cancer, the psychological benefit of exercise programs has been routinely noted anecdotally by

investigators. Aerobic exercise appeared to serve as a stress management behavior that influences perceptions of fatigue. Beneficial mood changes alone may enhance prognosis.

Winningham (1992) proposed that any symptom that tends to diminish activity can contribute to increased fatigue and decreased functional status. Belza (1994) stated that there is a potential for de-conditioning to result whenever a significant reduction occurs in intensity, frequency, and/or duration of exercise. Lengthening rest periods and time spent in bed may in fact lead to inactivity-related body organ system changes (Corcoran, 1991). Regular moderate physical activity has improved sleep patterns and decreased fatigue in healthy subjects (Crews & Landers, 1987; Eide, 1982a; Eide, 1982b; MacVicar & Winningham, 1986) and may also be helpful to the individual during treatment.

An 8-week exercise rehabilitation program for women with breast cancer which included a specially designed program of floor exercises and stretching and group discussion, was perceived as advantageous to 72% of the participants (Gaskin, LoBuglio, Kelly, Doss, & Pizitz, 1989). Physical changes included improved flexibility, improved stamina, and general overall physical improvement. Sixty-five percent of the women cited improved self-esteem, better coping, and positive psychological changes as a result of participation in the rehabilitation program. Sleep quality and the forgotten symptom of fatigue were not measured.

The work of MacVicar and Winningham (1986), MacVicar, Winningham & Nickel (1989), Winningham and MacVicar (1988) and Winningham et al. (1989) offers promise that moderate level aerobic exercise can modify a variety of symptoms (nausea, mood and increasing body weight) of breast cancer patients undergoing CT. In MacVicar et al's 1989

study, the use of a 10-week aerobic interval-training program on functional capacity in 45 women being treated for Stage II breast cancer was examined. Results demonstrated that the group using the cycle ergometer showed a mean 40% improvement on pre- to post-test functional capacity (V_O2/Lmax) as compared to placebo and control groups ($p=0.05$). Winningham (1992) proposes that patients who are chronically ill with cancer become enmeshed in a negative cycle of debilitation, reduced physical activity, and deconditioning, manifested by rapid fatigue upon exertion, which fosters a further decrease in physical activity. Any symptom that tends to diminish activity could therefore contribute to increased fatigue and decreased functional status. In a survey about activity and exercise, 95% of 192 patients with cancer who were ambulatory stated that their physical activity was restricted by physical limitation, pain, weakness, and/or inability to control movement (Frank-Stromborg, Wright, Segella, & Diekmann, 1984). These data support the impact of cancer treatment on activity patterns. Researchers and clinicians are urged to examine whether this cycle could be reversed or modified by early implementation of a personally designed physical activity regimen combined with effective symptom management for each individual.

Other researchers have examined the interaction between exercise and positive well-being, an indication of positive energy balance. Young-McCaughan & Sexton (1991), compared questionnaire answers of 42 women who exercised with 29 women who did not exercise. All of the women were diagnosed with breast cancer (most stages I and II) 6 months to over 2 years prior to the study. Women with breast cancer who exercised experienced a higher quality of life ($t(1,69)= -2.16, p=0.03$). The exercisers were more likely

to be married or living with a significant other (χ= 5.0, p=0.02), and more likely to have been exercisers before they were diagnosed with cancer (χ= 29.8, p=0.001). Additional research is needed that simultaneously explores the relationships between various lifestyle behaviors of patients with cancer and fatigue. Fatigue was not measured in this study, but has been identified as a variable that influences QOL perceptions (Berger, 1993).

Nelson (1991) selected a random sample of 55 women who had experienced stage I breast cancer without receiving adjuvant chemotherapy, and matched them to a cohort of women in the community who had not experienced cancer. Seventy-four percent (N=40) of the women who experienced breast cancer reported participating in some form of exercise, while in the matched cohorts, 46 women (85%) reported participating in some form of exercise. No significant differences in perceived health, self-esteem, and health habits were found between women who had experienced breast cancer and the matched cohorts. There was a difference in both perceived benefits of and barriers to exercise between groups (t=2.4, df=106, p= 0.018) with the matched cohorts scoring higher on perceived benefits and barriers to exercise. These results should be viewed cautiously since there was a 45% refusal rate to participate, and the single treatment modality of surgery without adjuvant treatment could under-estimate the impact of breast cancer on women. This limited number of studies describe the positive value of physical activity behavior on a variety of variables related to fatigue, but often omit the direct measurement of fatigue. Investigation is warranted to further understanding of the relationship between these variables and fatigue in ambulatory patients with cancer.

Mock et al. (1994), in a randomized prospective trial, investigated the effects of a self-directed walking exercise program and a support group led by an oncology clinical nurse specialist in development of physical stamina and coping skills, and thus promotion of more adaptive responses to the newly diagnosed breast cancer diagnosis and treatment. While baseline pretest scores were equivalent, the mid-chemotherapy testing period revealed significant differences between the exercise and support group and the control group on intensity of fatigue ($U=7$; $p=0.02$), nausea ($U=7.5$; $p=0.02$), and depression ($U=6.5$; $p=0.01$). The self-paced walking program was well tolerated, and walking longer distances was correlated with higher physical performance scores, a finding consistent with research on healthy subjects (Duncan, Gordon, & Scott, 1991). The finding of lower levels of fatigue in the subjects in the intervention group supports previous research findings of a beneficial effect of exercise on fatigue in cancer patients (MacVicar & Winningham, 1986). A serious limitation of the study was the small sample size ($N=14$). Additional weaknesses included the self-reported exercise patterns, and simultaneous introduction of two interventions. An important finding that needs to be replicated was that subjects in the experimental group reported that they were able to consistently increase their level of physical activity over the course of chemotherapy (ranging from 3 to 6 months), while the control group experienced a progressive decrease in activity in response to comparable treatments. A larger sample and biological activity measurements are needed to validate these findings.

Graydon, Bubela, Irvine and Vincent (1995) conducted interviews at the beginning and mid-point of any cycle of chemotherapy in a sample of women receiving treatment for breast and gynecological cancers. Women reported that the more effective the fatigue relieving

strategy employed, the less fatigue experienced at the second interview ($p<0.001$). Sleep and exercise were among the most effective strategies reported at both interviews, but details regarding the interventions were not included in the report. There was a wide range of scores for each strategy used, indicating varying evaluations by subjects regarding the effectiveness of the strategy. Future studies are needed that clarify activity prescriptions, test these interventions, and evaluate their effect in the modification of fatigue in early-stage disease.

Activity/rest cycles include the indices that reflect body motion within each 24-hour period. Actigraphs enable the continuous monitoring of body movement over time (Brown, et al., 1990). Monitoring body motion over time, a component of the science known as chronobiology, provides an important quantitative index of daily cycles of rest and activity, relative activity within days and across days, and the timing, duration and disruption of sleep (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992; Redmond & Hegge, 1985). Fluctuations in body functioning are thought to affect such things as emotional level, pain tolerance, and levels of energy and fatigue, but these hypotheses need to be tested.

Nursing research has explored the potential of these human body rhythms to influence the management of health and illness. Studies have examined the relationship between chronobiology and the cardiovascular system, post-surgical recovery, mood disorders, and aging (Elmore & Burr, 1993). No nursing research was reported that involved patients with cancer.

Studies by Mormont and De Prins (1995) and Mormont et al. (1996) are the only reported studies using actigraphy in patients with cancer. In the first study, 96 patients with metastatic colo-rectal cancer wore the actigraph for 3 to 5 days before chemotherapy.

Circadian rhythms were estimated from the actigraphy auto-correlations and harmonic analysis of data. Correlations of circadian rhythm with mean activity variables suggested that the most active patients maintained better activity/rest circadian rhythms. As compared to healthy control data, 50% of the patients with cancer had lower values for all activity parameters. The significance and prognostic value of this finding deserves further investigation.

In a related study by the same authors (1996), 109 ambulatory patients with colo-rectal cancer wore the actigraphs for 3 to 5 days. Significant correlations were found between auto-correlation coefficients and scores for global quality of life ($p=0.01$), and the subscales of social functioning and fatigue (both $p=0.01$), and physical functioning, sleep disturbances, appetite loss and depression (all $p=0.05$) as measured on the QL questionnaire (QLQ-C30). The relationship between activity/rest cycle patterns and indicators of quality of life, particularly fatigue, may assist researchers in designing interventions to modify fatigue.

In summary, the relationships between activity/rest patterns as measured by physical activity behaviors and fatigue in patients receiving cancer treatment have been examined in a few studies. One study was found that quantified activity/rest cycles in association with fatigue measurements in patients with cancer. While reduction of activity is commonly believed to benefit an individual after receiving chemotherapy treatments, no empirical evidence exists to demonstrate that this conservation of energy reduces fatigue, and, in fact, may promote it (Corcoran, 1991). The cited studies describe the relationship between low to moderate intensity physical activity behaviors with both higher functional status and lower levels of fatigue. These findings suggest that patients with cancer being treated with intent

of cure can benefit from an individualized physical activity prescription intended to maintain the highest possible functional status and to modify fatigue.

Energy and Energy Substrate Patterns

Investigators have examined the central nervous and muscular systems at the cellular level in animal and human models in an attempt to further understand energy and energy substrate patterns. Nutrition behaviors and nutritional status are the variables selected to measure energy intake and storage patterns in this study. Although these variables are broad representatives of these cellular processes, they do provide quantitative data that can be used to classify subjects on a continuum that represents inadequate, normal or excess nutritional behaviors and reserves.

The work of cellular physiologists provides information regarding the cellular mechanisms that influence central and peripheral muscle fatigue. Physiologists have identified a "command chain" of electrical and biochemical processes which sequentially lead to muscle contraction that may result in fatigue at any point where breakdown occurs (Edwards, 1981). Central mechanisms include decreased efficiency in the generation of the motor command in the motor cortex related to changes in availability of neuro-transmitters (Brazil-Neto, et al., 1993). The accumulation and depletion of neuro-transmitters were proposed to result from the decreased amplitude of motor evoked potentials. A growing body of evidence has implicated alterations in intracellular Ca^{++} exchange as playing a major role in the fatigue process (Williams & Klug, 1995).

Peripheral fatigue mechanisms include changes in excitation-contraction coupling, muscle contractility, muscle membrane excitability, and neuromuscular transmission (Baker,

Kostov, Miller, & Weiner, 1993; Boska, Mourssavi, Carson, Weiner & Miller, 1990; Reid, Grubwieser, Stokic, Koch & Leis, 1993). Baker's findings, consistent with earlier studies, suggested that impaired excitation-contraction coupling plays a role in producing long duration, low frequency fatigue. Boska pointed to increased $H_2PO_4^-$ as a more important factor in both fatigue and recovery of human muscle than pH, and Reid et al. (1993) suggested that lactic acidosis and accumulation of inorganic phosphate are contributors to mechanical failure of muscle fibers through inhibition of the actin-myosin interaction.

These studies have attempted to explain the physiological basis of muscle fatigue, but the complexity of the subject has limited efforts attempting to draw conclusions regarding biochemical mechanisms which are associated with treatment-related whole body fatigue. Bench research cannot address the subjective nature of the phenomenon or the variety of individual behaviors manifested in response to physiologic changes.

Studies of muscular fatigue in clinical populations have focused primarily on the experience of individuals with heart failure, where changes in the muscle itself were found to be responsible for accelerated muscle fatiguability (Minotti, Pillay, Chang, Wells, & Massie, 1992). The data from animal model research reported by St. Pierre, Kasper, and Lindsey (1992) suggested that fatigue in cancer patients which is associated with tumor necrosis factor may involve changes in electrical activity at the neuromuscular junction. Additional research is needed to further understanding of the biochemical characteristics of the perceived sensation of fatigue, and to clarify the etiology of this symptom.

In the cancer patient, changes in energy production may result from numerous changes in nutrition behavior and status (Tait & Aisner, 1989). The mechanism of weight gain

observed in 50-90% of all early stage breast cancer patients receiving adjuvant chemotherapy is not clearly understood, but appears to be related to the changes in nutrition behaviors secondary to the chemotherapy regimen, duration of treatment, menopausal status, activity levels, appetite and coping styles (DeMark-Wahnfried, Winer, & Rimer, 1993). The factors associated with weight gain in 70% of subjects in Knobf's 1986 sample of 78 women receiving CMF with or without vincristine and prednisone were depressed mood, decreased activity, increased appetite, mild nausea, and taste changes. Menopausal status, specific drug regimen, and duration of treatment were believed to influence the amount of weight gained in a second study by Knobf (1990).

Nutritional status as measured by body mass index (BMI) has been shown to influence exercise behavior, and may influence perceptions of fatigue in patients with cancer. Pender (1987) found total body weight a significant predictor of intention to engage in exercise; the higher the total body weight, the lower the intention to exercise regularly, which may influence fatigue. Neuberger, Kasal, Smith, Hassanein and DeViney (1994) identified factors that influenced exercise behavior and aerobic fitness in 100 outpatients with arthritis. Patients with high BMI scores were among those felt to need more encouragement and direction in implementing an exercise program. The relationship between body mass index, mood, physical activity behaviors, nutritional behaviors, nausea and fatigue has not been reported over time in women receiving adjuvant chemotherapy, and this merits examination.

Winningham, et al, (1989) have contributed a study which provides empirical data on the benefits to nutritional status of controlled aerobic exercise during breast cancer treatments. The researchers randomized 24 subjects to exercise treatment and control groups

(usual activity) and found that moderate aerobic exercise had a moderating effect on gain in body fat and altered the subcutaneous body fat profile in both obese and non-obese women undergoing chemotherapy for stage II breast cancer. Results of this study may be useful while designing studies aimed at weight-control during breast cancer chemotherapy.

Moderate aerobic activity was also found by Winningham and MacVicar (1988) to be significant [χ(df=4,42)=10.55,p=0.032] as an adjuvant self-care measure to anti-emetic therapy in controlling chemotherapy-induced nausea. Mock et al., (1994) also reported lower levels of nausea in subjects who performed aerobic exercise three times a week and participated in a support group while receiving chemotherapy (U=7.5, p=0.02). Aerobic exercise and decreases in nausea and fatigue perceptions may be related, but the mechanism of interaction is unclear. Further investigation into the relationship between nausea and physical activity is needed to clarify this interaction. Healthier nutritional behaviors are expected when nausea is effectively managed, and may be associated with lower levels of fatigue. A secondary benefit from reduction in nausea in patients after chemotherapy is decreased use of anti-emetic medications, with the side effects of central nervous system depression and reduction in activity.

The literature reports an unclear relationship between fatigue and hematocrit values (Piper, 1993a). Piper et al. (1989c) found that women with higher hematocrit values on day 10 or 14 of the first cycle had more vigor than those with lower values (p=0.05), and that more mood disturbance was experienced by women who had lower hematocrit and hemoglobin values at the nadir of the second chemotherapy treatment. The POMS was used to measure mood and vigor. Bruera and MacDonald (1988) reported that anemia is probably

a factor in fatigue only when hemoglobin/hematocrit levels are extremely low; a statement which supports the inconsistent findings regarding the correlations between degree of anemia and fatigue intensity. Acute reductions in hemoglobin/hematocrit levels can influence fatigue levels, with resultant reductions in activity, that in turn compounds fatigue intensity (Piper et al., 1987).

In summary, nutritional behaviors and status affect available energy and energy substrates and have been found to be associated with weight gain, loss, nausea and anemia. Change in hematocrit is one measurable indicator of oxygen carrying capacity that affects nutrition of the cell. Body mass index is one method to quantify body fat stores and is a gross indicator of nutritional status. Adequate diet is needed for cellular repair after surgery and CT treatments, yet a relationship between these measurements and fatigue has not yet been clarified and deserves attention.

Psychological Patterns

Several psychological patterns may influence fatigue in cancer patients (Piper et al., 1987). This review will be limited to the relationship between stress management behaviors and fatigue. Reaction to stressors related to cancer and cancer treatment may influence fatigue. Information needs and psychological needs dominate the diagnostic phase of the breast cancer trajectory, while psychological distress dominates the treatment phase regardless of the treatment selected (Knobf, 1990). Multi-modal therapies for cancer can represent a source of physical and mental stress which depletes available energy and makes patients vulnerable to fatigue (Aistars, 1987) and immune system depression. Effective stress

management behaviors may assist the individual in coping with change and avoiding fatigue and physical and psychological exhaustion.

Ganz, Schag, Polinsky, Heinrich, & Flack (1988) reported the most frequent psychological problems of women in the first month after surgery for breast cancer as fear of recurrence, anxiety, depression, overwhelming emotions and worry about self. Ganz also reported the concerns regarding body image to be a result of discomfort with body changes, discomfort showing the scar, clothes not fitting, and embarrassment with bodily display. Findings from this study suggest that the stress that accompanies adjuvant therapy has an impact on the rehabilitation and recovery process of newly diagnosed breast cancer patients which is independent of the experience of the cancer diagnosis and primary surgical treatment.

Group psychotherapy has been reported to reduce emotional and physical distress in patients with cancer (Decker, Cline-Elsen, & Gallagher, 1992; Fawzy, 1995; Fawzy, et al, 1990; Forester, Kornfeld, Fleiss, & Thompson, 1993; and Heinrich & Schag, 1985). The effect of stress reduction by relaxation training and imagery was studied by Decker et al., (1992) using an experimental design in 82 outpatients who were undergoing curative (73 patients) or palliative (9 patients) radiotherapy. On pre- and post-tests of the POMS, the treatment group showed reductions in tension [$F(1,61)=14.35,(p=0.001)$], depression [$F(1,61)=6.99,p=0.01$], anger [$F(1,61)=6.81,P=0.001$)], and fatigue. The control group experienced an increase in fatigue ($p=0.01$). These results suggest that relaxation training improves several psychological parameters which influence well-being in patients receiving radiation therapy.

Fawzy (1995) utilized a randomized experimental design to determine if a psychoeducational nursing intervention that included (a) health education, (b) stress management, and (c) teaching of coping skills could enhance the coping behavior and affective state of 61 newly diagnosed Stage I/II malignant melanoma patients. By 3 months, there was a complete reversal of the baseline trend in Profile of Mood Scores (POMS) total mood disturbance , suggesting that the experimental subjects were experiencing less distress over time ($p<0.05$). Experimental patients also were using significantly fewer ineffective passive resignation coping strategies that controls at 3 months ($p<0.05$).

Interventions recommended by Fawzy et al. (1990) consisted of health education, enhancement of problem-solving skills, stress management (e.g., relaxation techniques), and psychological support, after examining a psychiatric group intervention for post-surgical patinets with malignant melanoma (N=66). Baseline levels of psychological distress were high in this sample, compared with other cancer patients (Fawzy, et al, 1990). At the end of a 6-week intervention, the experimental subjects (n=38) exhibited higher vigor ($r=0.33$, $p=0.04$) and greater use of active-behavioral coping ($r=0.33$, $p=0.04$) than did controls (n=28). At 6 months, the intervention group showed significantly less depression, fatigue, confusion, and total mood disturbance and more vigor (all ($p=0.001$).

Forester, et al., (1993) conducted a 10-week group psychotherapy intervention program that resulted in differences between the randomly selected experimental and control groups in levels of emotional and physical symptoms in patients undergoing radiotherapy. Anorexia, fatigue, and nausea and vomiting scores were summed, producing a physical symptom score which decreased significantly by the end of psychotherapy ($F(1,23)=3.18, p=0.01$). These

studies support the use of psychotherapy to assist in stress and symptom management of patients with cancer, and reinforces the mind-body connection.

An activity group treatment, in addition to a stress management program, was conducted with 26 patients with commonly occurring cancers and their spouses (Heinrich & Schag, 1985). Twenty-five patients/spouses served as controls in this longitudinal design study. Repeated measures multi-variate analysis of covariances (MANCOVA) were calculated on the outcome variables of psychosocial adjustment and activity, and no significant differences were found between groups over time. It was suggested that both groups became better adjusted with the passage of time, and that initially high physical activity levels among subjects created an unexpected ceiling effect.

Cella (1990) described a "cancer wellness doctrine" that can serve in the future as a basis for a cognitive restructuring intervention along with stress management techniques to promote wellness in people with cancer. Results from use of this intervention have not been reported. Gruber, et al. (1993) conducted an 18-month study of immune system and psychological changes in stage I breast cancer patients provided with relaxation, guided imagery, and biofeedback training. Significant effects were found in natural killer cell activity ($p=0.017$), mixed lymphocyte responsiveness ($p=0.001$), concanavalin A responsiveness ($p=0.001$), and the number of peripheral blood lymphocytes ($p=0.01$), showing that behavioral interventions can be correlated with immune system measures. No significant psychological changes were detected, but reductions were seen in anxiety scores on a psychological inventory. Reduced anxiety may reduce the impact of the stress response in promoting fatigue. These findings replicated the results of earlier pilot work done by the

research team (Gruber, Hall, & Hersh, 1988). Inconsistent study results to date regarding the beneficial impact of psychosocial interventions on the immune system will require that studies be replicated to clarify relationships (Ironson, Antoni, & Lutendorf, 1995).

In summary, strong evidence exists in the psychiatric literature that fatigue is frequently reported by individuals who are psychologically distressed, and experiencing anxiety. Psychological needs can dominate the early months after an individual is told of a cancer diagnosis. Research on psychosocial interventions for breast cancer patients after surgery and during treatment yield mixed results. Group psychotherapy interventions in patients with cancer have been shown to result in the following: reductions in tension, depression, anger and fatigue; higher vigor and greater use of active-behavioral coping; lower levels of emotional and physical symptoms, and positive changes in immune cell populations including natural killer cells. Future studies of psychosocial interventions to improve stress management and coping among women with breast cancer should include randomized trials of promising strategies with large samples and control for extraneous variables. In addition, interventions designed to promote stress management behavior and cognitive restructuring are needed for those individuals not interested in group participation or psychotherapy.

Social Patterns

Social patterns influence fatigue and are comprised of support from those individuals who are close to the patient and to the patient's perceived social support, cultural beliefs and economic factors (Piper et al. 1987). Social networks exert a powerful influence on how people think and react. Social networks can help individuals set personal goals or deal with demands of a particular situation in both tangible and intangible ways (Pender, 1987). Bloom

(1982) reported that the perception of social support, measured by family cohesiveness and the frequency of social contact, is the strongest predictor of healthy coping responses to mastectomy. Successful adjustment has been found in women with breast cancer who experience communication and support from others, believe they have control over the disease process, and take responsibility for changing their lifestyle and complying with medical regimens (Taylor, Lichtman & Wood, 1984).

Social networks maintained by positive interpersonal relations behaviors appear to be key influences in long term adaptation to cancer, however life crises may overwhelm significant others, and result in reduced ability to provide interpersonal support. Bolger, Vinkovur, Foster and Ng (1996) studied 102 breast cancer patients and their significant others at 4 and 10 months after diagnosis. Results confirmed the negative account of relationship functioning, and reported withdrawal of support by significant others in response to women's emotional distress between the two time points [β=-0.26, t(1,98)=-2.64, p=0.01]. Timing of interviews may have seriously influenced results, and intensive, repeated measures designs have potential to more accurately capture interactions.

Three main sources of support for the breast cancer patient have been identified: family support, support from physicians and other medical personnel, and support from other patients (Meyerowitz, et al. 1979). Such support and behavior is influential in the patient's adjustment to breast cancer (Feather & Wainstock, 1989). Use and frequency of communication behaviors that meet the need for intimacy and closeness within these supportive networks is believed to influence fatigue perceptions.

A prospective study using multi-variate methods that examined the effects of social relationships on survival for women with breast cancer found that the number of supportive friends, the number of supportive persons, whether the woman was employed, her marital status, the extent of contact with friends, and the size of her social network had independent effects (all p=0.001) on survival (Waxler-Morrison, Hilsop, Mears, & Kan, 1991). It was concluded that the woman's social context, particularly friendships and work outside the home, are statistically important for survival. The lack of socially supportive relationships during a crisis (new diagnosis of cancer) was predictive of the increased severity of the individual's stress 2 years later in a study by Vachon (1986). Socially supportive relationships enhance health outcomes and reduce mortality, whereas stressful social relationships prolong health problems (House, Landis, & Umberson 1988; Kaplan & Toshima, 1990).

Roberts, Cox, Shannon and Wells (1994) explored the effects of perceived social support from friends, family and spouses on the psychological adjustment of 135 newly diagnosed breast cancer patients. The findings, consistent with those of Wortman (1984), cautioned that the apparent correlation between support and adjustment may in fact lie within the person rather than within the objective considerations of the support network. Individuals with a history of emotional problems and recent life stressors may demonstrate fewer positive interpersonal relations lifestyle behaviors and a poorer adjustment to illness regardless of the extent of the objective support network. Additional study is needed to examine the types of interpersonal relations behaviors perceived as most helpful to ambulatory cancer patients and to develop interventions to meet the needs for such relationships.

A significant improvement in the mood of patients who participated in a cancer support group versus patients who did not was described by Spiegel, Bloom, and Yalom (1981). Spiegel, Bloom, Kraemer, & Gottheil (1989) reported the median survival for patients who participated in a support group was 36.6 months (n=50), as opposed to 18.9 months for the control group (N=36) ($p<0.05$). No comment was made on any differences in treatment received after randomization. The findings of a lower level of anxiety and depression in subjects who attended a support group is in agreement with previous research correlating increased social support and lower levels of psychosocial distress in breast cancer patients (Irvine, Brown, Crooks, Roberts, & Browne, 1991a). The effects of social relationships on the immune system during and after adjuvant chemotherapy for breast cancer was examined by Lekander, Furst, Rotstein, Blomgren, and Fredrikson (1996). After, but not during treatment, patients with high attachment ratings had higher numbers and proportion of granulocytes ($F=(1,30)8.31$, $p=0.05$], and lower proportions of lymphocytes and ($F=(1,30)6.52$, $p=0.05$).

The information age offers promise in offering methods of communication and support to women through telecommunication. A computer-based support system, called the Comprehensive Health Enhancement Support System (CHESS), is being developed to help people experiencing a health crisis overcome barriers to obtaining information and referrals as well as decision and emotional support (Gustafson, et al., 1993). Pilot data revealed that the CHESS Discussion Group service was used by the sample of 20 women with newly diagnosed breast cancer to inquire about the side effects of treatment, such as fatigue, weight gain and sleeplessness. In addition, they expressed interest in self-help and wellness

information. Advantages of CHESS over traditional support services that the women listed included the anonymity, proceeding at their own pace, at any time, and that the system was capable of providing support from many women. Further testing via a randomized trial that examines CHESS's effect on health status, use of health services, and health behavior of patients and families will clarify the future role of such interpersonal support services.

Additional prospective studies of the effects of interpersonal relations behavior on perceived fatigue in patients with cancer undergoing adjuvant therapy are needed. Inter- and intrapersonal social patterns play a key role in influencing psychological and immunological response to cancer diagnosis and treatment, and positive interpersonal relations behavior may modify mood and increase the likelihood to engage in health-promoting lifestyle behaviors.

In summary, maintaining healthy interpersonal relations behaviors and social support networks have been identified as the strongest predictor of healthy coping responses to mastectomy and cancer treatment. Successful adjustment to breast cancer is related to socialization patterns and positive attitudes of each woman that come from within and are influenced by support from others. The benefits of support groups in influencing mood, immune and health status and long-term survival have been demonstrated. Results may be biased in support of groups as helpful during the initial periods of treatment, and number of rejections and drop-outs must be tallied and reported with study results. No study has examined the linkages between interpersonal relations behaviors of individuals and fatigue perceptions during treatment.

Symptom Patterns

The presence and the severity of distress from other symptoms associated with chemotherapy may influence fatigue in cancer patients. In this study, the severity of symptoms previously identified as distressing to women with breast cancer receiving chemotherapy were measured by subjects and included: difficulty sleeping, mood and nausea, in addition to the dependent variable of fatigue. Increasing levels of these distressing sensations that result from treatments are recognized as contributing to a secondary fatigue state, which has been described as the common denominator of acute symptom distress.

Symptoms other than fatigue in patients with cancer undergoing active treatment include pain, nausea, vomiting and dyspnea (Piper, et al, 1987). McCorkle and Young (1978) found that fatigue, pain, appetite and coughing were the four most frequent contributors to symptom distress in a sample of 53 of lung and breast cancer patients. Ehlke (1988) reported fatigue, insomnia, nausea and pain as the four most commonly encountered symptoms producing distress in a group of 107 outpatients with breast cancer. Blesch et al. (1991) reported a highly significant correlation present between pain severity and fatigue ($r=0.48$, $p<0.001$), and between total mood scores on the POMS and fatigue ($r=0.48$, $p<0.001$) in a sample of 77 of people with lung ($n=33$) and breast ($n=44$) cancer. A relationship between nausea and fatigue in patients receiving chemotherapy has not been reported, but they have often been anecdotally reported as occurring simultaneously. Fatigue correlated with depressed mood ($p=0.01$) and difficulty concentrating in Knobf's 1986 study of 78 women with stage II breast cancer receiving adjuvant chemotherapy.

Kurtz, Kurtz, Given, and Given (1993) investigated the trajectories of symptom distress and loss of physical functioning over time in a sample of 279 patients with a variety of types of cancer. Upon study entry, age and co-morbidity were significantly correlated, and loss of physical functioning was associated primarily with symptoms, and to a lesser degree, with advancing age. The most frequently occurring symptoms at study entry were fatigue, insomnia, pain, and nausea, which confirmed the previous findings reported by Ehlke (1988). Six months later, symptoms were associated with those at study entry, but were at lower levels. These results are consistent with the view that cancer treatment is often associated with acute onset of fatigue and other symptoms that are not reported by the entire sample to be significantly different at 6 months, possibly due to measurement issues, a re- setting phenomena, or a broad range of responses to treatment.

Further scientific study of the relationship between symptom patterns and fatigue is needed to identify predictors and correlates of fatigue which require modification in order for fatigue reduction to occur. Primary symptoms that reflect distress from the chemotherapy regimens used for adjuvant breast cancer include nausea, mood, and difficulty sleeping, and the relationship between symptom distress from these variables and fatigue needs to be clarified in women with early-stage breast cancer.

Initial Reaction to the Diagnosis of Cancer.

Recognizing that fatigue is a variable correlated with psychological health and mood, research supports investigation into the influence of a confronting versus distressful initial reaction to the diagnosis of cancer on lifestyle behaviors and perceptions of fatigue. Four mutually exclusively categories of psychological responses to the diagnosis of cancer

obtained 3 months after diagnosis have been identified based on the patients' descriptions of their moods: fighting spirit, helpless/hopeless, stoic acceptance, and denial (Greer, Morris & Pettingale, 1979). After 5 years, a positive outcome was more frequent in patients with active denial or fighting spirit (75%), than in patients who responded with stoic acceptance or helplessness/hopelessness (35%). After 10 years, using a multi-variate regression and eight prognostic factors, psychological response was the most significant individual factor influencing death from any cause (p=0.003), death from breast cancer (p=0.003), and first recurrence of disease (p=0.008) (Pettingale, Morris, Greer & Haybittle, 1985). Derogatis (1979) found that women who experienced long-term survival were more anxious and hostile at diagnosis than short-term survivors. Questions regarding the timing of data collection, and the validity and reliability of the instruments limit the generalizability of these findings, but the variable deserves further investigation (Morris, Blake & Buckley, 1985; Nelson, Friedman, Baer, Lane & Smith, 1989).

The ability to respond to the diagnosis in a confronting versus distress reaction manner may influence fatigue during treatment. Frank-Stromborg (1990) pilot tested the "Reaction to the Diagnosis of Cancer" (RDCQ) instrument and the most common comment related to how well certain statements generated clear recall by patients of earlier emotional responses. Subjects were studied at a variety of lengths of time after diagnosis, ranging from 2 to 24 months. The strongest predictors of variance in health-promoting lifestyle as measured by the RDCQ among the 385 ambulatory cancer patients were education levels, self-rating of health, and the confronting dimension of the reaction to cancer (all beta's= 0.187-0.191; explaining 23.5% of the variance). These results suggest that the confronting response to a

cancer diagnosis predicts participation in health-promoting lifestyle behaviors during and after adjuvant therapy, and may directly and indirectly influence fatigue, other symptoms, and survival. Findings from this study assist in identification of adults with cancer who are likely to incorporate health-promoting lifestyle behaviors into their lifestyle, or who would benefit from programs that would encourage a "confronting" orientation to the diagnosis of cancer.

Lavery and Clarke (1996) examined causal attributions, coping strategies, and adjustment to breast cancer in 244 Australian women at a mean time of 9.1 (SD=7.88) years after diagnosis. Women who rated their long-term adjustment as excellent initially displayed lower levels of helplessness, made fewer changes to their social behavior, were more anxiously preoccupied with their illness, sought more alternatives to medical therapy, and exhibited more information-seeking behavior than did those who currently rated themselves as less well-adjusted. The Mental Adjustment to Cancer Scale was used to rate the extent to which patients initially adjusted to the diagnosis with fighting spirit, helplessness, anxious preoccupations, fatalism, or avoidance (Watson, Greer, Young, Inayat, Burgess, & Robertson, 1988).

Glanz and Lerman (1992) reviewed recent literature and determined that as many as one-quarter of women with breast cancer suffered marked psychological morbidity associated with diagnosis and treatment, though for many this declined substantially within one year of treatment. Coping style, which included reaction to the diagnosis, appeared to moderate the impact of breast cancer on mood.

Determining the cognitive response to the diagnosis offers potential as a predictor variable for symptom distress. Changes in mental health may occur early, possibly during the initial diagnosis, in which case it would become an important predictor of symptom experience and physical functioning (Given, Given & Stommel, 1994). If this proposed relationship is supported in this study, health care team members could identify those individuals with a distressed response to diagnosis who are at greatest risk of experiencing more intense fatigue in order to closely monitor response to treatment.

Background Characteristics.

Several socio-demographic variables and co-morbidities which may influence fatigue are included in this study to describe the sample in terms of these variables. Data regarding factors such as age and marital status are limited and results are often conflicting in regard to the relationship between these factors and fatigue (Piper, 1993b). Age was not a significant predictor of risk for chronic fatigue in Piper's 1993 longitudinal study of women receiving chemotherapy treatments for breast cancer. Conversely, Stanton and Snider (1993) reported that the most promising demographic attribute of the person with a breast cancer diagnosis that is likely to influence adjustment is age, with reasonably consistent evidence that older women fare better than younger ones. There were no significant associations between severity of fatigue and age, but there was a strong association between fatigue and anxiety and depression.

A secondary analysis of data collected from a large group of community-based women in a U.S. Northwest urban community was reported by Lee, Lentz, Taylor, Mitchell, & Woods (1994). In this random sample of non-pregnant women ages 18 to 45 from the general

population, fatigue and vitality were found to be associated with internal environmental demands such as depression and poor sleeping patterns, and were not significantly correlated with marital status, income, occupation, employment status, level of education, number and age of children, role demands, and/or social support. Background characteristics of subjects will assist in describing the study sample and identifying variables that place women at increased risk of moderate to severe fatigue associated with adjuvant chemotherapy.

Summary

Fatigue is a multi-dimensional concept, the etiology of which is not well understood. A variety of physiological, biochemical, and behavioral patterns were proposed to be factors influencing fatigue in health and in patients with cancer. A review of the literature resulted in a synthesis of what is known about fatigue's relationship with the variables selected for this study. The literature review provided varying amounts of support for the hypothesis that fatigue may be influenced by health and functional status, chemotherapy protocols, activity/rest cycles, the lifestyle behaviors of physical activity, nutrition, stress management and interpersonal relations, nutritional status, symptom distress and by initial reaction to the diagnosis of cancer. Numerous studies reported inter-relationships between lifestyle behavior dimensions, but these results are seriously limited by study design and issues of reliable measurement. Clarification of inter-relationships among all selected influencing factors and fatigue will provide cancer rehabilitation programs knowledge needed to enhance program design and expected outcomes. Understanding the relationships among these variables will assist researchers in designing intervention studies aimed at the modification of fatigue.

This literature review indicates the need for both behavioral and physiological research that examines the relationship among the selected variables and fatigue in a variety of treatment situations. Participating in healthy lifestyle behaviors while undergoing adjuvant therapy may increase perception toward higher level wellness on a health-illness continuum, and result in lower perceptions and manifestations of fatigue.

CHAPTER 3

DESIGN & METHODS

A prospective, descriptive, repeated measures design was used to generate data regarding patterns of fatigue and selected factors influencing fatigue in women newly diagnosed with stage I or II breast cancer during the first three cycles of adjuvant chemotherapy. Purposive sampling at multiple sites in a metropolitan area was used to collect objective and subjective data from 72 participants who were between the ages of 30 and 69 years, and functioning at a level of unassisted or minimally assisted self-care at study entry. Data were collected for 3 to 4 days at 6 times coinciding with the first three treatments and the midpoint of each cycle. They included self-reports, height/weight, laboratory blood results and wrist actigraphy. Data analysis included descriptive statistics, correlations, paired t-tests, simple ANOVA's, repeated measures analysis of variance (RM-ANOVA), and regression/path analysis. Additional analysis of the wrist actigraphs included interval summary statistics, sleep analysis and full and daily cosinor analysis.

Pilot Studies

A series of 3 pilot studies were conducted in preparation for this study.

Fatigue and Quality of Life in Cancer Patients Receiving Out-Patient Chemotherapy

The first pilot study, conducted in 1992, was designed to test the use of two tools to measure the amount and characteristics of fatigue experienced and the quality of life (QOL) perceived by patients receiving outpatient chemotherapy. The convenience sample of 20 subjects ranged in age from 29 to 74 ($\bar{X}$=56). The majority were females, married, retired, and diagnosed within 1 year of study entry. The Piper Fatigue Scale (PFS) (Piper, et al., (1989a) and the Quality of Life Index-Cancer Version (QLI-CA) (Ferrans & Ferrell, 1990)

were both completed with minimal or no assistance within a 15-20 minute period by subjects during a scheduled appointment in an oncology clinic. Alpha reliability of the total PFS in this sample was 0.979, with subscale alpha's ranging from 0.782 (temporal) to 0.979 (sensory). Reliability analysis of the QLI-CA indicated an overall alpha of 0.933, and subscale alphas ranging from 0.700 (family) to 0.920 (psychological/spiritual). The correlation coefficient for overall QLI-CA with overall PFS was r= -0.805, (p=0.01), indicating that as fatigue scores increased, QOL scores decreased. Results of One-way ANOVA were significant between Karnofsky performance status (KPS) scores (Mor, Laliberte, Morris, & Wiemann (1984) and the overall QLI-CA scores (F= 3.12,p =0.04), and with the health and functioning subscale scores (F= 3.93, p =0.023). Differences in performance status were associated with varying QOL scores, and individuals at the lowest functional level reported the lowest levels of QOL. The PFS instrument was determined to be appropriate for use with patients undergoing chemotherapy in the planned dissertation research. Limitations identified were the cross-sectional design and variety of diagnoses and chemotherapy protocols. The results of this pilot study were presented at a national conference (Berger, 1993). A decision ultimately was made not to measure QOL in the larger study, in consideration of subject burden with multiple instruments.

Women's Response to Breast Cancer

A second pilot study, conducted in 1993, was designed to explore the relationship between initial reaction to the diagnosis of cancer and lifestyle behaviors in women with early stage breast cancer. Women were asked to recall lifestyle behaviors before knowledge of any breast disease and to also report on current lifestyle behaviors approximately 1 month after surgery. The study served as a pilot test of recruitment procedures and of two

instruments, the Reaction to the Diagnosis of Cancer Questionnaire (RDCQ) (Frank-Stromborg, 1989) and the Health-Promoting Lifestyle Profile II (HPLPII) (Walker & Hill-Polerecky, 1996). This study involved the first reported use of the RDCQ at a consistent time early in treatment (1 month after surgery) and the first use of the HPLPII with cancer patients. Women scheduled to begin adjuvant therapy who were 2-4 weeks post-operative for mastectomy or breast conservation were asked to participate in this cross-sectional design study. Ninety percent of the eligible women agreed to participate. The sample consisted of 29 women, ranging in age from 32-76 ($\bar{X}$=52, SD=9.68), the majority of whom were married, working full or part-time, and high-school graduates. Women reported clear recall of their reaction to the diagnosis approximately 4-6 weeks prior to data collection. A limitation of the study was that reliability of the data was questionable due to the passage of time and multiple stressors.

Among the demographic variables examined in relation to the RDCQ, the only significant relationship was found between higher family income and a confronting response to the reaction to cancer ($r=0.459$, $p=0.002$). Higher frequency of health-promoting lifestyle behaviors prior to diagnosis was weakly correlated with a distress response in reaction to the cancer diagnosis ($r=0.367$, $p=0.05$). Higher frequency of health-promoting lifestyle behaviors 1 month after surgery was not significantly correlated with a distress ($r=0.307$, $p=0.135$) or confronting ($r=0.135$, $p=0.519$) response. Comparison of lifestyle behaviors pre- and postoperatively revealed significant positive differences in total health-promoting lifestyle scores ($t=4.51$, $p<0.001$). Post-operatively, all four subscale scores reflected movement by women toward adoption of more frequent health-promoting behaviors: Spiritual Growth

(t=2.44, p=0.02), Stress Management, Interpersonal Relations and Health Responsibility (all p<0.001). Conclusions included a willingness of women to participate in a study 1 month after surgery, a relationship between a distress response and higher frequency of health-promoting lifestyle behaviors prior to diagnosis, and a movement toward adoption of healthier lifestyle behaviors after surgery. These findings suggested that there may be potential in clinical practice for oncology health care team members to assist women with adoption of health-promoting lifestyle behaviors during treatment, and supported further study. Pilot study results were presented at local, regional, and national conferences (Berger, 1994, 1995a, 1995b, 1995c). Recruitment procedures were developed and refined during this pilot, and both instruments were determined to be appropriate for use in the larger study. Investigation into the relationship between reaction to the diagnosis and subsequent response to treatment (i.e. lifestyle changes, fatigue) is warranted in a larger study. Linkages between specific responses to the diagnosis (confronting, distressful) and lifestyle behaviors may be associated with higher levels of fatigue, and assist the health care team to target areas for interventions.

Women's Response to Breast Cancer-II

In the third pilot study, conducted in 1994, the Piper integrated fatigue model framework was employed to examine activity/rest patterns and perceived fatigue and sleep quality in relation to health-promoting lifestyle behaviors during the first week of intravenous chemotherapy for breast cancer. The study subjects were 10 women with a mean age of 56 (range= 39-69), with some college education, half employed outside the home, who had been diagnosed with Stage I or II breast cancer within the previous month. The instruments used

to measure fatigue daily between 10 AM and 2 PM were the intensity/severity subscale of the PFS and the Pearson-Byars' (1956) Fatigue Symptom Checklist (FSC). In addition, a Visual Analog Scale (VAS) was used to measure fatigue six times a day. All instruments were completed during the 2 days prior to and for the 7 days after each woman received the initial chemotherapy treatment. Perceived sleep quality was measured daily using the Richards-Campbell Sleep Questionnaire (RCSQ) (Richards, 1987), grip strength was quantified by a hand-grip dynamometer, and activity/rest cycles were quantified by an actigraph worn continuously on the non-dominant wrist for 9 days and nights (Ambulatory Monitoring Inc.).

Women reported the highest intensity of fatigue 48-72 hours after receiving chemotherapy on all fatigue measurements. Mean daily fatigue intensity/severity subscale scores (PFS) were correlated with total fatigue symptom scores on the FSC, suggesting that as fatigue intensified, it was accompanied by an increasing number and intensity of fatigue symptoms such as feeling tired over the whole body, feeling tired in the legs, and wanting to lie down. Mean VAS fatigue scores at the six time points each day were in the mild range, gradually rising upward in a linear pattern from 15 upon awakening to 33 at bedtime (range 0-100). Age was negatively correlated with fatigue intensity as measured by the VAS during the week after treatment ($r= -0.998$, $p=0.01$). Age was also negatively correlated with overall presence of fatigue, with younger women reporting higher mean fatigue intensity scores as recorded on the PFS ($r= -0.998$, $p=0.01$).

Correlations between RCSQ sleep measurements and reported fatigue intensity by the VAS revealed that higher perceived sleep disturbance scores were associated with a higher

reported intensity of fatigue during the first week after chemotherapy (r=0.997, p=0.01). Correlations between the RCSQ and the PFS scores revealed a similar finding (r=0.881, p=0.01), and between the RCSQ and intensity of symptoms as measured by the FSC (r=0.998, p=0.01). Nighttime restlessness and increased fatigue were significantly correlated on a number of measurements.

Wrist actigraphy provided a valuable objective measurement in this pilot study. The mean activity index per 60-second collection unit for the chemotherapy administration day plus the next 4 days reached a significance level with total fatigue for the week (r= -0.850, p=0.05), indicating that lower activity per 60-second collection unit was associated with higher perceptions of fatigue. The mean activity index per 60-second collection unit for night time rest, an indirect measurement of sleep quality, was correlated with the RCSQ scores, indicating that perceptions of restlessness were correlated with increased number of recorded body movements during sleep (r=0.793, p=0.01). Alpha reliabilities of both tools in this sample were high; RCSQ =0.955, and the PFS=0.981. Limitations of the study included measurement issues regarding reporting of the intensity of fatigue (missing data, under-reporting), and technical problems with the wrist actigraphs failing to operate satisfactorily in 3/11 cases.

Conclusions of the study were that younger women may report higher levels of fatigue and need additional support and assistance during their first week after chemotherapy, especially 48-72 hours afterwards. Higher subjective fatigue scores were correlated with lower daily mean activity indexes and poorer subjective sleep quality was correlated with higher night-time mean activity indices. Fatigue and activity scores appeared to change

simultaneously and did not clarify the mechanism involved in this reciprocal relationship. This study reinforced the need to further investigate activity/rest patterns and fatigue in a larger study. Patient teaching regarding expectations after chemotherapy may be enhanced by incorporating results from this study into practice and describing the "lived experience". This study was presented at local, regional and national conferences (Berger, 1995d, Berger, 1995e, Berger, 1995f). It was decided to use the wrist actigraphs in the larger study to further understanding of the relationship between perceived fatigue and activity/rest scores derived from wrist actigraphy. Measurement of perceived sleep quality was also determined to be an important factor when examining fatigue after chemotherapy administration. A decision was made to obtain data for 4 days after chemotherapy administration in the larger study because fatigue scores returned close to baseline on the fourth day after chemotherapy in the pilot sample.

Institutional Review Board Approval

The research proposal was approved by the Institutional Review Board (IRB) of the University of Nebraska Medical Center on October 18, 1994. After committee approval of the proposal with revisions in late June, 1995, a request for change in protocol was submitted and approved in July, 1995. IRB approval was also obtained at the following agencies in the Omaha-Council Bluffs area: Bergan Mercy Medical Center, Clarkson Hospital, Creighton University-St. Joseph Hospital, Methodist Hospital, Midlands Hospital, and Immanuel Hospital. Letters from the Institutional Review Boards are included in Appendix I.

Sample

Women with stage I or II breast cancer were chosen for study because this population is treated with intent of cure, and appears to experience fatigue during chemotherapy that might be influenced by lifestyle behaviors. After surgery, this group of women had the bulk of tumor removed, so that no or minimal cancer cells remained to release substances including tumor necrosis factor, that are believed to influence fatigue.

Sample size was determined by power analysis for multiple regression. With a level of significance set at 0.05, a power of 0.80, and a medium effect size of 0.30 determined from Piper's works and this investigator's pilot studies and calculated for fatigue regressed on 18 independent variables, the size of the necessary sample was determined to be 63 (Cohen, 1988). Local hospital tumor registries were contacted to assure that an adequate sample (including 17, or 25% over-sampling) of women could be obtained within a 9-12 month period. During a 12 month period, a purposive sample of 72 women (including 15% over-sampling) who were diagnosed with stage I or II breast cancer were recruited into the study. Potential subjects names were obtained by screening hospital surgery schedules, and then tracked through local oncologist's offices. Women were not contacted until after an appointment had been made to receive adjuvant chemotherapy following modified radical mastectomy (MRM) or breast conservation surgery plus radiation therapy (BC). The sample was distributed across eight sites, with 50% of the sample (n=36) recruited from one oncology office. The remaining half were divided among 7 sites; these oncology offices provided 10, 9, 6, 5, 4, 1, and 1 cases, respectively, to the sample.

Inclusion criteria were confined to women, ages 30-69, diagnosed for the first time with stage I or II breast cancer, scheduled to begin intravenous chemotherapy following recent MRM or BC, English-speaking and able to complete the research instruments, and a score of 60 or above on the Karnofsky Performance Scale. Women who receive chemotherapy sometimes receive radiation treatments at some point between chemotherapy treatments, and lumpectomy patients who might receive radiation treatments were accepted into the study. Age was restricted to these four decades because of the rare occurrence of the disease prior to age 30, and the possibility that women over 70 might have fatigue associated with aging and various co-morbid diseases that could threaten the validity of the results. Exclusion criteria were co-morbid diagnoses of congestive heart failure, chronic obstructive pulmonary disease, insulin-dependent diabetes, or neuromuscular disease such as multiple sclerosis, and current steroid therapy. There were very few women excluded from the study solely because of these criteria. When these conditions were present, they occurred almost exclusively in women ages 70 and over who were ineligible for the study.

Upon approval to begin data collection, the researcher arranged with participating agencies to receive the names of women who had undergone a modified radical mastectomy or breast conservation procedure. These names were then transferred to a data collection form and presented to receptionists at medical oncology offices. Frequent visits to the offices as well as phone calls provided the researcher with the information needed to screen for eligibility to the study and to determine if and when any chemotherapy treatments had been scheduled. The office staff was instructed regarding criteria for the study. A flyer briefly describing the study was given to the woman by the doctor or nurse at the end of the

visit after the decision to receive chemotherapy was made. After the woman made an appointment to receive one of the 3 adjuvant chemotherapy protocols, a phone call was made by the researcher or her assistant to request participation in the study. If a positive response was obtained, arrangements were made for a personal meeting in the patient's home, the doctor's office or a mutually convenient place to describe the study, provide instructions regarding subject expectations, and obtain written consent prior to the first treatment.

Demographic characteristics of the sample of women who entered the study are shown in Table 1. The sample included 72 women, ages 33 to 69, split almost evenly between women with stage I or II disease, between positive or negative lymph node status, and between breast conservation or modified radical mastectomy surgical procedures. The sample was balanced between women pre and post with fewer who were peri- menopausal, and between the three adjuvant chemotherapy regimens. Table 1 also displays demographic data on the 60 women who completed the entire study.

A decision not to participate in the study was made by 5 women, or 6% of those contacted. Reasons given included feeling too overwhelmed at the time, too upset, or too busy.

Population and Setting

Approximately 75% of women diagnosed with early stages of disease have historically selected MRM in this midwestern city, and a smaller percentage have selected BC, but the BC percentage is increasing (NE State Dept. of Health, 1994). A large percentage of those diagnosed with Stage I or II disease receive adjuvant intravenous chemotherapy in accordance with the most recent guidelines released by the National Cancer Institute (NIH,

Table 1

Demographic Characteristics of Women with Stage I or II Breast Cancer Receiving Adjuvant Chemotherapy

Characteristics	Time 1 (N = 72)	Time 6 (N = 60)
Age	$\bar{X}$= 49.5 (33-69)	$\bar{X}$= 48.7 (33-69)
Marital Status	(SD = 8.64)	(SD = 8.53)
Single	5	4
Married	47	44
Separated	1	1
Divorced	11	7
Widowed	8	4.
Employment		
Full-time	42	38
Part-time	11	8
Homemaker	11	9
Retired	7	5
No response	1	0
Number of Children at Home		
0	36	30
1	15	14
2	14	11
3	5	4
4 or >	1	1
No response	1	0
Education		
Less than High School Graduate	1	0
High School Graduate	26	22
Some College	19	18
College Graduate	16	12
Post-Graduate Work	7	6
No Response	3	0

(table continues)

Characteristics	Time 1 (N = 72)	Time 6 (N = 60)
Household Income		
< $20,0000	8	5
$20,000-$40,000	22	20
> $40,000	32	29
No Response	10	6
Residence		
Own Home	63	54
Rent home	1	1
Rent Apartment	6	4
Other	1	1
No Response	1	0
Ethnic/Racial Background		
Black, non-Hispanic	3	1
White, non-Hispanic	69	59
Number of Prescribed Medications Taken:		
0	41	36
1	16	15
2	1	1
3	6	4
4	5	4
No Response	3	0
Number of days between surgery & chemotherapy	$\bar{X}$= 29.7 (12-83) (SD = 13.20)	$\bar{X}$= 29.2 (13-83) (SD = 13.0)
Surgical Procedure		
Breast-conserving lympectomy	34	27
Mod. Rad. Mastectomy (MRM)	28	23
MRM with reconstruction	10	10

(table continues)

Characteristics	Time 1 (N = 72)	Time 6 (N = 60)
Radiation		
Yes, prior to chemo	1	1
Yes, during chemo	12	10
No	59	49
Stage of Breast Cancer		
I	32	26
II	40	34
Lymph Node Status		
Positive	33	28
Negative	39	32
Menopausal Status		
Pre-menopause	33	19
Peri-menopause	10	18[a]
Post-menopause	29	23
No response	0	1
Chemotherapy Protocol		
Cytoxan (IV) Methotrexate, 5-FU	1	1
Cytoxan (oral) Methotrexate, 5-FU	25	22
Cytoxan, Adriamycin	20	15
Cytoxan, Adriamycin, 5-FU	26	22
Number of Support Group Meetings Attended		
0		35
1		12
2		5
3 or >		7
No Response		2

[a]Incudes women who had not had a menstral period since beginning chemotherapy.

1990). Conclusions from that report support the use of adjuvant systemic chemotherapy as standard therapy in node-negative patients, especially in women with tumors measuring 2 cm or more in diameter (Goodman, 1991), in addition to women with node positive disease. Only patients with tumor < 1 cm and no evidence of nodal metastasis do not require adjuvant therapy outside of a clinical trial (Dow, 1991).

The sample was recruited from eight metropolitan hospitals and out-patient clinics in Iowa and Nebraska that treat women with breast cancer. IRB approval was obtained from hospitals. Medical oncologists who receive referrals from surgeons affiliated with the hospitals were contacted, the study discussed with them, and letters of agreement were obtained (Appendix J). Clinical Nurse Specialists and nursing staff in cooperating agencies and clinics were contacted and cooperated fully with the study. Health care facilities that treat people from diverse ethnic backgrounds were utilized in attempt to obtain a sample representative of the local racial/ethnic diversity, which is 89% Caucasian, 8% Black, 1% Asian, 0.5% American Indian, and 1% other (Bureau of the Census, 1990). Minorities were recruited into the study in an attempt to represent the local population ethnic diversity statistics and included the following distribution: Caucasian, 96%, Black 4%. There were no refusals to participate from the diverse ethnic groups, but simply a lack of subjects diagnosed at an early stage of disease. Of the three Black women recruited into the study, two dropped out after the second data collection time. Both women expressed no interest in continuing with the study.

Procedure for Data Collection

This study was designed in a manner that was labor intensive for the researcher and relatively easy for the subject in order to assist with recruitment and reduce drop-out rates. A research assistant was hired to assist in subject recruitment activities, data collection and data entry. Training of the assistant in all procedures was conducted by the researcher to insure consistency and reliability of instrument completion.

After obtaining verbal consent to participate in the study over the telephone, an appointment was made with each woman to explain the study prior to the scheduled chemotherapy treatment. The initial meeting took place in the medical oncologist's office or in the patient's home, according to patient preference. Later data collection took place primarily in the home, with only weight and blood samples obtained routinely during visits to the office. The teaching plan to orient women to the study included: signing the written consent, a description of written instruments, wrist actigraphy, laboratory work, and the schedule of data completion times. A 9-minute video presentation also was available if desired to describe the study and outline procedures. The video was viewed either in the home or in the oncology clinic by approximately 25% of the sample. After this introduction, the written consent was signed by the subject and the investigator (Appendix K).

Written instruments were explained to subjects in a brief and clear manner that reflected awareness of their anxiety level regarding chemotherapy treatments. At each time, an instruction sheet was included as the first page of the notebook to give step by step instructions on how to complete the instruments each day at home. All instruments were completed in the same manner, by circling the number that best answered the question asked.

Women were asked to complete the instruments during the same 4-hour block of time of day at all six data collection points unless lifestyle habits included awake at night and sleep during the day. Only one participant worked the night shift and slept in the day. Biological rhythms were accounted for by determining the 4-hour block of time of day that corresponded to 12 hours following the mid-point of the individual's usual night's sleep (for most women, this was between 2-6 PM).

Table 2 is the data collection time table, which outlines the variables and the measurements used during the investigation, the time points, and the requirements for completion of the instruments. The six data collection times included: Time 1- Treatment 1, (days 1-4); Time 2- Mid-point 1, (3 mid-point days); Time 3- Treatment 2, (days 1-4); Time 4- Mid-point 2, (3 mid-point days); Time 5- Treatment 3, (days 1-4); Time 6- Mid-point 3, (3 mid-point days). The instruction sheet and video presentation both emphasized the importance of filling out the instruments on the scheduled days and for allowing adequate uninterrupted time for completion. Every attempt was made to select instruments with established reliability and validity and careful consideration was given to minimize the amount of subject fatigue. Copies of all instruments are included in Appendices B-H, and letters of permission to use the instruments can be found in Appendix L.

Women were asked to wear the wrist actigraph for 96 hours beginning on awakening on the day of the chemotherapy treatments, and for 72 hours at the mid-point of the cycles. For 21-day cycles, these were days 10, 11, and 12; for 28-day cycles of CAF, these were days 13, 14 and 15; and for 28-day cycles of CMF with oral Cytoxan, days 16, 17, and 18). Subjects were instructed to keep the actigraph on at all times day and night except when it

Table 2

Data Collection Timetable

Variable	Measurement	Time 1 Treatment 1 Days (1-4)	Time 2 Midpoint 1 Days (1-3)	Time 3 Treatment 2 Days (1-4)	Time 4 Midpoint 2 Days (1-3)	Time 5 Treatment 3 Days (1-4)	Time 6 Midpoint 3 Days (1-3)
Fatigue	Piper Fatigue Scale	(3)	(2)	(3)	(2)	(3)	(2)
Physical Function	MOS (SF-36) (acute)	Recall(1)				(3)	
Role/Physical							
Role/Emotional							
Social							
Mental Health							
General Health							
Physical Activity Behaviors	Health-Promoting	Recall (1)		(3)		(3)	
Nutrition Behaviors	Lifestyle Profile II	(3)					
Interpersonal Relations Behaviors							
Stress Management Behaviors							
Activity/Rest Cycles	Wrist Actigraph	96'	72'	96'	72'	96'	72'
Nutrition Status							
Hematocrit	Hematocrit	(1)	(2)	(1)	(2)	(1)	(2)
Body Mass Index	Body Mass Index (BMI)	(1)		(1)		(1)	
Symptom Distress	Modified Symptom Distress Scale	(1,2,3,4)	(1,2,3)	(1,2,3,4)	(1,2,3)	(1,2,3,4)	(1,2,3)

table continues

Variable	Measurement	Time 1 Treatment 1 Days (1-4)	Time 2 Midpoint 1 Days (1-3)	Time 3 Treatment 2 Days (1-4)	Time 4 Midpoint 2 Days (1-3)	Time 5 Treatment 3 Days (1-4)	Time 6 Midpoint 5 Days (1-3)
Reaction to Diagnosis of Cancer Confronts Distress	Reaction to Diagnosis of Cancer Questionnaire	React (1)					
Chemotherapy Protocol	Chemotherapy Protocols Index	(1)					
Background Data	Background Data Form	(1)					
	Follow-Up						(3)
Time Requirements for Completions		60"	15"	25"	15"	35"	25"

[1]Recall = indicates recall measurement of the variables prior to knowledge of abnormality of breast, completed on day 1.

React = indicates recall measurement of the variables at the time of diagnosis, completed on day 1.

Numeral = indicates the days at each time when tools were completed. Treatment days 1-4 begin the day chemotherapy is given; Midpoint days #1-3 are dependent on protocol, as shown in Appendix D.

might get wet. They were given permission to remove the actigraph if it became annoying or added to the burden of the experience.

This study placed minimal additional burden on the clinic staff during the appointment, and did not extend the length of the appointment time. Routine laboratory samples and height and weight were collected before each treatment by clinic personnel. The researcher obtained the values for hematocrit at all 6 times, and height and weight at times 1, 3, and 5 by a chart review. Laboratory samples were collected at times that closely approximated completion of written tools. At times 1, 3, and 5, values were obtained 48 hours prior to completion of the PFS; the value was not expected to change during the interim. At times 2, 4, and 6, values were retrieved from the chart that corresponded closest to the mid-point day.

The schedule of data completion times was coordinated by the researcher and the assistant who met weekly to coordinate drop-offs and pick-ups of instruments. The researcher or the assistant always telephoned in advance to arrange to meet the subject at a convenient time and place. The monetary value of the wrist actigraph necessitated direct transfer of the instrument from the researcher to the woman or her designate. The mail was used for questionnaires only when subjects lived outside the metropolitan area. This aspect of the study was extremely labor intensive and had to be carefully coordinated to assure that adequate wrist actigraphs were available at the scheduled times. Length of time in the study for each subject was approximately 10-12 weeks.

Measurement of Variables

Piper Fatigue Scale

The Piper Fatigue Scale (PFS) is the first multidimensional subjective fatigue measure

with reliability and validity established in patients with cancer (Piper, Lindsey, Dodd, Ferketich, Paul, & Weller, 1989a). The revised PFS (Piper, et al., 1996) contains 22 horizontal continuous data items (range= 0 - 10) that measure four dimensions of subjective fatigue: Behavioral/Temporal (6 items), Sensory (5 items), Cognitive/Mood (6 items), and Affective/Emotional meaning (5 items). Each of the 22 items is anchored by two words (i.e. strong/weak, vigorous/sluggish) between which the individual makes a circle around the number between 0 and 10 that best describes the fatigue which she is experiencing. The total item scores range from 0 to 220; the mean score is obtained by dividing the sum of all scores by 22, with lower scores reflecting less perceived fatigue. Four open ended questions regarding perceived cause, effect, and associated symptoms complete the tool. Content validity has been reported by the authors. A principal components factor analysis with varimax rotation was performed using data from over 700 women with breast cancer in the Philadelphia area. Construct validity was established for the four factors/subscales. Alpha reliability for the entire revised scale was 0.966 (Piper, 1996). Alpha coefficients in the current study ranged from 0.978 to 0,999 for the total and 0.929 to 0.960 for the subscales.

This instrument was completed approximately 48 hours after each chemotherapy treatment and on the middle day at each cycle midpoint. A total and four subscale scores were obtained. The timing of instrument completion was selected for approximately 48 hours after the chemotherapy administration as a result of pilot work that determined that peak intensity of fatigue occurs at that time (Berger, 1995d). There is no "gold standard" with which to compare findings from this instrument, and the PFS is the current instrument of choice for use with oncology patients. A copy of the PFS can be found in Appendix B.

Medical Outcomes Study Short-Form General Health Survey (MOS-SF-36 acute)

The Short Form 36 survey was constructed to include eight of the most important health concepts from the MOS and other widely used health surveys (Ware & Sherbourne, 1992). It provides a common yardstick to compare patients with health problems to those sampled from the general population. The instrument was designed to measure quickly the patient's perceptions of health and provided the researcher with a solid baseline of physical and mental health dimensions.

Reliability and validity were established by its developers using samples from across all socio-economic groups. Across patient groups, all scales passed tests for item internal consistency (97% passed) and item discriminant validity (92% passed). Median alpha reliability across scales was 0.85 (range= 0.65 - 0.94). Findings support the use of the SF-36 survey across diverse populations (McHorney, Ware, Lu & Sherbourne, 1994). Baseline scores on the MOS-SF-36 have been reported for the first 9749 participants in the Breast Cancer Prevention Trial (Ganz, Day, Ware, Redmond, & Fisher, 1995). Construct validity of the entire instrument and convergent and discriminant validity of the physical functioning and mental health components were established (McHorney, Ware & Raczek, 1993). Alpha reliabilities for the MOS-SF-36 in this study ranged from .773 to .900 at the Time 1 recall measurement to .803 to .901 at the third treatment.

Six of the eight subscales of the 36 item survey were used in this study at 2 time points. Each subscale score ranges from 0 to 100, with 100 being the most favorable score. Subjects were asked to complete the SF-36 survey at Time 1 recalling their health status prior to diagnosis. Subjects again completed the SF-36 at Time 5 in order to determine health status

at the time of the third chemotherapy treatment. The subscales measured include: (a) physical functioning, (b) role limitations due to physical health problems, (c) general health, (d) social functioning, (e) role limitations due to emotional problems, and (f) mental health. Pain and vitality subscales were not included in this analysis because pain was not expected to be a concern among the healthy sample prior to diagnosis and 12 weeks after surgery, and vitality was redundant with the dependent variable of fatigue. Items are numerically scaled in a Likert format. Instructions are to circle one number that best describes the individual's functioning in the conceptual areas tested. The mental health subscale was used to identify women in the sample who may be experiencing emotional problems since complaints of fatigue are commonly associated with depression. A diagnosis of depression is often not made by those caring for women in the initial phase of treatment, and may not have been included in the demographic and health history completed by the woman. This permitted examination of fatigue associated with chemotherapy, controlling for mental health status. A copy of the SF-36 tool is found in Appendix C.

Chemotherapy Protocol

Adjuvant chemotherapy protocols utilized as standard adjuvant chemotherapy for Stage I or II breast cancer were selected for this study. An index of chemotherapy protocols was developed that identified current standard protocol drugs, dosages and cycle lengths. Regimens were divided into two groups to reflect likelihood of toxicity with treatment: those containing intravenous Adriamycin and Cytoxan, and those that did not contain these drugs by the intravenous route. When examinations involved activity/rest patterns and fatigue, the groupings remain the same, but are reported in a manner consistent with previous reports as

non-Adriamycin and Adriamycin-based regimens. A copy of the Chemotherapy Protocols is in Appendix D.

Health-Promoting Lifestyle Profile II (HPLPII)

The original 48-item HPLP was developed in order to measure health-promoting lifestyle behaviors, which are defined as "patterns of self-initiated actions and perceptions that serve to maintain or enhance the level of well-being, self-actualization and fulfillment of an individual" (Walker, Sechrist and Pender, 1987). The revised HPLPII is a 52-item summated rating scale that employs a 4-point response format from 1=never to 4=routinely to measure the frequency of six behavioral dimensions of health-promoting lifestyle: spiritual growth, health responsibility, physical activity, nutrition, interpersonal relations and stress management among adults. A principal axis factor analysis supported the presence of these six subscales (Walker & Hill-Polerecky, 1996). Construct validity and reliability have been established. Cronbach's alpha was 0.941 for the total scale and ranged from 0.792 to 0.871 for the subscales.

Scores on four subscales of the HPLPII were used in this study; physical activity (8 items), nutrition (9 items), interpersonal relations (9 items) and stress management (8 items). Mean scores were computed for each of these four subscales. Scores can range from a low of 1.00 to a high of 4.00, reflecting increasing frequency of health-promoting lifestyle behaviors. The HPLPII was included in the study to determine the individual's baseline lifestyle behaviors one month prior to diagnosis, and at the time of each chemotherapy treatment. Alpha reliabilities in this study ranged from 0.885 to 0.899 for physical activity; 0.828 to 0.891 for nutrition; 0.852 to 0.897 for interpersonal relations; and 0.747 to 0.869

for stress management across four administrations. A copy of the HPLPII is found in Appendix E.

Wrist Actigraphy

Wrist actigraphy measurements of activity and rest cycles such as mesor, amplitude, day high and nighttime awakenings offer a useful non-invasive method of objectively quantifying actual movement of an individual (Kripke, et al., 1978). Actigraphy enables continuous monitoring of activity/movement using a device worn on the non-dominant hand. The piezoelectric sensor in the wrist-sized actigraph recorded movement for 5 seconds at regular 1 minute intervals for the selected periods of days. Subjects were told to remove the actigraph for activities in which it might get wet. Data were then downloaded and edited prior to analysis using the ACTION 3 software program.

Reported calibrations of the actigraph were within plus or minus 10% (Brown, et al., 1990). Wrist actigraph estimation of sleep time was compared to electroencephalogram (EEG), electro-oculagram (EOG), and submental electromyogram (EMG), and correlation between the two methods for total sleep period was r=0.90, with estimations agreeing 94.5% of the time (Mullaney, Kripke, & Messin, 1980). These findings were repeated in a follow-up study by Webster, Kripke, Messin, Mullaney and Wyborney (1982). Sleep percentage and sleep latency estimates by actigraph correlated 0.82 and 0.90 (p=0.001), with corresponding parameters measurements from the polysomnogram in a study by Cole, et al., (1992), demonstrating the ability to discriminate activity from sleep.

In this study, the mini-motionlogger actigraph device (Ambulatory Monitoring, Inc.) was used to quantify and record the activity/rest cycle movements for the first four days (96

hours) and the three mid-point days (72 hours) of each chemotherapy cycle. Mesor and amplitude were selected because these values reflect overall mean activity levels and ability to respond to both increased and decreased energy requirements over a designated period of time. Their summed score on day 3, referred to as Day high 3 in this study, provided an overall index of activity over 24 hours. Awakenings were selected based on the widely accepted findings in sleep research that day-time fatigue perceptions are strongly associated with number of night-time awakenings. This information was obtained from and analyzed using interval summary statistics, sleep analysis and daily and full cosinor analyses, a method by which to analyze data for circadian rhythmic parameters. The data from each subject at each time were fitted to a model cosine curve, using a curvi-linear least squares regression which yielded statistical estimates of circadian rhythms of activity and rest (Farr, Campbell- Grossman & Mach, 1988). Additional analyses were programmed in SPSSX to determine the relationship between activity/rest variables, other study variables, and fatigue.

Hematocrit

Blood samples were obtained routinely by laboratory personnel to monitor the effects on the oxygen carrying capacity of the blood. Hematocrit values were retrieved from the patient's medical record by the researcher for the purpose of determining the relationship between the oxygen carrying capacity of the blood and subjective reports of fatigue. It was recognized that hydration status affects hematocrit levels, however a subject's fluid balance was expected to be within normal limits at the time of the blood samples. A variety of instruments were used in cooperating agencies to measure blood levels of hematocrit, however these instrument all have established precision and undergo routine maintenance

and checks for accuracy according to laboratory standards for hospitals and clinics. Hematocrit values were routinely obtained on the day of each chemotherapy treatment and at the mid-point of each cycle.

Body/Mass Index (BMI)

BMI is calculated as the total body weight in kilograms divided by the square of the stature, or meters squared (Kg/M^2), and is highly correlated with body fatness (Zeman & Ney, 1988). A BMI greater than 27 is indicative of obesity, and a value of 24-27 reflects excess fat stores (Zeman & Ney, 1988). Heights and weights were obtained on the first day the woman received chemotherapy by the clinic staff and were used to calculate chemotherapy dose. Weight was obtained at each successive chemotherapy treatment using the same scale at the physician's office to calculate the BMI. The BMI was calculated at Times 1, 3 and 5 to determine if BMI values were associated with the intensity of fatigue experienced with each treatment cycle.

Modified Symptom Distress Scale (M-SDS)

The Symptom Distress Scale (SDS) was originally designed to measure the degree of discomfort associated with 10 symptoms commonly experienced by patients during cancer treatment (McCorkle & Young, 1978). When using that instrument, subjects were asked to put a circle around the number that most closely measured how much nausea they had, how they were feeling at the moment, how well they slept last night and how tired they were feeling today, in addition to 6 other symptoms. A revised SDS was made available in 1983 by McCorkle, but was determined to be inappropriate for this study because it asks about

symptoms over the last week, and includes phrases with each rating for each symptom that were not appropriate for daily use.

In the current study, a modified version of the 1978 SDS (M-SDS) was used to reduce subject burden and to concentrate on the primary symptoms reported by breast cancer patients undergoing adjuvant chemotherapy. On the revised scale subjects are asked to put a circle around the number (range= 0-10, with higher numbers reflecting more distress) that best indicates the severity of the nausea they are experiencing, their mood today, their sleep last night and the severity of the fatigue they are experiencing. Each item is anchored by a phrase (i.e. "A good night's sleep"/ "A bad night's sleep"). Although subjects answered these items on the M-SDS in regard to severity rather than to a perceived distress level, it is assumed that increasing intensity of these symptoms is distressing in most situations.

Reliability coefficient alpha was reported as 0.821 and the standardized alpha was 0.826 in the original study by McCorkle and Young (1978). Content validity for the modified tool was established by literature review and a panel of 3 advanced practice oncology nurses. Alpha reliabilities in the current study ranged from 0.844-0.925. The fatigue scores obtained on the M-SDS were not included in this analysis. The instrument was completed in less than 5 minutes daily at each time in this study. A mean of M-SDS scores was calculated for the combined total of the 3 symptoms for 3 or 4 days (range = 0-90/9 at times 2,4,6 or 0-120/12 at times 1,3,5) to indicate mean symptom severity during that time. A copy of the M-SDS is found in Appendix F.

Reaction to the Diagnosis of Cancer Questionnaire (RDCQ)

This instrument was completed at Time 1 to report women's recall of their initial reaction to the diagnosis of cancer. The RDCQ (Frank-Stromborg, 1989) is a 28-item questionnaire with a modified 5-point forced choice Likert format ranging from 1= "no, I did not feel that way" to 5= "yes, I felt that way extremely". The instrument measures a cancer-specific cognitive-perceptual variable of emotional state in the domains of "confront" (9 items) and "distress" (19 items) responses. The 2 scales contain items that reflect an attitude of fighting to overcome the cancer or of feeling helpless and hopeless regarding the diagnosis. Subscales of items scores were summed, and higher scores indicated a stronger response in a particular domain that may have influenced perceived fatigue.

Construct validity was assessed with 441 ambulatory general oncology patients and the two domains identified by factor analysis. Test-retest reliability over a 2 week interval was reported as 0.92 for the distress subscale and 0.83 for the confronting subscale, and alpha reliability coefficient as 0.92 for the distress subscale and 0.83 for the confronting subscale by Frank-Stromborg et al (1990). Pilot study results by this researcher (N=30) indicated an alpha reliability coefficient of 0.87 for the distress subscale and 0.81 for the confronting subscale (Berger, 1995a). Alpha reliabilities in the current study were 0.888 for confront and 0.894 for distress. A copy of the RDCQ is in Appendix G.

Background Data

A questionnaire was developed for the study to obtain baseline data and final data point information about subjects. Background data are those characteristics used to identify and define the study population. Items on the form included age, ethnic/racial background,

marital status, number of dependents and ages of those at home and away from home, education, employment status, household income, disease stage including lymph node status, estrogen and progesterone status, surgical procedure and date, menopausal status and housing status (see Appendix H-1). A listing of co-morbid conditions and medications taken, chemotherapy protocol toxicity and cycle length were also included. The Karnofsky Performance Status score (Mor et al., (1984) was used only to determine eligibility for the study (must be 60 or above). Information about employment status, changes in drugs taken in addition to chemotherapy, attendance at support groups, and menopausal status was collected again at Time 6 (see Appendix H-2). This information provided descriptive information about the study sample.

Procedures for Data Analysis

The data were analyzed utilizing the Statistical Package for the Social Sciences (SPSS) (Norusis, 1990). Data were coded according to the criteria established by the researcher and entered into the EPI-info data base software program (Dean, 1994). Data were double entered by the research assistant and validated for accuracy. SPSSX programs were set up to analyze the data. Data cleaning and inspection of data for extremes and outliers were performed by running frequencies and plots, and examining the skewness and kurtosis of all variables. Three study variables from the SF-36 were found to be negatively skewed at a level >2.00. Skewness was addressed by performing a cubic power transformation of these variables. Results lowered skewness below 2.00, but magnified kurtosis >2.00. Analyses were run with both the original and transformed variables. Use of the transformed variables did not change any conclusions or significance values. Therefore, for ease of interpretation, original

variables were used in the analysis that is reported. Sample median substitutions were performed on all scales if <10% of the responses on a scale were omitted.

Research Question 1. What are the patterns of fatigue and of selected factors influencing fatigue among women with stage I or II breast cancer across the first three cycles of chemotherapy?

Descriptive statistics were used to describe patterns of fatigue and of selected influencing factors on fatigue at each time. RM-ANOVA was used to analyze data for changes over time in (a) fatigue as reported by total and 4 subscale scores on the Piper Fatigue Scale (PFS), and (b) 6 health and functional status scales, chemotherapy protocol, physical activity behavior, activity/rest cycles, nutrition behavior and status, stress management behavior, interpersonal relations behavior, and symptom distress. Simple ANOVAs and t-tests were used to describe patterns between two time points. RM-ANOVA was used to determine how fatigue and the variables that contribute to fatigue vary across the three cycles of chemotherapy treatment. Follow-up analyses were performed to further knowledge regarding when significant changes occurred. Data for activity/rest variables were available at some of the six times for the majority of the women. Comparisons were made whenever sets of data on selected variables were available. The activity/rest variables were then compared to fatigue scores on the PFS by correlations, One-way ANOVAs, and simple regressions. Data baseline measurements were examined to determine if any baseline behaviors or biological variables were related to higher levels of fatigue during the study.

Research Question 2. To what extent do health and functional status, chemotherapy protocols, physical activity behaviors, activity/rest cycles, nutrition behaviors and status, stress management behaviors, interpersonal relations behaviors, symptom distress patterns, and reaction to the diagnosis of cancer explain fatigue 48 hours after each of three cycles of chemotherapy treatments?

Path analyses, employing ordinary least squares regression, were used to examine the direct and indirect relationships posited in Figure 1 during the first three cycles of chemotherapy. R^2 values were examined to determine the variance in fatigue at each time explained by influencing factors, including current and past lifestyle behaviors. Beta weights were used to calculate direct and indirect effects and to determine the relative influence of each variable on fatigue. Data for activity/rest variables were available for the complete measurement interval at all 6 times for a subset of women. These values were then compared to fatigue scores on the PFS to evaluate longitudinal and predictive changes in activity/rest over time.

Research Question 3 To what extent do health and functional status, chemotherapy protocols, physical activity behaviors, activity/rest cycles, nutrition behaviors and status, stress management behaviors, interpersonal relations behaviors, symptom distress patterns, and reaction to the diagnosis of cancer predict fatigue at the mid-points of each of three chemotherapy treatment cycles?

Path analyses employing ordinary least squares regression were used to examine the direct and indirect relationships posited in Figure 1 between the first four days of chemotherapy and the mid-point days of each cycle of treatment. R^2 values were examined

to determine the variance in fatigue at each time explained by influencing factors, including current and past lifestyle behaviors. Beta weights were used to calculate direct and indirect effects in order to determine the relative influence of each variable on fatigue.

CHAPTER 4

ANALYSIS OF DATA

A variety of analyses were employed in order to answer the study questions. Results of data analyses are organized and presented according to each research question. All subjects' data were included in answering research question 1. Only subjects for whom data were available at all times were included in the analyses to answer questions 2 and 3.

Research Question 1:

Patterns of Fatigue and Factors Influencing Fatigue Over Time

Research Question 1 was: What are the patterns of fatigue and of selected factors influencing fatigue among women with stage I or II breast cancer across the first three cycles of chemotherapy?

Patterns of Fatigue

Repeated Measures-Analysis of Variance (RM-ANOVA) was used to analyze data for changes in fatigue over time as measured by the total and four subscale scores of the revised Piper Fatigue Scale (Piper, et al., 1996). This scale contains 22 horizontal continuous data items (range 0-10) that measure the intensity of fatigue in four dimensions. Higher mean scores reflect more intense fatigue. As shown in Table 3, there was a significant difference ($F(5,295)= 7.70$, $p<.001$) for the total score on the PFS, indicating a significant time effect. To determine where the differences were, post hoc comparisons were done and results indicated significant differences between fatigue scores at the time of treatments (T1,3, & 5) and fatigue scores at the mid-point times (T2,4, & 6). The only non-significant effect was in the sensory subscales between T4 and T5. A tri-modal pattern emerged where scores were

Table 3

Analysis of Variance of Patterns of Fatigue Across Time in Women With Stage I or II Breast Cancer Receiving Adjuvant Chemotherapy (N = 60)

Piper Fatigue Scale	Time							
	1	2	3	4	5	6	F[a]	p
Total								
Mean	4.82	3.58	4.55	3.68	4.63	3.41	7.70	
S.D.	(2.37)	(2.59)	(2.17)	(2.50)	(2.37)	(2.53)		<.001
Temporal								
Mean	4.49	2.90	4.15	3.24	4.27	3.09	6.81	
S.D.	(2.90)	(2.76)	(2.50)	(2.74)	(2.73)	(2.84)		<.001
Sensory								
Mean	4.81	3.50	4.54	3.81	4.46	3.49	4.87	
S.D.	(2.51)	(2.90)	(2.50)	(2.85)	(2.57)	(2.92)		<.001
Cognitive								
Mean	5.76	4.61	5.37	4.37	5.40	4.11	6.95	
S.D.	(2.48)	(2.80)	(2.44)	(2.68)	(2.54)	(2.77)		<.001
Emotional								
Mean	4.38	3.46	4.29	3.43	4.48	3.06	9.15	
S.D.	(2.27)	(2.60)	(2.12)	(2.27)	(2.22)	(2.24)		<.001

[a]Degrees of Freedom = (5,295) in all analyses.

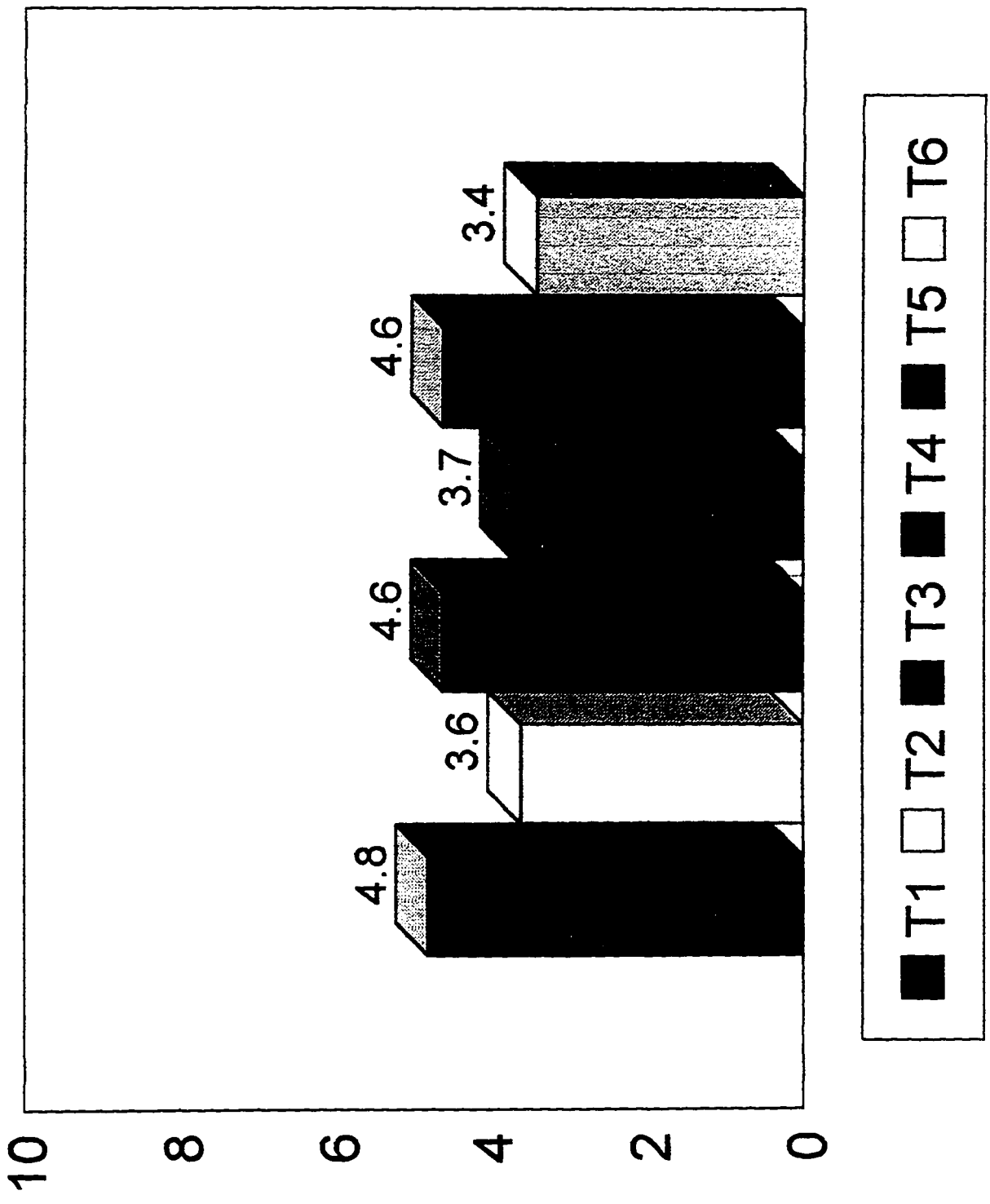
higher at the three treatment times (T1,3,5) than at the three mid-point recovery times (T2,4,6), creating a roller-coaster effect. As illustrated in Figure 3, fatigue scores were highest in the cognitive subscale dimension over time, followed by the sensory, emotional and temporal dimensions. Highest levels of total and all subscale fatigue scores except emotional were reported by the sample at the first chemotherapy treatment (T1). Emotional fatigue subscale scores were highest at the third treatment, (T5). The fatigue was perceived as being approximately the same intensity with each treatment by this sample of women. They did not report increased fatigue with successive treatments, but they also did not report less fatigue over time.

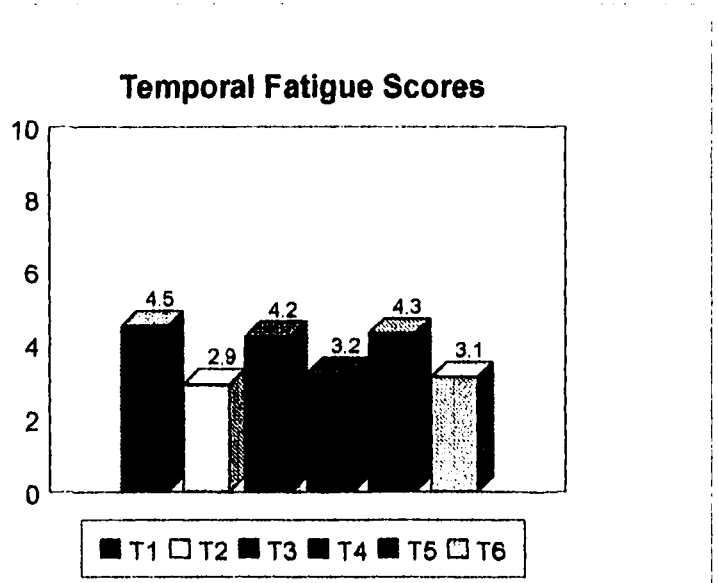
Patterns of Selected Factors Influencing Fatigue over Time

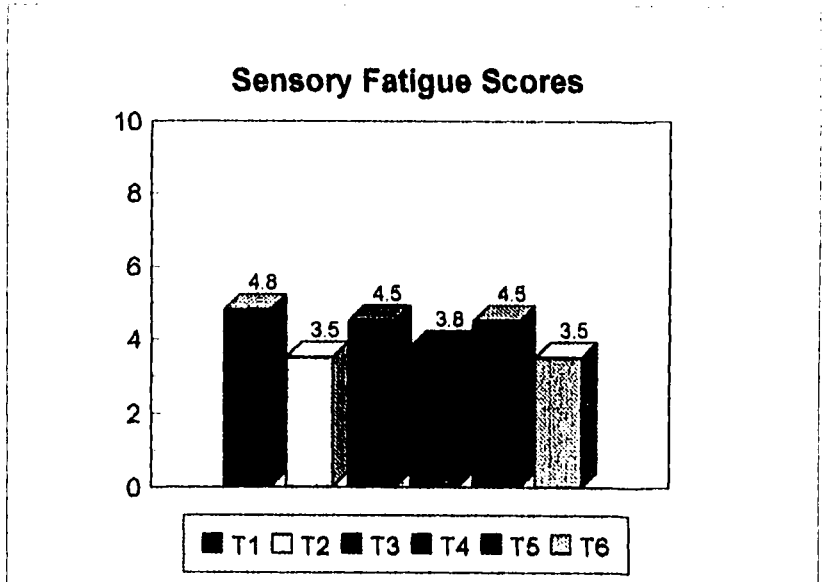
Eight of the ten factors influencing fatigue selected for this study were measured at more than one time point across the first 3 cycles of chemotherapy treatments. Chemotherapy protocol and initial reaction to the diagnosis of cancer were measured only once because they did not vary across time.

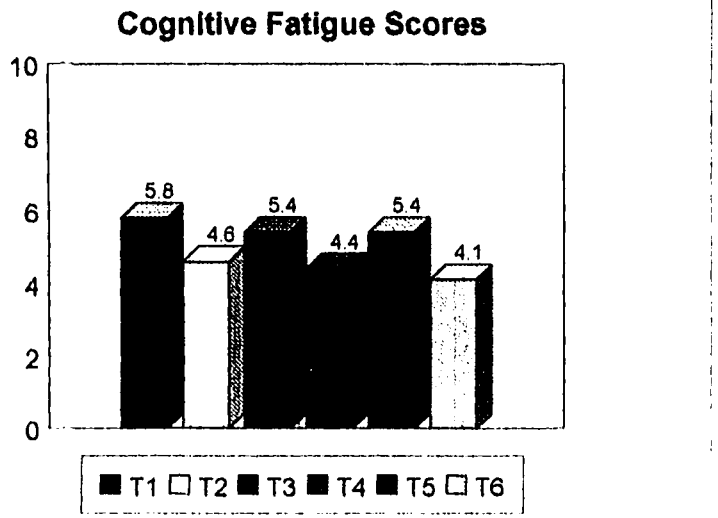
Health and Functional Status. A series of paired t-tests were used to analyze data for changes over time in health and functional status as measured by six subscales of the MOS-SF-36 instrument (Ware & Sherbourne, 1992). Each subscale score ranges from 0-100, with 100 being the most favorable score. Table 4 presents means, standard deviations, and t-test comparisons of the six subscales measured by recall of status prior to diagnosis at the first treatment (T1) and for current status at the time of the third chemotherapy treatment (T5). Subjects were asked to recall at T1 their health status prior to any knowledge of breast disease, in almost all cases less than 2 months previously. Perceptions of health and well-

Figure 3 Means for Total and Subscales of Fatigue Across Time in Women Receiving Adjuvant Chemotherapy for Breast Cancer. Total scores at each of the three treatments were higher than at the mid-point recovery time. Scores were highest at the first treatment, and lowest at the mid-point of the third treatment.









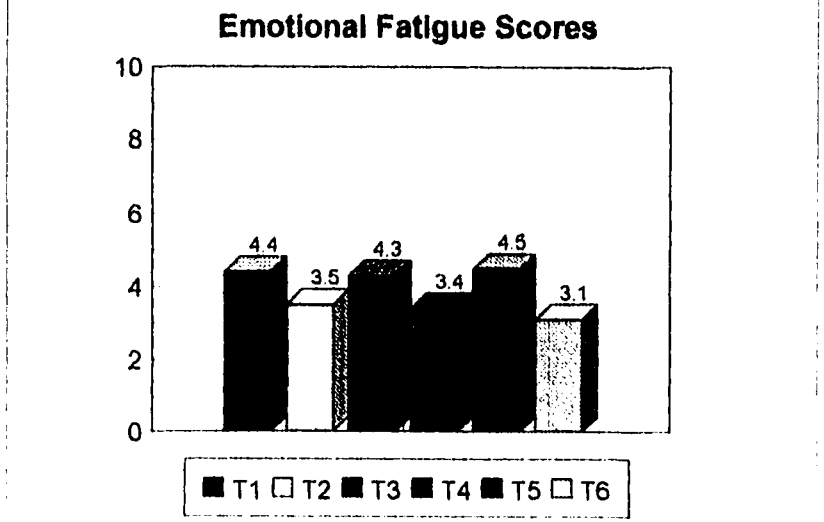


Table 4

Changes in Health and Functional Status From Prior to Diagnosis to the Third Chemotherapy Treatment (N = 61)

MOS Subscale	Prior to Diagnosis[a]	T_5	t	p
Physical Functioning	92.59 (13.12)	70.60 (23.42)	8.57	<.001
Role-Physical	96.12 (15.89)	39.22 (42.69)	10.05	<.001
Role-Emotional	89.65 (24.34)	58.62 (45.16)	5.11	<.001
Social	92.24 (14.20)	68.53 (26.93)	6.69	<.001
Mental Health	76.62 (16.34)	72.20 (17.98)	1.84	=.070
General Health	82.03 (16.74)	66.64 (20.18)	6.44	<.001

[a] = Measurement at time 1, recall back to prior to diagnosis.

being decreased from that time to the third treatment time. All subscales except for mental health (t=1.84, p=0.070) were significantly lower at T5 (p= 0.001 level). The role-physical subscale scores decreased the most from 96.12 (15.89) prior to diagnosis to 39.22 (42.69) at T5, reflecting limitations in vigorous and moderate intensity activities.

Health-Promoting Lifestyle Behaviors. RM-ANOVA was used to analyze data for changes over time in frequency of health-promoting lifestyle behaviors as measured by four subscales (physical activity, nutrition, interpersonal relations and stress management behaviors) of the Health-Promoting Lifestyle Profile II (HPLPII). Mean scores were computed for each of these four subscales. Scores can range from a low of 1.00 to a high of 4.00, reflecting increasing frequency of health-promoting lifestyle behaviors. As shown in Table 5, physical activity behaviors decreased and stress management behaviors increased significantly over time. Examination of HPLPII subscale scores from the recall of status prior to diagnosis until the first chemotherapy treatment by ANOVA revealed that physical activity behavior scores decreased, while stress management behaviors scores increased. No significant behavior changes occurred in the interpersonal relations or nutrition subscales during this same period. No significant behavior changes occurred in any of the four subscale scores from the first (T1) through the third treatment (T5). Means and standard deviations for subscales of the HPLPII are diagramed in Figure 4. When examined as a group, it is apparent that few changes in lifestyle behaviors occurred once chemotherapy was initiated.

Nutrition Status.

Both body mass index (BMI) and hematocrit nutrition status indicators were examined for changes over time using RM-ANOVA. Table 5 demonstrates the decreasing mean

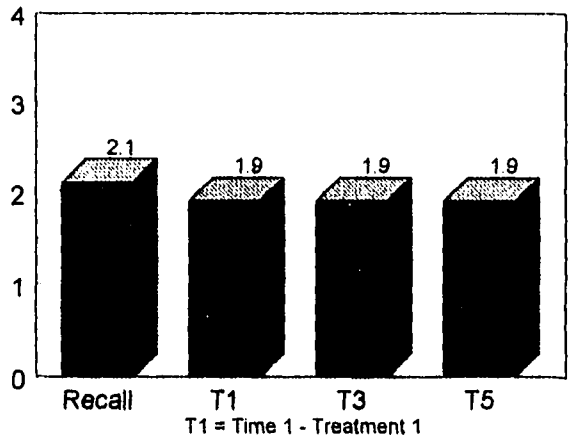
Table 5

Changes Over Time in Mean Scores of Factors Influencing Fatigue in Women With Stage I or II Breast Cancer Receiving Adjuvant Chemotherapy

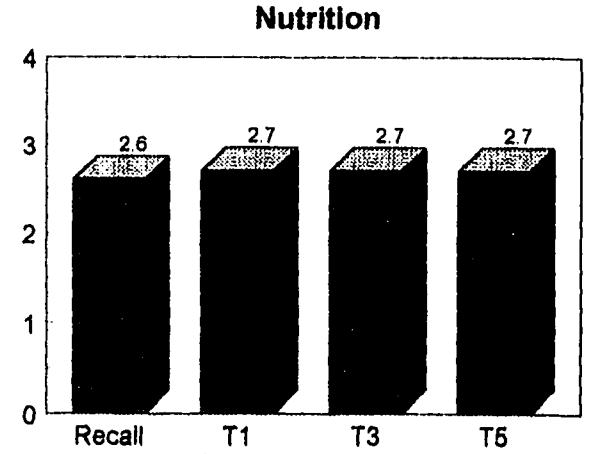
Variable	Time								
	Prior to Diagnosis[a]	1	2	3	4	5	6	F	p
	$\bar{X}$, (SD)	$\bar{X}$, (SD)	$\bar{X}$, (SD)	$\bar{X}$, (SD)	$\bar{X}$, (SD)	$\bar{X}$, (SD)	$\bar{X}$, (SD)		
Health -Promoting Lifestyle Behaviors									
Physical Activity	2.12 (.761)	1.90 (.650)		1.91 (.671)		1.93 (.663)		5.01	.005
Stress Management	2.52 (.489)	2.61 (.485)		2.64 (.498)		2.65 (.586)		3.37	.024
Interpersonal Relations	3.12 (.558)	3.15 (.535)		3.11 (.504)		3.14 (.564)		0.42	.708
Nutrition	2.61 (.610)	2.66 (.610)		2.74 (.584)		2.65 (.663)		1.74	.178
Nutritional Status									
Body Mass Index		24.84 (10.21)		23.17 (11.52)		23.19 (11.45)		3.68	.058
Hematocrit		38.48 (3.10)	35.08 (3.43)	36.39 (3.65)	33.57 (3.78)	35.22 (3.47)	32.73 (3.70)	69.28	<.001
Symptom Distress									
Total		3.70 (1.57)	2.55 (1.77)	3.11 (1.58)	2.29 (1.84)	3.21 (1.88)	2.40 (1.85)	15.58	<.001
Nausea		2.52 (2.05)	0.98 (1.75)	2.12 (1.98)	1.22 (1.92)	2.59 (2.43)	1.28 (1.99)	15.99	<.001
Sleep		4.53 (1.98)	3.68 (2.17)	3.70 (1.82)	2.94 (2.00)	3.59 (1.97)	2.96 (2.17)	9.49	<.001
Mood		4.07 (1.78)	2.97 (2.27)	3.51 (1.85)	2.70 (2.03)	3.45 (2.00)	2.94 (2.30)	8.66	<.001

[a]Measurement at time 1, recall of status prior to diagnosis.

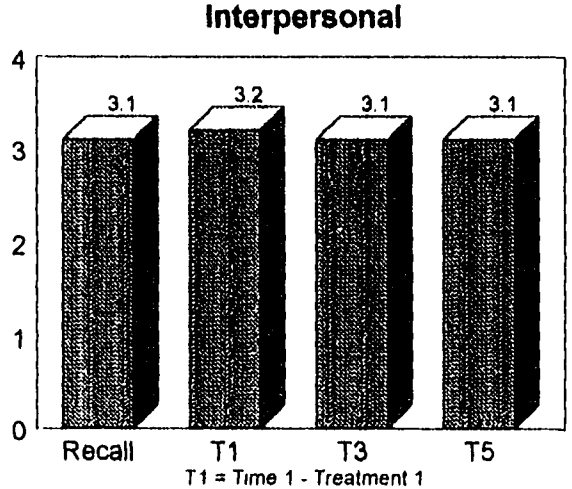
Figure 4 Mean Scores for Health-Promoting Lifestyle Behaviors Across Time in Women Receiving Adjuvant Chemotherapy for Breast Cancer.



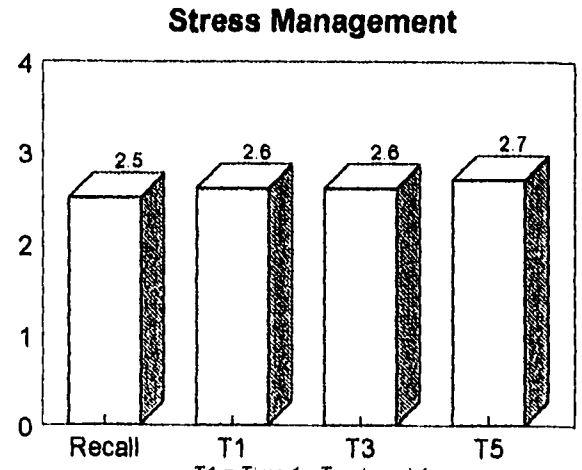
T1 = Time 1 - Treatment 1
T3 = Time 3 - Treatment 2 T5 = Time 5 - Treatment 3
Recall = T1, recall of behaviors prior to diagnosis



T1 = Time 1 - Treatment 1
T 3 = Time 3 - Treatment 2 T5 = Time 5 - Treatment 3
Recall = T1, recall of behaviors prior to diagnosis



T1 = Time 1 - Treatment 1
T3 = Time 3 - Treatment 2 T5 = Time 5 - Treatment 3
Recall = T1, recall of behaviors prior to diagnosis



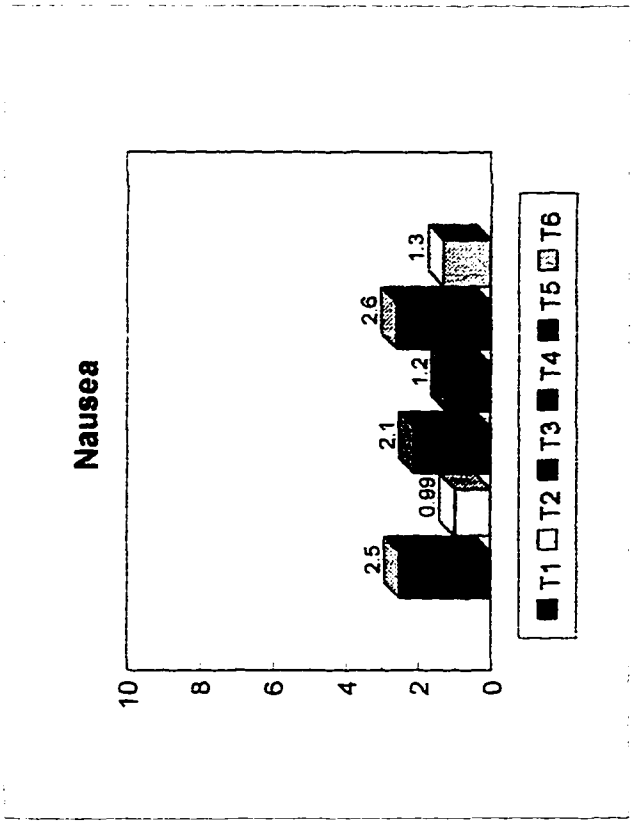
T1 = Time 1 - Treatment 1
T3 = Time 3 - Treatment 2 T5 = Time 5 - Treatment 3
Recall = T1, recall of behaviors prior to diagnosis

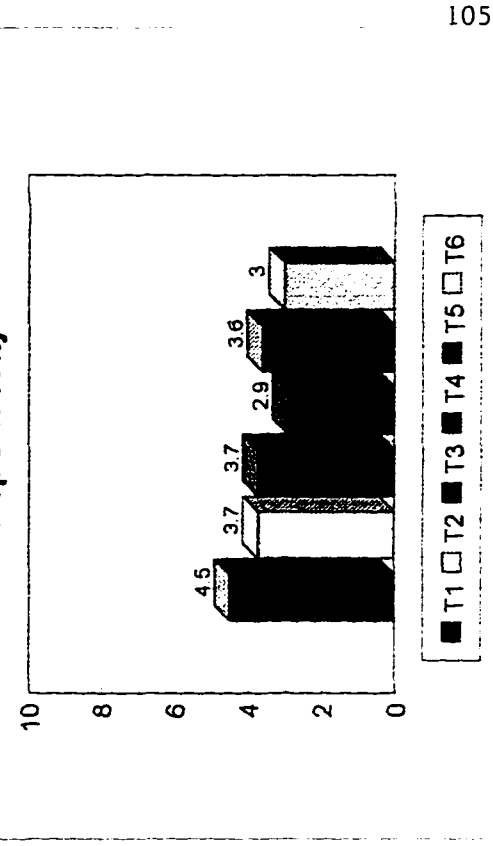
hematocrit levels over time [F=(5,290) 69.28, p<0.001], which represents a decrease of approximately 15% in hematocrit levels in the sample. Despite a return of hematocrit closer to baseline between each mid-point and subsequent treatment date, hematocrit levels on each treatment day decreased over time [F(2,118)=53.09, p<.001]. Values at the mid-point recovery also decreased over time [F(2,116)=20.25, p=<.001].

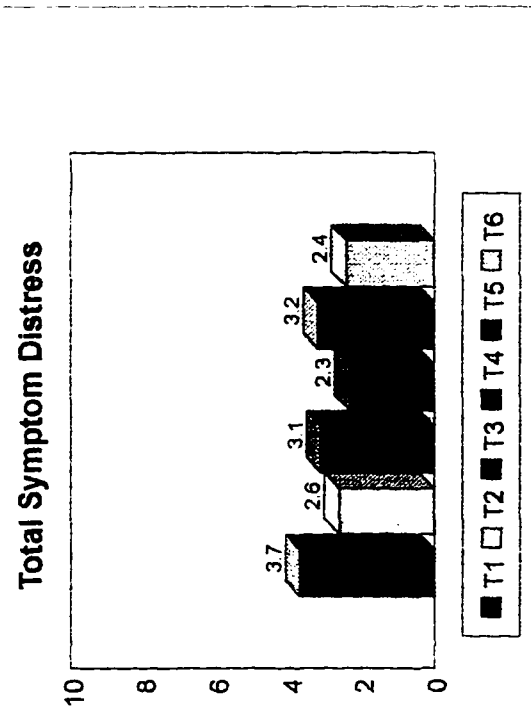
Mean BMI decreased slightly over the 6-8 weeks between treatment 1 and treatment 3 [F=(2,142) 3.68, p=.058]. For all subjects, BMI did not change significantly over the course of the study. However, women who were heavier at time 1 experienced more weight loss (r= -0.287, p=0.025) than women who were lighter.

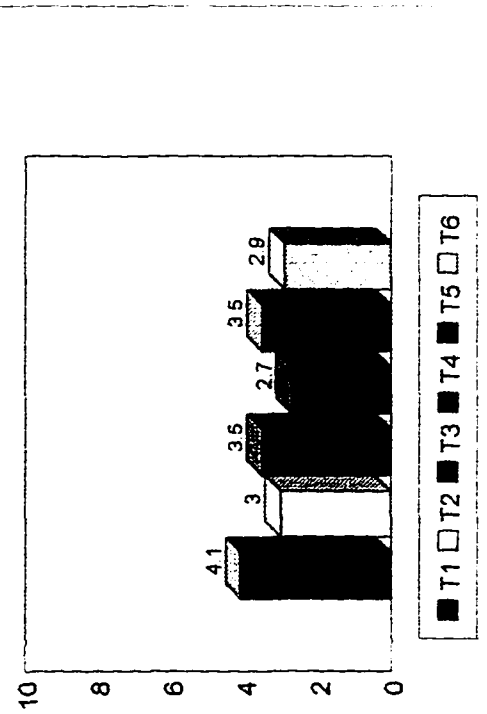
Symptom Distress. RM-ANOVA was used to analyze data for changes over time in severity of symptoms that are generally most distressing to women undergoing breast cancer chemotherapy, as measured by the Modified Symptom Distress Scale (M-SDS). The M-SDS captured mean perceived severity of, rather than distress from, nausea, sleeping difficulty, and mood state. As shown in Table 5, total symptom distress was significantly different over the six times, with higher scores reported at each treatment and lower scores reported at the midpoint between treatments, creating a roller-coaster effect. Figure 5 illustrates that levels of sleep difficulty were scored as most severe ($\bar{X}$= (4.36, SD=2.03), and nausea least severe ($\bar{X}$=2.42, SD=2.03) at the first treatment (T1) and throughout subsequent data collection times. Although mean scores reflect satisfactory relief of nausea, the range (0-10) and standard deviation of scores at each time demonstrate that not all women reported relief of nausea.

Figure 5 Mean Scores for Symptom Distress Over Time in Women Receiving Adjuvant Chemotherapy for Breast Cancer. Scores on nausea, mood and sleep difficulty were obtained on each of the four days of measurement with each treatment (T1, T3 & T5) and each of the three days of measurement at the cycle mid-point (T2, T4 & T6) then summed and the mean calculated.









RM-ANOVA was then used to compare symptom distress scores across the times of the three treatments (T1,3,5) and again at the mid-point recovery times (T2,4,6). When examining symptoms across all treatments, results indicated that total symptom distress decreased over time [F(2,118)=6.23, p=.004]. However, mid-point recovery scores remained stable over time. Sleep difficulty scores decreased over time at both treatment [F=(2,118)=8.16, p=.001] and midpoint recovery [F(2,116)=4.48, p=.015]. Scores reflecting negative mood feelings declined across treatments [T1,3,5) [F(2,118)=5.39, p=.007], but remained unchanged at mid-point recovery times. Mean nausea scores did not change across time at treatment times or at mid-points.

Patterns of Activity/Rest Cycles obtained by Actigraph over Time

RM-ANOVA was employed to evaluate patterns of selected activity/rest cycle variables (mesor, amplitude, day high 3, night-time awakenings) obtained by actigraphs from women over time. Selected activity/rest variable scores were collected at all 6 times whenever possible. Reasons why actigraph data were missing included: patient preference not to wear the actigraph, skin irritation from the wristband, unable to wear at work, bothersome to wear at night, out of town, failure to activate, and faulty operation. Only 17 women wore the actigraph for the entire time (72-96 hours) at all six times. Mean scores and standard deviations for all measured variables in the entire group of women fluctuated over time in a tri-modal fashion, creating significant changes over time in a roller-coaster pattern of highs and lows (Table 6 and Figure 6).

RM-ANOVA was then used to compare activity/rest cycle variable scores across the time of the three treatments and again at the mid-point recovery times. The entire group of

Table 6

Analysis of Variance of Activity/Rest Cycle Variables Obtained by Actigraph[a] Across Time in Women[b] With Stage I or II Breast Cancer Receiving Adjuvant Chemotherapy[c] (N=17)[d]

Variable	Time							
	1	2	3	4	5	6	F	p
	X, (SD)	X, (SD)	X, (SD)	X, (SD)	X, (SD)	X, (SD)		
Mesor								
Entire sample	104.14 (22.77)	119.22 (21.45)	103.61 (17.65)	112.98 (20.17)	100.50 (22.64)	110.55 (14.29)	3.72	.029
Amplitude								
Entire sample	81.46 (19.02)	93.31 (13.93)	82.55 (18.14)	93.51 (19.17)	80.45 (23.64)	87.58 (21.79)	2.54	.097
Mesor plus Amplitude (Day Hi 3)								
Entire group	189.75 (48.24)	231.19 (48.24)	192.77 (57.21)	211.63 (33.55)	179.86 (61.05)	205.56 (42.25)	3.83	.032
Awakenings at night								
Entire sample	35.82 (15.61)	27.18 (15.97)	32.35 (16.07)	22.41 (14.34)	33.59 (17.40)	25.13 (14.05)	3.93	.007

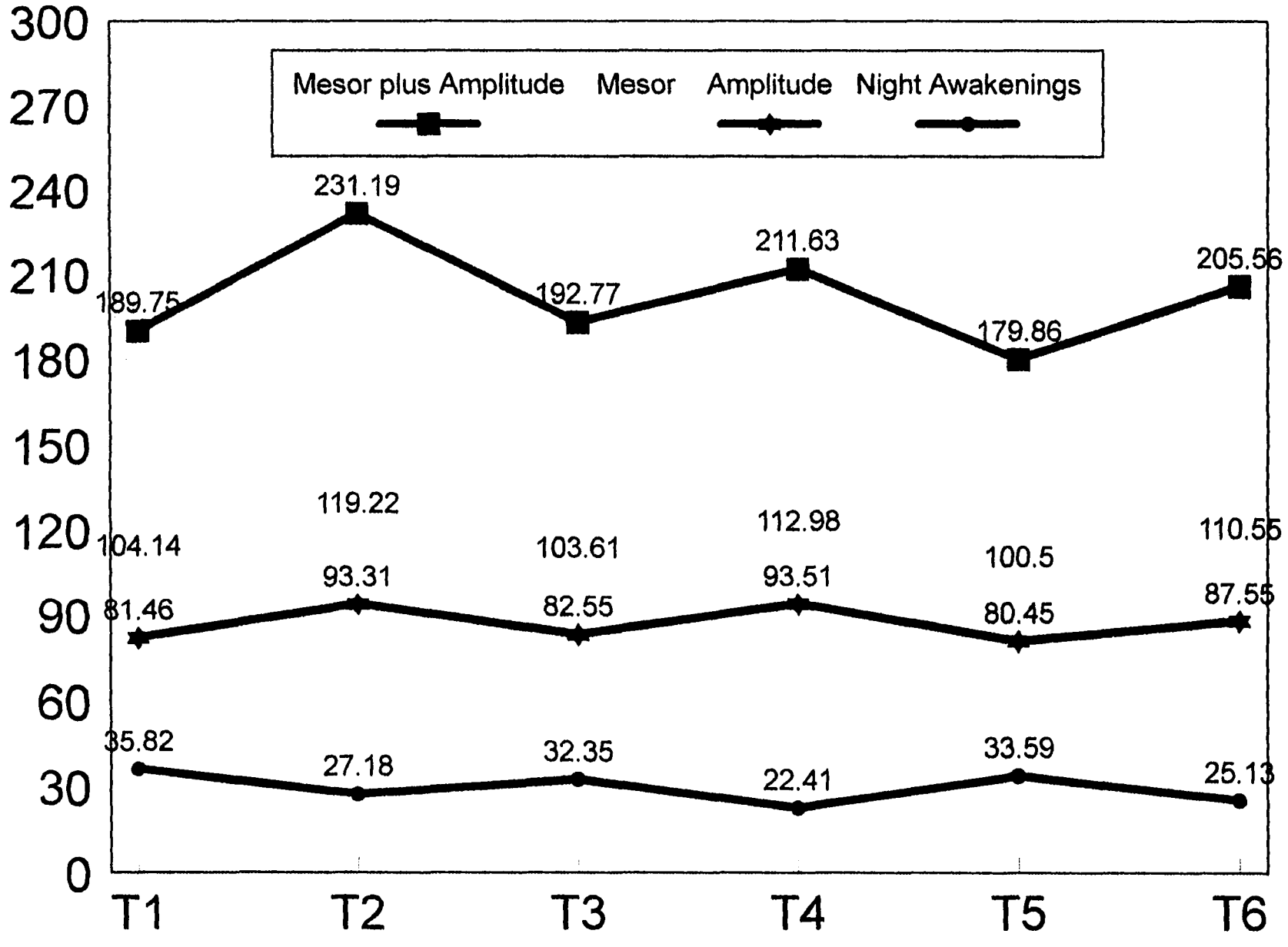
[a]Mesor, Amplitude, Mesor plus Amplitude (Day High 3), Awakenings at night.

[b]Only women for whom complete data were available at all 6 times were entered into this analysis.

[c]Non-Adriamycin group=10, Adriamycin group=7.

[d]Healthy adult norms: Mesor = 138.20 (8.377); Amplitude = 112.35 (4.93) (Farr & Boen, 1996)

Figure 6. Graphic illustration of mean values for activity/rest cycle variables across time. Patterns fluctuated from lower values at treatment times to higher levels at cycle mid-points.



M = Mesor (mean value of the fitted cosine curve over time)
A = Amplitude (height of the cosine curve at its peak over time)
M & A = Sum of M & A (overall mean activity over 24' Day 3)
N = Number of Night-time Awakenings/Night (averaged/# days)

NOTE
Times 1, 3, & 5 are 96" recordings.
Times 2, 3, & 6 are 72' recordings.

subjects (N=29) with complete actigraph data available at all treatments (T1,3,5) were examined first, and no significant differences were found in the patterns over time (Table 7). The entire group of subjects (N=23) with complete actigraph data available at all three mid-point recoveries (T2,4,6) also did not demonstrate changes in activity/rest cycle patterns over time (Table 8). These results resemble those obtained when measuring fatigue where successive treatments were tolerated similarly to the first treatment.

Summary of Patterns Over Time

In summary, fatigue and symptom distress followed similar fluctuations in patterns over time, with activity/rest values reflecting a mirror image pattern. Health and functional status showed a significant decline from the pre-diagnosis recall to the third chemotherapy treatment. Lifestyle patterns moved toward more frequent stress management behaviors between the time prior to diagnosis (measured by recall) and the first treatment but physical activity levels at T1 fell below reported pre-diagnosis levels. Women reported no significant changes in lifestyle behaviors during treatment but did maintain similar patterns of lifestyle behaviors over time. Moderate levels of symptom distress were pervasive at Times 1-5, with sleeping difficulty most intense, followed by mood and nausea severity. Mean activity scores (mesor, amplitude day high 3) were similar at the 3 treatments and higher but stable over time at the cycle mid-points, creating significant changes over time in a roller-coaster pattern. Mean awakenings at night were elevated, and followed a similar pattern of significant differences between treatments and mid-points. Women receiving adjuvant chemotherapy for breast cancer experience numerous changes over time in patterns related to health and functioning, health-promoting lifestyle behaviors, hematocrit levels, symptoms, and

Table 7

Analysis of Variance of Activity/Rest Cycle Variables Obtained by Actigraph[a] Across Treatment Times in Women[b] With Stage I or II Breast Cancer Receiving Adjuvant Chemotherapy[c] (N=29)[d]

Variable	Time							
	1	2	3	4	5	6	F	p
	$\bar{X}$, (SD)		$\bar{X}$, (SD)		$\bar{X}$, (SD)			
Mesor								
Entire sample	100.01 (22.35)		102.96 (22.29)		96.76 (26.56)		1.83 (1,3,5)	.171
Amplitude								
Entire sample	78.61 (17.25)		81.35 (20.26)		78.60 (22.94)		.42 (1,3,5)	.616
Mesor plus Amplitude (Day Hi 3)								
Entire group	179.09 (52.45)		181.96 (51.68)		172.18 (63.50)		.55 (1,3,5)	.582
Awakenings at night								
Entire sample	34.51 (15.80)		36.17 (17.73)		34.76 (19.95)		.10 (1,3,5)	.880

[a]Mesor, Amplitude, Mesor plus Amplitude (Day High 3), Awakenings at night.

[b]Oly women for whom complete data were available for times 1, 3, & 5 were included in this analysis.

[c]Non-Adriamycin group=14, Adriamycin group=15.

[d]Healthy adult norms: Mesor = 138.20 (8.377); Amplitude = 112.35 (4.93) (Farr & Boen, 1996).

Table 8

Analysis of Variance of Activity/Rest Cycle Variables Obtained by Actigraph[a] Across Midpoint Recovery Time in Women[b] With Stage I or II Breast Cancer Receiving Adjuvant Chemotherapy[c] (N=23)[d]

Variable	Time							
	1	2	3	4	5	6	F	p
		$\bar{X}$, (SD)		$\bar{X}$, (SD)		$\bar{X}$, (SD)		
Mesor								
Entire sample		113.29 (24.02)		109.04 (20.93)		108.26 (17.35)	1.09 (2,4,6)	.345
Amplitude								
Entire sample		90.61 (17.19)		91.78 (19.36)		88.18 (19.54)	.71 (2,4,6)	.488
Mesor plus Amplitude (Day Hi 3)								
Entire group		109.09 (34.25)		181.25 (46.50)		197.31 (59.70)	.22 (2,4,6)	.798
Awakenings at night								
Entire sample		27.80 (18.84)		22.48 (13.45)		24.48 (13.58)	1.44 (2,4,6)	.248

[a]Mesor, Amplitude, Mesor plus Amplitude (Day High 3), Awakenings at night.

[b]Only women for whom complete data were available for times 2, 4, & 6 were included in this analysis.

[c]Non-Adriamycin group=12, Adriamycin group=11.

[d]Healthy adult norms: Mesor = 138.20 (8.377); Amplitude = 112.35 (4.93) (Farr & Boen, 1996)

activity/rest, as well as in perceived fatigue. Further investigation to clarify the relationships between these variables is described in questions 2 and 3.

Research Question 2:

Factors Explaining Fatigue

Research Question #2 was: To what extent do health and functional status, chemotherapy protocols, physical activity behaviors, activity/rest cycles, nutrition behaviors and status, stress management behaviors, interpersonal relations behaviors, symptom distress patterns, and reaction to the diagnosis of cancer explain fatigue 48 hours after each of three chemotherapy treatments?

The proposed path diagram of factors influencing fatigue in women receiving chemotherapy is shown in Figure 7. Activity/rest cycles were omitted from this analysis because of incomplete and missing actigraph data from numerous subjects. The relationship between these variables and fatigue was analyzed separately for those subjects with actigraph data and is described in Appendix M.

Path Analyses

Path analyses, employing ordinary least squares regression, were used to determine the relative weight of study variables in explaining fatigue at the three treatment times (T1,3,&5). The results of the path analysis of factors influencing fatigue at these three treatment times are illustrated in Figures 8, 9, and 10, respectively. Standardized Beta weights and their level of significance are displayed on the paths. While the alpha level for significance was set at 0.05, variables with probabilities up to 0.10 are shown so that trends can be identified. Each path diagram is followed by a table that includes the results of the

associated regressions of fatigue on directly influencing variables at the current time (Tables 9, 11, & 13). Each of those tables is followed by a summary table that displays the direct, indirect, and total effects for influences on fatigue at the corresponding time (Tables 10, 12, & 14).

Cumulative and adjusted R^2's at each of the three treatments signify that significant variance in fatigue was explained by the influencing factors as shown in Tables 9, 11, and 13. Symptom distress had the strongest direct path to perceived fatigue 48 hours after each chemotherapy treatment, with Beta weights ranging from .54 to .62 ($p<.001$) at the three treatment times (T1, 3, 5). Additional significant direct influences at the first treatment included chemotherapy protocol and IPR behaviors. Women who received intravenous Adriamycin and Cytoxan containing regimens reported higher levels of fatigue only at the first chemotherapy treatment (T1) (Figure 8). After the first treatment, factors other than the regimen itself apparently were stronger influences on fatigue in this sample. Women who reported fewer IPR behaviors reported higher levels of fatigue at the first treatment (T1), as shown in Table 10. Nine of the 12 subjects who withdrew from the study were not married, and the analysis did not include data from these women that may have further explained the influence of IPR behaviors on fatigue.

A stronger confronting initial reaction to the diagnosis was indirectly related to fatigue through IPR behaviors at the first treatment (T1), as shown in Table 10. At the same time, a weaker confronting response was indirectly related to fatigue through symptom distress. A higher confronting initial response to the diagnosis of cancer directly influenced all four health-promoting lifestyle behaviors at both the second and third treatments (T3 & T5, as

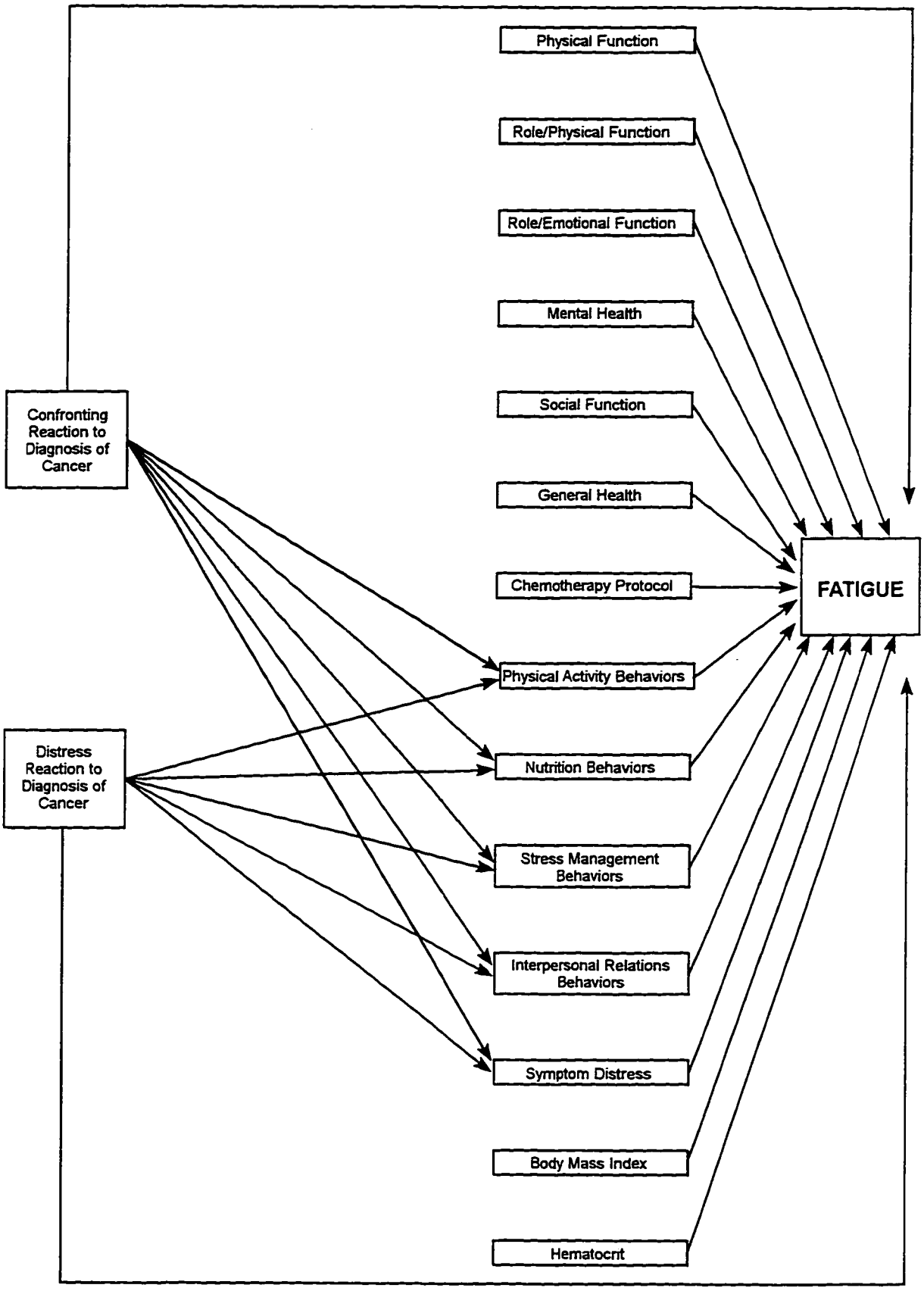


Figure 7. Path Diagram of Factors Influencing Fatigue in Women Receiving Chemotherapy for Breast Cancer (Model)

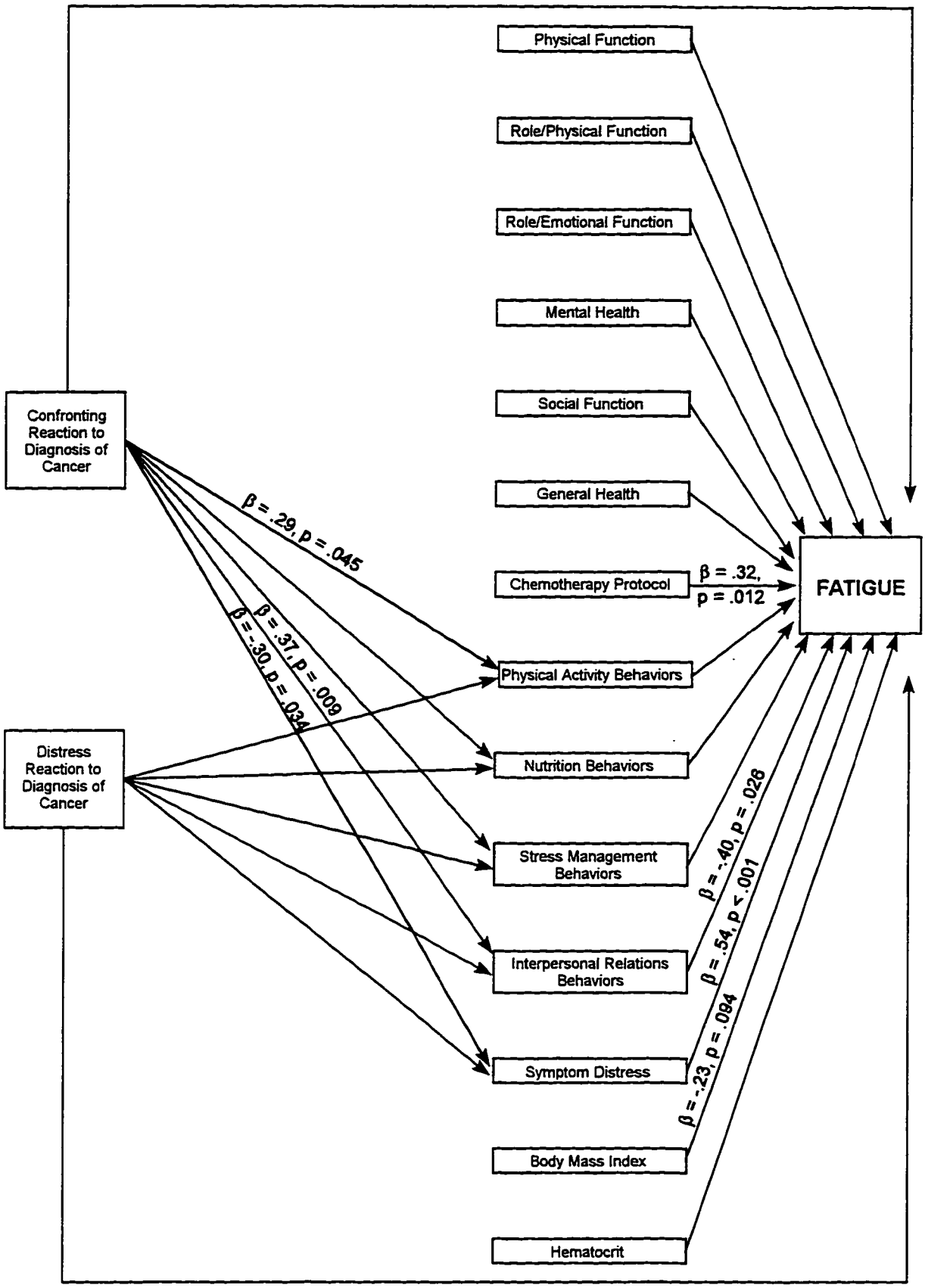


Figure 8. Path Diagram of Factors Influencing Fatigue in Women Receiving Chemotherapy for Breast Cancer at Time 1

Table 9

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Treatment 1 (T1) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.519[c]	.340				
Physical Functioning			-.185	1.17	.285	-.060
Role-Physical			-.217	1.91	.451	-.030
Role-Emotional			-.040	0.04	.838	.016
Social			-.028	0.66	.419	-.171
Mental Health			-.067	0.40	.750	-.242
General Health			.145	0.73	.397	-.270
Chemotherapy Protocol[d]			.319	6.87	.012	.301
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			-.188	1.39	.246	-.294
Nutrition			.204	1.63	.209	-.114
Interpersonal Relations			-.404	5.29	.026	.393
Stress Management			.098	0.23	.633	-.360
Nutrition Status[e]						
Hematocrit			-.125	0.95	.335	-.052
Body Mass Index			-.233	2.94	.094	.046
Symptom Distress[e]			.536	14.62	.001	.561
Reaction to Diagnosis of Cancer[f]						
Distress			-.057	0.13	.717	.070
Confront			.028	.03	.853	-.166

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement at Time 1 - recall of status prior to diagnosis.

[c]Overall F = 2.90 (p = .003).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measured at current time (T1).

[f]Measurement at Time 1 - recall of reaction to diagnosis.

Table 10

Summary of Standardized Effects of Path Model Variables on Fatigue in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Treatment 1 (T1) (N =60)

Variables	Direct Effects	Indirect Effects	Effects Coefficients
Health and Functional Status			
Physical Functioning	-.185		-.185
Role-Physical	.217		.217
Role-Emotional	-.040		-.040
Social	.028		-.028
Mental Health	-.067		.067
General Health	.145		.145
Chemotherapy Protocol[a]	.319		.319
Health Promoting Lifestyle Behaviors[b]			
Physical Activity			
Nutrition	-.188		-.188
Interpersonal Relations	.204		.204
Stress Management	-.404		-.404
	.098		.098
Nutritional Status			
Hematocrit	-.125		-.125
Body Mass Index	.233		.233
Symptom Distress	.536		.536
Reaction to Diagnosis of Cancer			
Distress	-.057	-.003 Thru physical activity .015 Thru nutrition -.058 Thru interpersonal relations -.015 Thru stress management .006 Thru symptom distress **-.055 Sum**	-.112
Confront	.028	-.054 Thru physical activity .039 Thru nutrition -.149 Thru interpersonal relations .020 Thru stress management -.023 Thru symptom distress **-.167 Sum**	-.139

[a]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[b]Health-Promoting Lifestyle Behaviors at current time (T1).

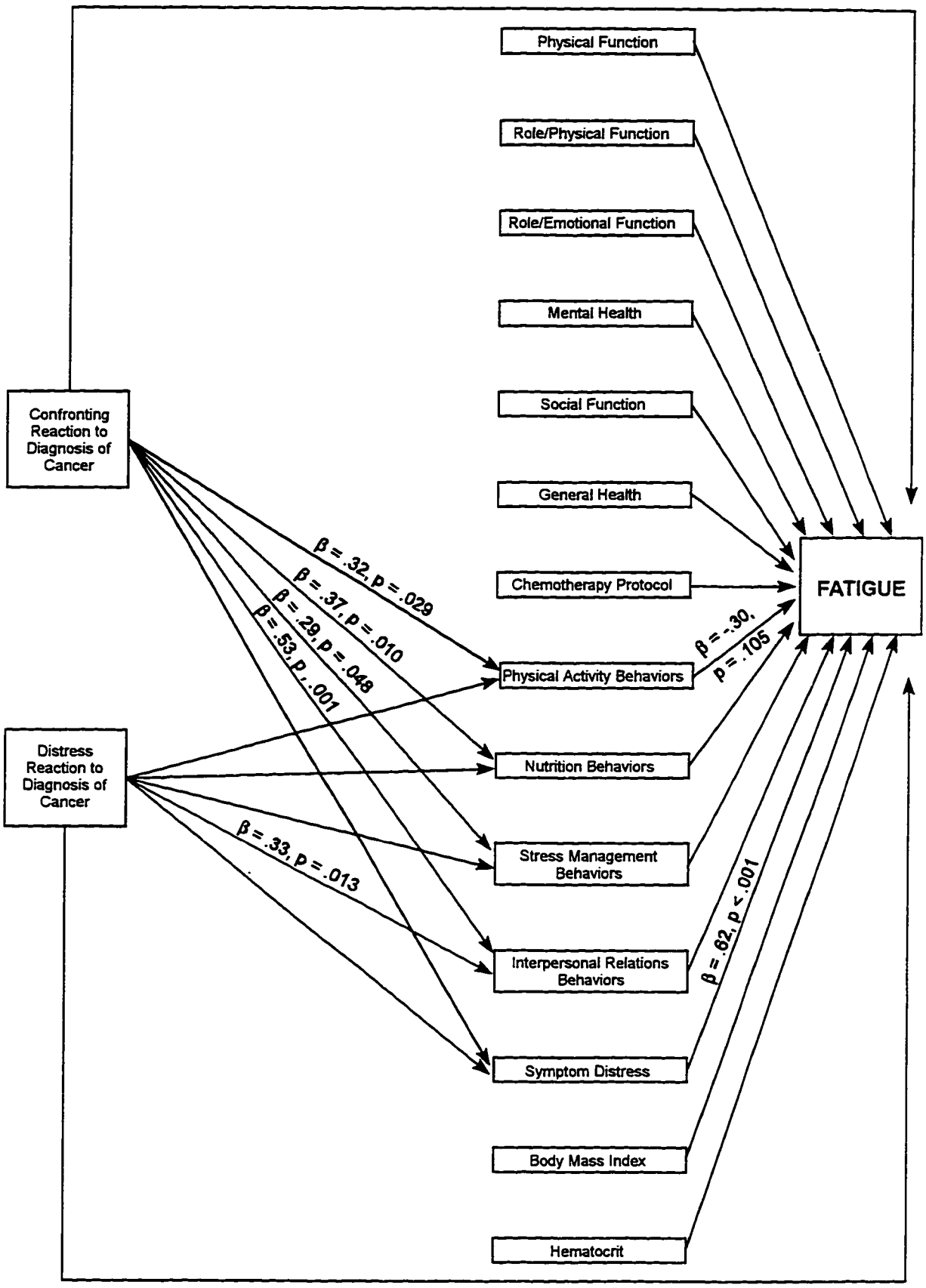


Figure 9. Path Diagram of Factors Influencing Fatigue in Women Receiving Chemotherapy for Breast Cancer at Time 3

Table 11

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Treatment 2 (T3) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.541[c]	.370				
Physical Functioning			-.127	0.58	.450	-.309
Role-Physical			.011	0.01	.942	-.162
Role-Emotional			.151	0.65	.426	-.141
Social			-.346	2.34	.133	-.234
Mental Health			.314	2.42	.127	-.042
General Health			-.018	0.01	.914	-.311
Chemotherapy Protocol[d]			.156	1.78	.189	.175
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			-.301	2.73	.105	-.289
Nutrition			.276	2.15	.150	-.242
Interpersonal Relations			-.289	2.19	.146	-.161
Stress Management			.171	0.09	.360	-.197
Nutrition Status[e]						
Hematocrit			-.135	1.13	.294	-.069
Body Mass Index			-.123	1.01	.321	.113
Symptom Distress[e]			.616	23.5	.001	.623
Reaction to Diagnosis of Cancer[f]						
Distress			-080	0.26	.613	-.146
Confront			-.025	0.03	.869	-.010

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement at Time 1 - recall of status prior to diagnosis.

[c]Overall $F = 3.16$ ($p < .001$).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measured at current time (T3).

[f]Measurement at Time 1 - recall of reaction to diagnosis.

Table 12

Summary of Standardized Effects of Path Model Variables on Fatigue in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Treatment 2 (T3) (N =60)

Variables	Direct Effects	Indirect Effects	Effects Coefficients
Health and Functional Status			
Physical Functioning	-.127		-.127
Role-Physical	.011		.011
Role-Emotional	.151		.151
Social	-.640		-.640
Mental Health	.314		.314
General Health	-.018		-.018
Chemotherapy Protocol[a]	.156		.156
Health Promoting Lifestyle Behaviors[b]			
Physical Activity			
Nutrition	-.031		-.031
Interpersonal Relations	.276		.276
Stress Management	-.289		-.289
	.171		.171
Nutritional Status			
Hematocrit	-.135		-.135
Body Mass Index	-.123		-.123
Symptom Distress	.616		.616
Reaction to Diagnosis of Cancer			
Distress	-.080		
		-.039 Thru physical activit 043 Thru nutrition -.095 Thru interpersonal relations 002 Thru stress management -.040 Thru symptom distress **-.129 Sum**	-.209
Confront	.025	-.095 Thru physical activity .102 Thru nutrition -.152 Thru interpersonal relations .048 Thru stress management .060 Thru symptom distress **-.037 Sum**	-.012

[a]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.
[b]Health-Promoting Lifestyle Behaviors at current time (T3).

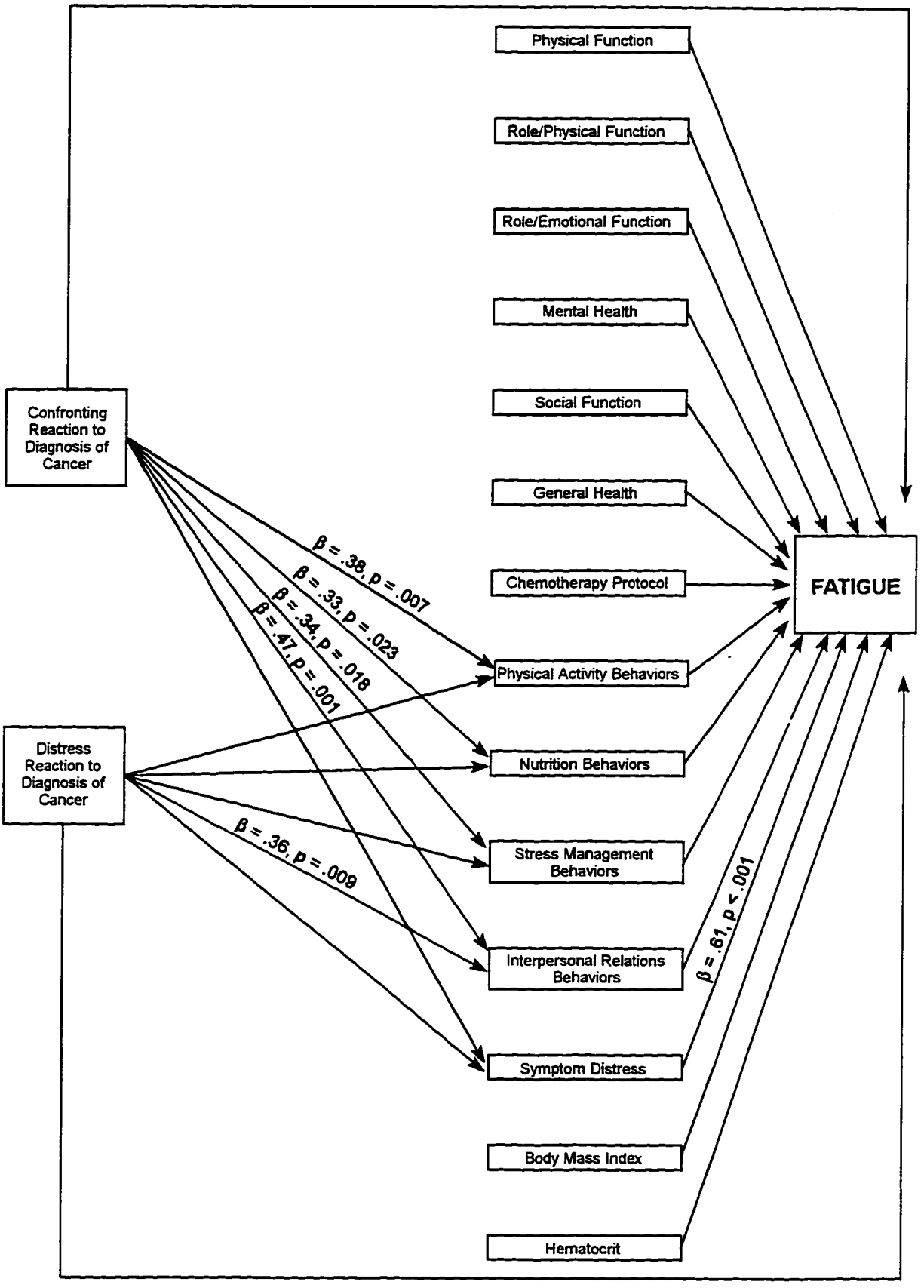


Figure 10. Path Diagram of Factors Influencing Fatigue in Women Receiving Chemotherapy for Breast Cancer at Time 5

Table 13

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Treatment 3 (T5) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.710[c]	.602				
Physical Functioning			-.174	1.73	.191	-.556
Role-Physical			-.114	1.05	.312	-.518
Role-Emotional			-.108	.81	.382	-.479
Social			-.167	1.20	.280	-.591
Mental Health			-.019	.12	.913	-.510
General Health			.193	2.54	.118	-.299
Chemotherapy Protocol[d]			.010	.01	.910	.177
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			-.170	1.60	.212	-.212
Nutrition			-.034	.06	.800	-.243
Interpersonal Relations			.194	1.55	.220	-.259
Stress Management			-.058	.17	.685	-.319
Nutrition Status[e]						
Hematocrit			.065	.43	.514	.136
Body Mass Index			-.091	.93	.339	.136
Symptom Distress[e]			.604	26.9	.001	.739
Reaction to Diagnosis of Cancer[f]						
Distress			.028	.05	.812	-.086
Confront			.099	.85	.361	-.024

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement at Time 1 - recall of status prior to diagnosis.

[c]Overall $F = 6.58$ ($p < .001$).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measured at current time (T5).

[f]Measurment at Time 3 - recall of reaction to diagnosis.

Table 14

Summary of Standardized Effects of Path Model Variables on Fatigue in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Treatment 3 (T5) (N = 60)

Variables	Direct Effects	Indirect Effects	Effects Coefficients
Health and Functional Status			
Physical Functioning	-.155		-.155
Role-Physical	-.113		-.113
Role-Emotional	-.109		-.109
Social	-.177		-.177
Mental Health	-.030		-.030
General Health	.196		.196
Chemotherapy Protocol[a]	.019		.019
Health Promoting Lifestyle Behaviors[b]			
Physical Activity			
Nutrition	-.165		-.165
Interpersonal Relations	-.049		-.049
Stress Management	.199		.199
	-.052		-.052
Nutritional Status			
Hematocrit	.054		.054
Body Mass Index	.088		.088
Symptom Distress	.608		.608
Reaction to Diagnosis of Cancer			
Distress	.018	.024 Thru physical activity -.005 Thru nutrition .070 Thru interpersonal relations .000 Thru stress management -.076 Thru symptom distress **- .035 Sum**	.017
Confront	.098	-.063 Thru physical activity -.016 Thru nutrition .093 Thru interpersonal relations -.017 Thru stress management -.095 Thru symptom distress **- .098 Sum**	0.00

[a]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[b]Health-Promoting Lifestyle Behaviors at current time (T5).

shown in Tables 12 & 14). A higher distress response also was associated with greater frequency of IPR behaviors at both the second and third treatments (T3 & T5), however none of these lifestyle behaviors were significant in relation to fatigue.

An alternative path analysis was conducted to determine whether behaviors prior to diagnosis rather than current measurements of health-promoting lifestyle behaviors might explain more variance in fatigue at each treatment. These values represent a baseline of lifestyle behaviors prior to diagnosis that were obtained at Time 1. Tables 29, 30, and 31 in Appendix N present the results of these regression analyses at the three treatments (T1,3,& 5), respectively. At all three times, less variance in fatigue was explained by the recall of lifestyle behaviors prior to diagnosis than by the current measures.

Activity/Rest Cycles

The relationship between activity/rest cycles and fatigue was analyzed separately from the path analyses since actigraph data were not available on all subjects at all times. Table 15 presents correlations between selected activity/rest variables and fatigue across time. Significant negative relationships between one or more activity/rest cycle variables and fatigue were found at every time. Values for activity/rest cycle variables in those subjects who wore the actigraph at each time (N=29-47) demonstrated negative correlations between the mesor, amplitude, and day high 3 values and fatigue at almost all times, indicating greater severity of fatigue in women who were less active. A relationships between night-time awakenings and fatigue scores was found in this study only at the mid-point of the second cycle (T4).

Table 15

Correlations Between Selected Activity/Rest Cycle Variables and Fatigue at Each Time in Women[a] Receiving Adjuvant Chemotherapy for Breast Cancer

Activity/Rest Variables	Fatigue[c]					
	T1	T2	T3	T4	T5	T6
Mesor						
r	-.299	-.395	-.394	-.024	-.349	-.343
(n)	(47)	(30)	(41)	(34)	(37)	(36)
p	.041	.031	.011	.892	.035	.040
Amplitude						
r	-.343	-.455	-.467	-.057	-.376	-.167
(n)	(47)	(30)	(41)	(34)	(37)	(34)
p	.018	.012	.002	.747	.022	.345
Mesor plus Amplitude (Day High 3)						
r	-.188	-.499	-.466	-.004	-.376	-.246
(n)	(42)	(29)	(38)	(31)	(34)	(32)
p	.234	.006	.003	.981	.028	.175
Awakenings at Night						
r	-.083	.181	.026	.403	.149	.212
(n)	(46)	(31)	(39)	(34)	(40)	(37)
p	.583	.329	.875	.018	.359	.207

[a]Sample includes all subjects for whom data were available at each time (pairwise).

Summary of Influences on Fatigue at Treatment Times

Path analyses identified direct and indirect influences on fatigue at treatment times among women receiving adjuvant chemotherapy. Symptom distress made the largest independent contribution to the explanation of fatigue at all three treatment times. Chemotherapy protocol drugs directly influenced fatigue only at the first treatment. The only health-promoting lifestyle behavior that influenced fatigue was interpersonal relations, although physical activity behaviors were close to significance ($p= 0.105$). A confronting initial response to the diagnosis of cancer was indirectly related to fatigue through IPR behaviors at the first treatment. Reaction to the diagnosis of cancer in a confronting manner directly influenced engagement in other health-promoting lifestyle behaviors, but these lifestyle behaviors did not influence fatigue. A less confronting reaction to the diagnosis was also indirectly related to fatigue through symptom distress at the first treatment. Wrist actigraphs provided a biologic measure with which to further understand the relationship between activity/rest cycle variables and fatigue. Although a smaller sample precluded inclusion of these data in the path analyses, significant negative correlations were found between selected activity/rest variables and fatigue at every time, indicating that more severe fatigue was associated with decreased movements/unit measurement. Results assist in understanding the relationship between all study variables and fatigue at treatment times.

Research Question 3

Factors Predicting Fatigue

Research Question #3 To what extent do health and functional status, chemotherapy protocols, physical activity behaviors, nutrition behavior, activity/rest cycles, and status,

stress management behaviors, interpersonal relations behaviors, symptom distress patterns and reaction to the diagnosis of cancer predict fatigue at the midpoints of each of three chemotherapy treatment cycles?

Path Analyses

Path analyses, employing ordinary least squares regression, were used to determine the relative weight of study variables in predicting fatigue at the three mid-point recovery times (T2,4,& 6). The results of the path analyses of factors influencing fatigue at the mid-points are illustrated in Figures 11, 12, 13. Activity/rest cycles were omitted from this analysis because of incomplete and missing actigraph data from numerous subjects. The relationship between these variables and fatigue was analyzed separately and can be found in Appendix M. Standardized Beta weights and their level of significance are displayed on the paths. While the alpha level for significance was set at 0.05, variables with probabilities up to 0.10 are shown so that trends can be identified. Each path diagram is followed by a table that includes the results of the associated regressions of fatigue on directly influencing variables (Tables 16, 18 & 20). Each of those tables is followed by a summary table that displays the direct, indirect, and total effects for influences on fatigue at the corresponding time (Tables 17, 19, & 21).

Conclusions from these analyses are that cumulative and adjusted R^2's at each of the three mid-points explained significant variance in fatigue that was predicted by the directly influencing factors, as shown in Tables 16, 18, and 20. Symptom distress again had the strongest direct path to perceived fatigue at the cycle midpoints during the first (ß=.43, p=0.002) and second (ß=.33, p=0.022) cycles of chemotherapy. Additional significant direct

influences at the mid-point of the first treatment (T2) included physical function (ß= -.39, p=0.020) and role/physical function (ß= -.41, p=0.009) (Table 16). A confronting reaction to the diagnosis of cancer and general health (ß= -.37, p=0.049) had strong significant direct paths to fatigue at the cycle 2 mid-point (T4). Physical function (ß= -.39, p=0.016) and general health status (ß= -.32, p=0.028) obtained at the third treatment had the strongest direct paths to fatigue at the third cycle midpoint (T6) as shown in Table 20.

When recall measurements of health and functional status prior to diagnosis were examined in further detail, the majority of study participants reported high levels of pre-diagnosis health, but a minority of women (n= 8-14) had baseline scores in 4 of the subscales that reflected lower levels of health and functional status. One-way comparisons between high and low health status scores and fatigue intensity were performed.

Table 22 compares the high and low health status scores on the 4 subscales with fatigue scores over time. A minority of women recalled at Time 1 lower levels of health and functional status prior to diagnosis. Individuals with low physical and social function scores reported fatigue scores at all mid-point times that were significantly higher than those with high physical and social function scores. It appears that the individuals with lower baseline health and functional status were more like those with higher baseline health and functional status at the first and third treatments, but different from them at the second treatment and at all mid-point times. The ability to "bounce back" from the severity of symptom distress experienced at the time of treatment was more difficult in the lower baseline physical and social function groups. Fewer IPR behaviors were also a significant indirect factor in

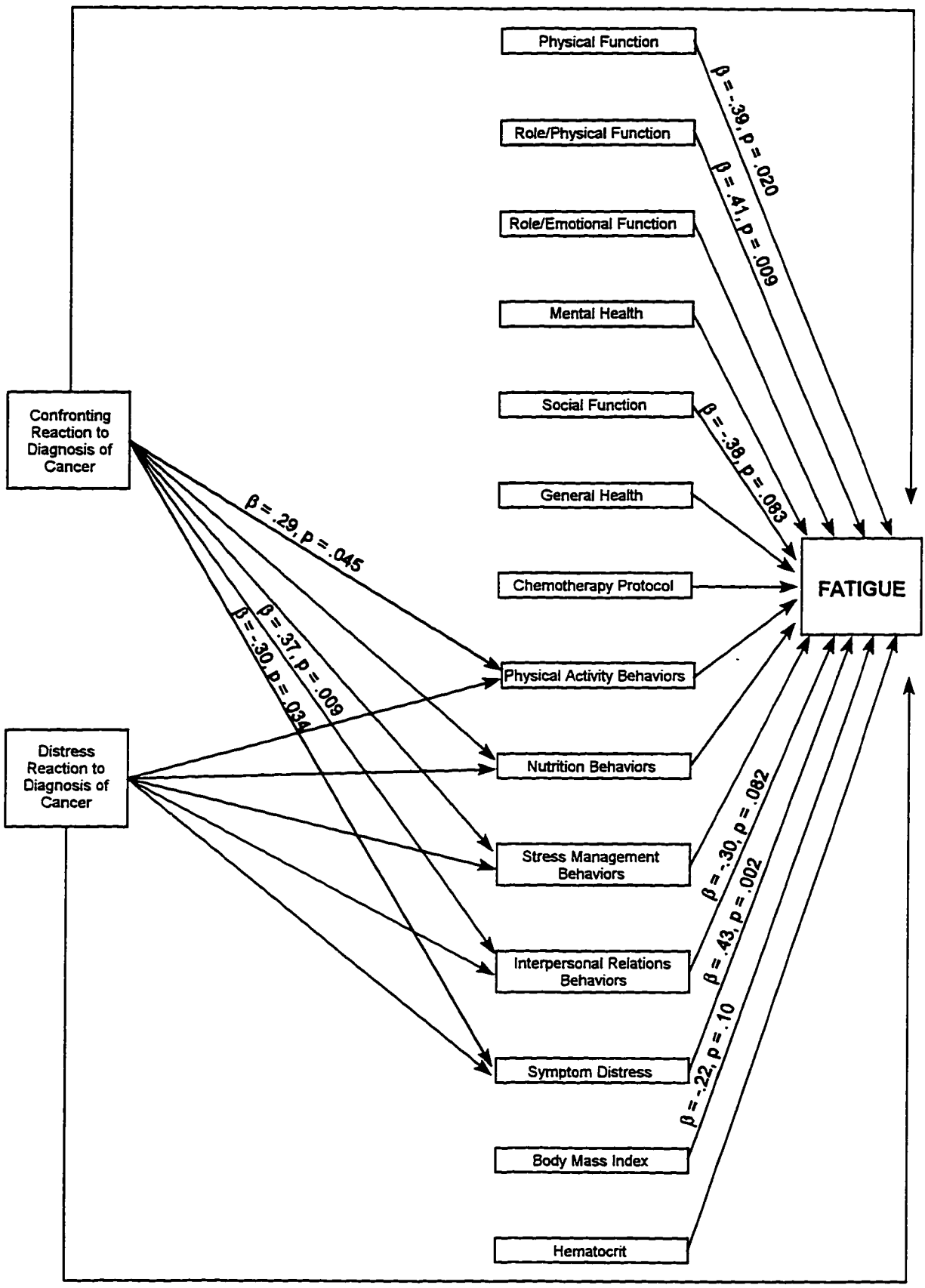


Figure 11. Path Diagram of Factors Influencing Fatigue in Women Receiving Chemotherapy for Breast Cancer at Time 2

Table 16

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Mid-point, Cycle 1 (T2) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.561[c]	.398				
Physical Functioning			-.394	5.81	.020	-.288
Role-Physical			.408	7.42	.009	-.016
Role-Emotional			.107	.33	.572	-.171
Social			-.382	3.14	.083	-.409
Mental Health			-.019	.01	.923	-.407
General Health			-.028	.03	.862	-.494
Chemotherapy Protocol[d]			.038	.11	.747	.156
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			-.125	.67	.417	-.402
Nutrition			-.111	.53	.472	-.314
Interpersonal Relations			-.300	3.18	.082	-.337
Stress Management			.194	.98	.328	-.386
Nutrition Status						
Hematocrit[f]			.028	.05	.823	-.026
Body Mass Index			-.216	2.76	.103	.149
Symptom Distress[f]			.429	10.27	.002	.525
Reaction to Diagnosis of Cancer[g]						
Distress			.143	.90	.349	.079
Confront			.142	.98	.327	-.134

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement at Time 1 - recall of status prior to diagnosis.

[c]Overall F = 3.44 ($p < .001$).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measured at Time 1 - current lifestyle behaviors 48 hours after chemotherapy.

[f]Measured at current time (T2).

[g]Measurement at Time 1, recall of reaction to diagnosis.

Table 17

Summary of Standardized Effects of Path Model Variables on Fatigue in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Mid-point, Cycle 1 (T2) (N =60)

Variables	Direct Effects	Indirect Effects	Effects Coefficients
Health and Functional Status			
Physical Functioning	-.394		-.394
Role-Physical	.408		.408
Role-Emotional	.107		.107
Social	-.382		-.382
Mental Health	-.019		-.019
General Health	-.028		-.028
Chemotherapy Protocol[a]	.038		.038
Health Promoting Lifestyle Behaviors[b]			
Physical Activity			
Nutrition	-.125		-.125
Interpersonal Relations	-.111		-.111
Stress Management	-.300		-.300
	.194		.194
Nutritional Status			
Hematocrit	.028		.028
Body Mass Index	-.216		-.216
Symptom Distress	.429		.429
Reaction to Diagnosis of Cancer			
Distress	.143		
		-.021 Thru physical activity -.008 Thru nutrition -.044 Thru interpersonal relations -.031 Thru stress management -.086 Thru symptom distress **-.190 Sum**	-.047
Confront	.142		
		-.036 Thru physical activity -.021 Thru nutrition -.111 Thru interpersonal relations +.039 Thru stress management -.096 Thru symptom distress **-.225 Sum**	-.083

[a]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[b]Measured at Treatment 1 (T1).

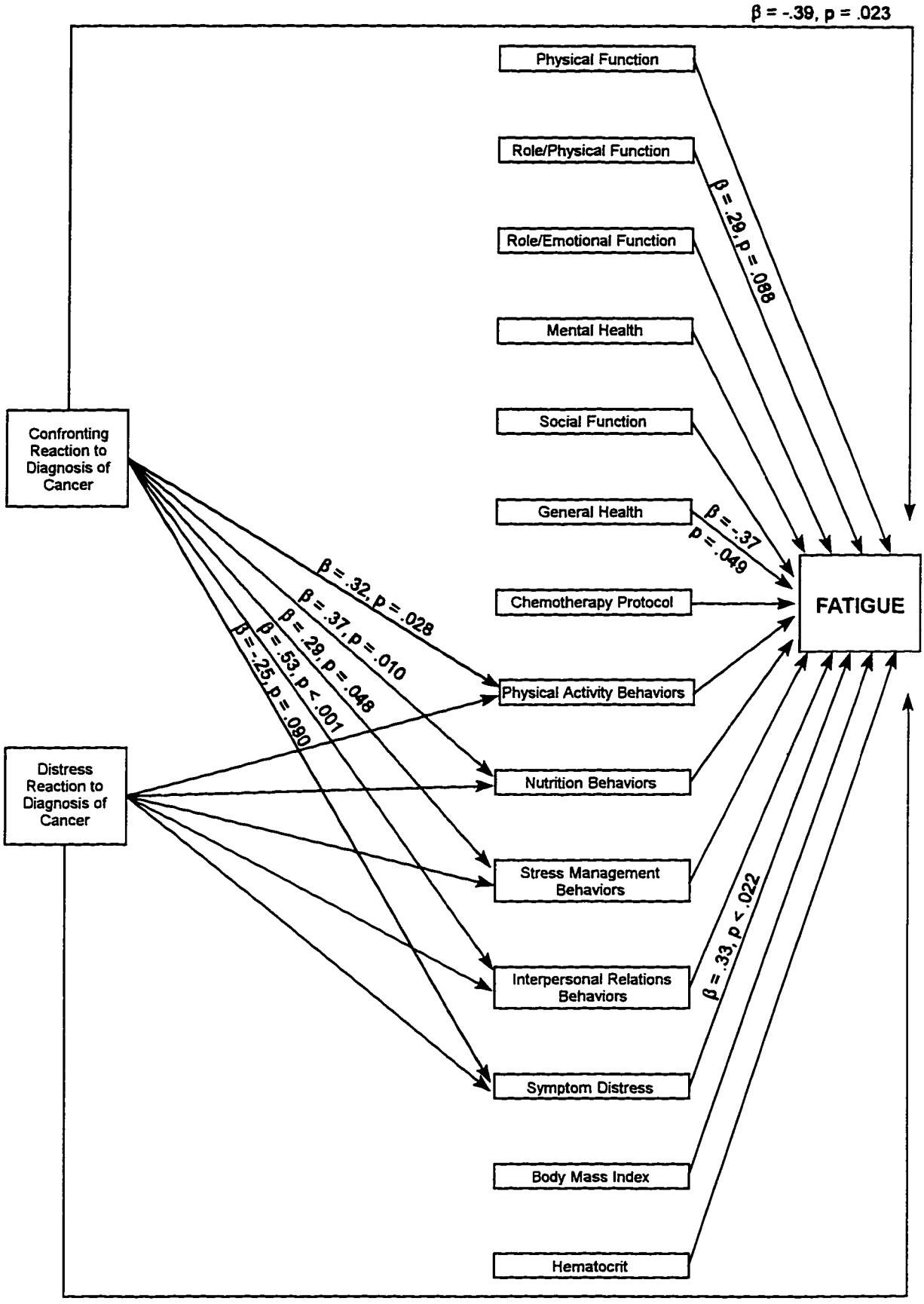


Figure 12. Path Diagram of Factors Influencing Fatigue in Women Receiving Chemotherapy for Breast Cancer at Time 4

Table 18

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Mid-point, Cycle 2 (T4) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.447[c]	.242				
Physical Functioning			-.179	0.95	.335	-.311
Role-Physical			.291-	3.03	.088	-.025
Role-Emotional			.167	0.65	.426	-.242
Social			.055	.05	.824	-.384
Mental Health			.279	1.59	.214	-.174
General Health			-.371	4.08	.049	-.439
Chemotherapy Protocol[d]			.034	0.07	.791	-.155
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			.094	.22	.641	-.200
Nutrition			-.054	.07	.792	-.181
Interpersonal Relations			.272	1.60	.212	-.061
Stress Management			-.167	0.67	.417	-.227
Nutrition Status						
Hematocrit[f]			.046	0.11	.743	.018
Body Mass Index			-.080	0.35	.559	.099
Symptom Distress[f]			-.331	5.67	.022	.467
Reaction to Diagnosis of Cancer[g]						
Distress			-.172	0.98	.328	-.064
Confront			-.392	5.57	.023	-.168

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement at Time 1 - recall of status prior to diagnosis.

[c]Overall $F = 3.44$ ($p < .001$).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measured at Time 1 - current lifestyle behaviors 48 hours after chemotherapy.

[f]Measured at current time (T4).

[g]Measurement at Time 1, recall of reaction to diagnosis

Table 19

Summary of Standardized Effects of Path Model Variables on Fatigue in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Mid-point, Cycle 2 (T4) (N =60)

Variables	Direct Effects	Indirect Effects	Effects Coefficients
Health and Functional Status			
Physical Functioning	-.179		-.179
Role-Physical	.291		.291
Role-Emotional	-.167		-.167
Social	.055		.055
Mental Health	.279		.279
General Health	-.371		-.371
Chemotherapy Protocol[a]	.034		.034
Health Promoting Lifestyle Behaviors[b]			
Physical Activity			
Nutrition	.094		.094
Interpersonal Relations	-.054		-.054
Stress Management	.272		.272
	-.167		-.167
Nutritional Status			
Hematocrit	.046		0.46
Body Mass Index	-.080		-.080
Symptom Distress	.331		.331
Reaction to Diagnosis of Cancer			
Distress	-.172		
		.012 Thru physical activity -.008 Thru nutrition .089 interpersonal relations .001 Thru stress management .032 Thru symptom distress **.126 Sum**	-.046
Confront	-.392	.029 Thru physical activity -.019 Thru nutrition .143 Thru interpersonal relations .047 Thru stress management +.081 Thru symptom distress **.281 Sum**	-.111

[a]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[b]Measured at Treatment 2 (T3).

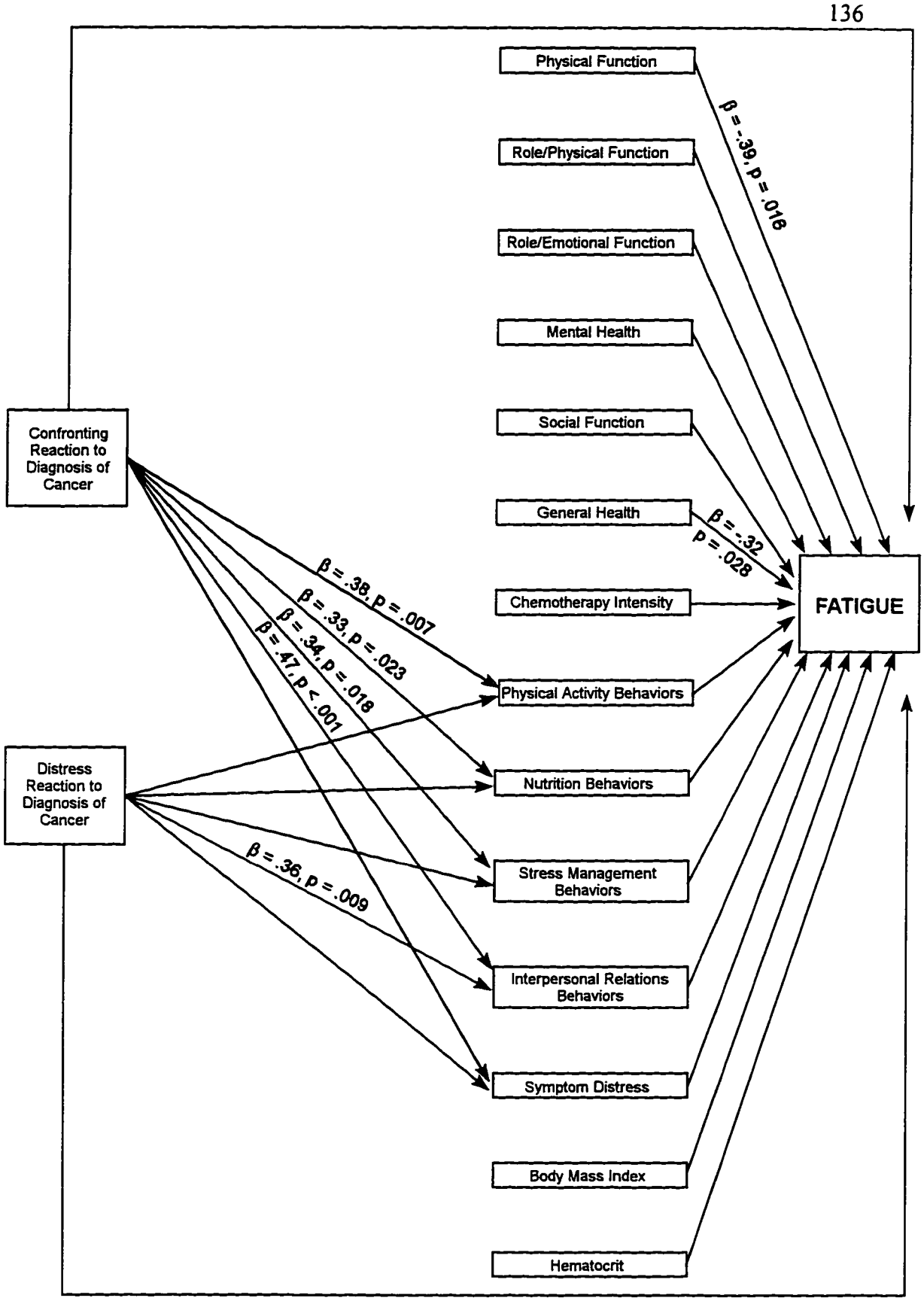


Figure 13. Path Diagram of Factors Influencing Fatigue in Women Receiving Chemotherapy for Breast Cancer at Time 6

Table 20

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Mid-point, Cycle 3 (T6) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.600[c]	.452				
Physical Functioning	-.386		6.27		.016	-.650
Role-Physical	.015		0.02		.904	-.329
Role-Emotional	.056		0.16		.693	-.249
Social	.009		0.00		.959	-.297
Mental Health	-.049		0.06		.810	-.386
General Health	-.322		5.15		.028	.566
Chemotherapy Protocol[d]	-.104		0.93		.339	.110
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity	-.155		0.97		.331	-.441
Nutrition	-.171		1.16		.288	-.418
Interpersonal Relations	.070		0.15		.703	-.147
Stress Management	.182		1.21		.277	-.240
Nutrition Status						
Hematocrit[f]	-.036		0.10		.754	-.097
Body Mass Index	.033		0.09		.763	.220
Symptom Distress[f]	.202		2.20		.146	.423
Reaction to Diagnosis of Cancer[g]						
Distress	.048		0.12		.730	.031
Confront	.020		0.03		.872	-.118

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement at T5.

[c]Overall F = 4.04 ($p < .001$).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measured at Time 1 - current lifestyle behaviors 48 hours after chemotherapy.

[f]Measured at current time (T6).

[g]Measurement at Time 1, recall of reaction to diagnosis

Table 21

Summary of Standardized Effects of Path Model Variables on Fatigue in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Mid-point, Cycle 3 (T6) (N =60)

Variables	Direct Effects	Indirect Effects	Effects Coefficients
Health and Functional Status			
Physical Functioning	-.386		-.386
Role-Physical	.015		.015
Role-Emotional	.056		.056
Social	.009		.009
Mental Health	-.049		-.049
General Health	-.322		-.322
Chemotherapy Protocol[a]	-.104		-.104
Health Promoting Lifestyle Behaviors[b]			
Physical Activity			
Nutrition	-.155		-.155
Interpersonal Relations	-.171		-.171
Stress Management	.070		.070
	.182		.182
Nutritional Status			
Hematocrit	-.036		-.036
Body Mass Index	.033		.033
Symptom Distress	.202		.202
Reaction to Diagnosis of Cancer			
Distress	.048	-.023 Thru physical activity -.019 Thru nutrition .025 Thru interpersonal relations 0 Thru stress management -.021 Thru symptom distress **-.038 Sum**	.010
Confront	.020	-.059 Thru physical activity -.056 Thru nutrition .032 Thru interpersonal relations .061 Thru stress management -.021 Thru symptom distress **-.043 Sum**	-.023

[a]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[b]Measured at Treatment 3 (T5).

Table 22

One-way Comparisons Between High and Low Health and Functional Status Scores[a] and Fatigue over Time in Women Receiving Adjuvant Chemotherapy for Breast Cancer

Variable	Total Fatigue Scores					
	Time					
	1	2	3	4	5	6
	F, (p) (N=65)	F, (p) (N=64)	F, (p) (N=61)	F, (p) (N=61)	F, (p) (N=61)	F, (p) (N=60)
Physical Function						
Low=14	.168 (.684)	3.83 (.054)	4.80 (.032)	5.70 (.020)	.817 (.369)	11.57 (.001)
High =54						
Role /Physical						
Low=8	.713 (.402)	1.23 (.273)	1.16 (.286)	1.59 (.286)	.132 (.717)	.022 (.961)
High=60						
Role/Emotional						
Low=13	.549 (.462)	.007 (.936)	.332 (.566)	1.53 (.220)	.376 (.542)	3.64 (.061)
High=55						
Social						
Low=14	.605 (.440)	11.95 (.001)	6.16 (.016)	5.16 (.027)	10.60 (.002)	20.95 (.001)
High=54						

[a]Measurement at time 1, recall of status prior to diagnosis.

predicting fatigue at the first cycle mid-point, a finding consistent with the social function domain described above.

A stronger confronting initial response to the diagnosis of cancer was indirectly related to fatigue through IPR behaviors (ß=.37, p=0.009) at the cycle 1 midpoint (T2). A stronger confronting initial response to the diagnosis was also directly related to participation in physical activity and IPR behaviors at T2, and to participation in all four health-promoting lifestyle behaviors at both cycle 2 and 3 mid-points (T4&6), but lifestyle behaviors did not directly influence fatigue (Tables 17, 19, & 21). In addition, a stronger distress initial response was directly related to participation in IPR behaviors (ß= .36, p=0.009) at the midpoint of cycle 3 (T6). A weaker confronting initial response was close to significance in indirectly influencing fatigue through symptom distress (ß= -.25, p=0.090) at the mid-point of cycle 2.

Alternative path analyses was conducted to determine whether recall of lifestyle behaviors prior to diagnosis, rather than current measures of lifestyle behaviors, might explain more variance in fatigue at each cycle mid-point. Tables 32, 33, and 34 in Appendix N present results of these regression analyses at all three midpoints (T2,4,& 6), respectively. At all three times, less variance in fatigue was explained by the recall of lifestyle prior to diagnosis than by the current measures. An additional path analysis was conducted to determine whether recall of pre-diagnosis, rather than current (T5), measures of health and functional status and current lifestyle behaviors might explain more variance in fatigue. Table 35, also in Appendix N, presents results of the analysis at the cycle 3 mid-point. In this analysis, the strongest direct paths to fatigue were physical function (ß= -.33, p=0.049) and

symptom severity (ß=.28, p=0.044). Additional influences with moderate beta weights included social function (ß= -.36, p=0.114) and physical activity behaviors (ß= -.28, p=0.075). This analysis adds another dimension to understanding of fatigue experienced over time.

Activity/Rest Cycles

The relationship between activity/rest cycles and fatigue was analyzed separately from the path analyses, since actigraph data were available only for a subset of the women (n=34-46) at each time. Table 23 presents correlations between selected activity/rest variables at treatment times and fatigue scores at cycle mid-points. A significant inverse association was found between amplitude at T1 and fatigue at T2. A positive correlation was found between increased number of night awakenings at T5 and fatigue at T6.

Summary of Influences on Fatigue at Midpoints

Path analyses identified direct and indirect influences on mid-cycle fatigue among women receiving adjuvant chemotherapy. Symptom distress from the previous treatment, physical function, role/physical function, general health status and the confronting response to the diagnosis of cancer explained the largest share of the variance in fatigue at the mid-points. A confronting initial reaction to the diagnosis of cancer influenced fatigue directly at the mid-point of cycle two and indirectly through symptom distress at the mid-point of cycle 1. A confronting reaction also directly influenced engagement in health-promoting lifestyle behaviors, but these behaviors did not significantly influence fatigue. A distress initial response to the diagnosis was directly related to participation in IPR behaviors at the mid-point of the third cycle. At the mid-point times, alternate path analyses using recall to

Table 23

Pairwise Correlations Between Selected Activity/Rest Cycle Variables at Treatment Times and Fatigue at Cycle Midpoints in Women Receiving Adjuvant Chemotherapy for Breast Cancer

Activity/Rest Variables at Treatment Time Preceeding Cycle Mid-Point	Total Fatigue Scores at Cycle Mid-Points		
	T2	T4	T6
Mesor			
r	-.228	.0871	-.102
(n)	(46)	(41)	(37)
p	.128	.588	.547
Amplitude			
r	-.319	-.208	-.238
(n)	(46)	(41)	(37)
p	.031	.192	.156
Mesor plus Amplitude (Day High 3)			
r	-.0298	-.223	-.067
(n)	(41)	(38)	(34)
p	.853	.178	.707
Awakenings at Night			
r	.0546	.044	.321
(n)	(45)	(39)	(40)
p	.722	.793	.044

pre-diagnosis, rather than current, measures of health-promoting lifestyle behaviors explained less variance in fatigue than the analysis using current lifestyle behaviors. A summary of all significant variables in the path models that directly influenced fatigue in women receiving adjuvant chemotherapy for breast cancer is presented in Table 24. In addition to path analyses results, correlations were performed on activity/rest cycle variables and fatigue. Amplitude values at treatment 1 were inversely associated with fatigue at that cycle mid-point and awakenings at night at treatment 3 were directly related to fatigue at that cycle mid-point.

Table 24

Significant Variables in Path Diagrams[a] of Factors Directly[b] Influencing Fatigue in Women Receiving Adjuvant Chemotherapy for Breast Cancer

	Time					
Variable	1	2	3	4	5	6
Health and Functional Status[c]						
Physical Functioning		X				X
Role-Physical		X				
Role-Emotional						
Social						
Mental Health						
General Health				X		X
Chemotherapy Protocol[d]	X					
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity						
Nutrition						
Interpersonal Relations	X					
Stress Management						
Nutritional Status						
Hematocrit						
Body Mass Index						
Symptom Distress	X	X	X	X	X	
Reaction to Diagnosis of Cancer[f]						
Confront				X		
Distress						

[a]Path diagrams = Figures 8-13.

[b]Only factors that directly influenced fatigue were included.

[c]Health and Functional status measured at Time 1 (recall of status prior to diagnosis) used at Times 1, 2, 3, & 4. Health and Functional Status measured at T5 used at Times 5 & 6 analysis.

[d] Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measured at each treatment (T1, T3, T5). Each measurement used at that cycle treatment and mid-point.

[f]Measured at Time 1 - recall of reaction when told of cancer diagnosis.

CHAPTER 5

SUMMARY, CONCLUSIONS, DISCUSSION, RECOMMENDATIONS AND IMPLICATIONS

Summary

This study was designed to further understanding of the patterns of fatigue and factors influencing fatigue among women receiving adjuvant chemotherapy for stage I or II breast cancer. The conceptual model for the study is drawn heavily from Piper's (1987) integrated fatigue model (IFM) for the conceptualization of fatigue in healthy and clinical populations. Initial reaction to the diagnosis of cancer as well as seven of the 13 biochemical, physiologic, and psychosocial patterns from the IFM believed to be the factors most likely to influence fatigue were selected for examination in this study. The seven patterns were represented by variables of physical function, role/physical function, role/emotional function, mental health, social function, general health, chemotherapy protocol, activity/rest cycles, hematocrit, BMI, symptom distress, and nutrition, stress management, interpersonal relations and physical activity behaviors. The major purposes of the study were to examine patterns of fatigue and of selected factors influencing fatigue across the first three cycles of chemotherapy and to determine to what extent the selected variables explained and predicted fatigue after each of three chemotherapy treatments.

All English speaking women ages 30-69 with a Karnofsky score of 60 or above who were beginning one of three adjuvant chemotherapy regimens after surgery for a first time diagnosis of stage I or II breast cancer were asked to participate in the study. Data were collected at six times: three were on the first 4 days of chemotherapy cycles, and three were

for 3 days at the cycle mid-point. Seventy-two women were enrolled in the study, with the three chemotherapy regimens represented almost equally among the subjects. The study sample was comprised of women from eight out-patient clinical settings who considered themselves to be in very good to excellent health prior to their recent diagnosis of breast cancer. Sixty women completed the study. Women who withdrew from the study were similar to the sample in most demographic characteristics except for race and marital status. Two of the three black women who entered the study withdrew prior to the second treatment, (T3). Because of disproportionate withdrawals by unmarried women, married women comprised 65% of the women who enrolled, and 73% of the sample from whom data collection were complete.

Questionnaires were completed by each subject within the same 4-hour block of time of day and included instruments to measure health and functional status, reaction to the diagnosis of cancer, health-promoting lifestyle behaviors, symptom distress, and fatigue. In addition, biologic measurements included wrist actigraph, body mass index (BMI) and hematocrit values.

Major findings were: (a) total and subscale fatigue scores were significantly different over time, with scores higher at treatment times, and lower at the mid-point between treatments in a roller-coaster fashion; (b) symptom distress, defined as the severity of symptoms that are usually most distressing to women receiving adjuvant breast cancer chemotherapy, made the greatest independent contribution to the explanation of the fatigue experienced, and fatigue also was explained by the chemotherapy protocol and the interpersonal relations behaviors of the women at each of the three treatments; and (c)

symptom distress at the time of treatment was the most significant predictor of fatigue at the mid-point of the first two chemotherapy cycles, followed by measures of health and functional status; at the third cycle, general health status at the time of that treatment was the strongest predictor of fatigue at the mid-point of the cycle; and (d) activity/rest patterns obtained by actigraphs were significantly different over time in women receiving adjuvant breast cancer chemotherapy and were below norms established for healthy individuals. Higher perceived fatigue levels were associated with lower daytime activity and higher number of night-time awakenings at some times.

Conclusions and Discussion

The conclusions based on each of the three research questions are presented below.

Research Question 1: What are the patterns of fatigue and of selected factors influencing fatigue among women with stage I or II breast cancer across the first three cycles of chemotherapy?

Patterns of Fatigue Over Time. Repeated measures analysis of variance (RM-ANOVA) revealed that total and subscale fatigue scores had a significant overall effect, as well as significant differences over time between treatment and mid-point scores. Mean scores followed a pattern with each chemotherapy cycle that resembled a roller-coaster effect such that scores were higher at treatments and lower at cycle mid-points. Despite the common perception that fatigue increases with each successive treatment, this study did not support that idea. In fact, fatigue scores were highest at the time of the first treatment and lowest at the mid-point of cycle 3.

These results are similar to Piper, et al.'s findings (1989b), where mean fatigue sensations were reported as most intense on day 1 of the first CT cycle. Meyerowitz (1983) also reported that women being interviewed who were receiving CMF chemotherapy expressed feelings of increases in energy levels between treatments. These findings differ from reports of higher scores on day 14 (mid-point) of the first cycle than on day 1 (Irvine et al., 1994). Greene et al. (1994), Piper, et al. (1989), Piper, et al. (1991), and Piper (1993b), all reported that fatigue scores were not statistically different over time and did not follow a pattern in studies ranging from 2 to 6 cycles. Two studies by Piper (1989, 1993) included mid-point perceptions of fatigue that were not different from perceptions of fatigue at the time of treatments. Greene et al. examined fatigue only at 2 and 5 days after the treatment, and did not collect data on mid-point fatigue perceptions. Therefore, the tri-modal patterns of fatigue found in the current study have not previously been reported in the literature.

Total fatigue scores at T1 were also correlated with younger age, a finding consistent with previous results reported by Berger (1995d) and Piper (1989b). No background data variable was correlated with fatigue in a consistent pattern across time in this study.

These results have generated new knowledge regarding patterns of fatigue over time in this population. Previous studies generally have limited measurements of fatigue at treatment times to that experienced on day 1, and have not reported such comprehensive assessments of fatigue during the recovery period between treatments. However, fatigue at the time of treatments was usually measured only on day 1, where in the present study, it was measured 48 hours after the treatment. The different timing of measurements may account for the different findings. It is important to recognize that under-reporting of fatigue sensations

throughout all studies may have biased results. Unconscious shifting of an individual's set-point may have resulted in lower scores over time that would be difficult to detect when measurements are taken on any one day of the chemotherapy cycle (Breetvelt & Van Dam, 1991). Pilot work by Berger (1994) identified peak intensity of fatigue to occur 48-72 hours after the treatment, and to vary during the day. The in-depth assessment of fatigue on a specific day after treatment strengthens the validity of the results regarding these variables. Reliability of results was also enhanced by controlling for time of day for instrument completion.

Fatigue in women at cycle mid-points is concerning, for it may perpetuate a cycle of increased fatigue, decreased activity, and mood changes. These women may be at an increased risk of experiencing higher fatigue levels at successive treatments, and require interventions to prevent morbidity and treatment delays from the treatment's cumulative effects.

Patterns of Selected Factors Influencing Fatigue Over Time.. Perceptions of health and functional status were significantly different over time using t-test comparisons of six subscales of the MOS-SF-36 instrument (Ware & Sherbourne, 1992). Scores in six subscales were examined by paired t-test for differences across time. All subscales were significantly lower at the 0.001 level except mental health ($t=1.84$, $p=0.070$) when comparing health status scores recalled from prior to diagnosis to measurements at the third treatment. Subjects may have been more likely to answer in a socially acceptable manner regarding mental health status, limiting validity of the results. Participation in the study also may have provided an intervention to support and sustain mental health.

Despite the relative stability of fatigue reported from the first to third treatments, perceptions of health and functioning in physical, emotional, and social roles declined significantly between the recall measurement and the third treatment in this sample. Pilot work by this author (Berger, 1993) concluded that fatigue measured by the Piper Fatigue Scale (PFS) (Piper et al, 1989) and the physical functioning subscale of the Quality of Life Index-Cancer version (Ferrans & Ferrell, 1990) were correlated ($r= -0.805$, $p=0.01$), indicating that physical functioning and fatigue have a reciprocal relationship. The MOS-36 instrument demonstrated sensitivity to changes over time in this sample, while values obtained from the PFS were similar at the time of each treatment. Therefore, the reciprocal relationship between health and functional status measurements and fatigue was not found in this study. Whether these results are valid or are erred due to lack of sensitivity of the PFS or because of under-reporting of fatigue over time due to a re-setting phenomenon is uncertain.

Oncology nursing research studies have not traditionally included an overall health and functioning measurement to examine the "cost" in terms of quality of life of treatment. Only Hughes' 1993 findings which included use of a shorter version of the MOS-36 instrument, MOS-20, support this result. Decreases in physical, role, and social functioning were reported in breast cancer patients from diagnosis to 8 weeks post-operation in that sample. These results tell us that multi-modal treatment protocols requiring chemotherapy to begin shortly after surgery create a challenging situation for women with early breast cancer that necessitates adaptation of the individual for short and long term survival. This adaptational

process can be either health-promoting, or can decrease reserves and bring the individual increased stress and fatigue.

Patterns of health-promoting lifestyle behaviors over time were examined by RM-ANOVA. Positive changes occurred in the period of time from pre-diagnosis to the first chemotherapy treatment. These findings are similar to pilot study results reported by Berger (1994) that compared lifestyle behaviors pre- and post-operatively for women with breast cancer about to begin adjuvant treatment. Findings from that study included significant positive differences in both stress management and interpersonal relations behaviors and significant negative differences in physical activity behaviors from prior to diagnosis (measured by recall) to approximately 1 month after surgery. These results tell us that behavior changes occur during this challenging period of time in both positive and negative directions. That study and this one are the first to use the HPLPII with cancer patients during treatment, limiting comparisons with other studies. Work by Frank-Stromborg (1986) using a *Health Diary*, revealed that patients undergoing treatment for cure of cancer were engaging in behaviors representative of the dimensions of a health-promoting lifestyle. It was concluded that responses in the *Health Diary* indicated a strong desire of subjects to increase their health potential through health-promoting activities in the areas of nutrition, stress management, exercise and social health. In the current study, no significant changes occurred in lifestyle behaviors once chemotherapy was initiated, however, health-promoting lifestyle behaviors were maintained across treatments. After receiving the first treatment, women may have lacked the knowledge or the physical and psychological energy to move toward

adoption of healthier lifestyle behaviors. Perhaps learning symptom management strategies was the priority effort during this vulnerable time for this sample.

Nutritional status patterns fluctuated over time across the first three cycles of chemotherapy. Hematocrit levels decreased significantly over time. Despite a recovery effect between each mid-point and subsequent treatment time, hematocrit levels also decreased significantly between treatment days over time. Because of these decreases in hematocrit levels over time, less oxygen was delivered to working muscle cells and significant cellular impairments could result (Winningham, 1996). This deficient oxygen supply delayed repayment of the oxygen debt at the cellular level when the body was working at moderate intensity, and could have led to perceived fatigue. These results describe a scenario of decline in hematocrit values that never reached a level where they were related to fatigue perceptions during this study. A weakness of previous nursing research studies on fatigue has been the lack of use of biologic measurements for comparison to fatigue scores. Hematocrit was selected as a biological measure that has been shown in the past to be related to vigor and mood using the POMS measurement (Piper et al, 1989c). Biological markers need to be identified that are stronger correlates of perceived fatigue.

Changes over time in total symptom distress scores, which measured the severity of the distressing sensations of nausea, difficulty sleeping, and mood, were examined by RM-ANOVA. Significant differences in symptom distress scores over time, as well as between each time, were found. Mean scores followed a tri-modal pattern over time similar to those reported with fatigue, where treatment scores were higher than recovery mid-point scores. Scores on symptom distress were again highest at the first treatment. Levels of sleep

difficulty were scored as most intense, nausea least intense, and mood intermediate at the first treatment and throughout subsequent data collection times. A common perception among oncology nurses is that nausea is the most intense symptom after chemotherapy. In this sample, both sleep difficulty and mood were scored as more severe than nausea at each treatment and mid-point time. This finding might be explained by the argument that since nausea was more effectively managed, the other two symptoms were increasingly evident to the women.

These results also inform nurses that symptoms experienced with the first treatment are not a passing phenomenon, but that the response at the first treatment is likely to continue with later treatments. With mean symptom distress scores at midpoints averaging 2.5 (SD=1.8) on a 1-10 scale, where 10 reflects the most severity, it could be concluded that lower scores could be expected if symptom relief were more complete. Examination of, and modification to, the anti-emetic regimens prescribed and level of patient compliance and benefit with the prescribed regimen is needed to further control nausea (Fessele, 1996). Assessment of sleep difficulties is as important as is nausea evaluation in this population. Prompt, effective symptom relieving interventions are indicated to modify acute fatigue and prevent development of a cumulative fatigue process that may lead to chronic fatigue and long-term negative outcomes in this population.

RM-ANOVA was employed to determine patterns of activity/rest cycle variables over time. When only subjects who had complete actigraph data for all 6 times were entered (N=17), significant differences across all six times were found for the selected activity/rest cycle variables. Mean values were again in a tri-modal pattern, but reversed in this situation,

such that lower activity scores were reported at treatment times and higher activity scores reported at cycle mid-points. Activity/rest cycle values during the three treatments and then during the three mid-point recoveries were analyzed in all women for whom complete data were available (n's = 29, 23), and were not found to be significantly different over time. Results need to be viewed cautiously, since women who did not wear the actigraph may have had different activity/rest cycle patterns than the women who wore the actigraph for the entire time. An example of this is a woman who removed the wrist actigraph in the middle of the first night after treatment because she was so nauseated and felt so poorly that the only thing that sounded good was a hot bath, and women were instructed not to wear the wrist actigraph near water.

The use of wrist actigraph measurements of activity/rest cycle variables has been reported in only a few nursing research studies, none of which involved patients with a cancer diagnosis (Elmore & Burr, 1993). Therefore, comparison of these findings with other nursing research studies is not possible. Medical researchers have reported that 50% of metastatic colo-rectal cancer patients who wore the actigraph for 3-5 days before beginning chemotherapy had lower values for all activity parameters compared to healthy controlled data (Mormont & DePrins, 1995). Researchers did not discuss if these patients had undergone a recent surgical procedure or if the metastases were to the liver; both situations may have influenced the findings. Chemotherapy is usually begun 4 weeks after surgery ($\bar{X}$=29 days in this sample), and surgical recovery is considered to be a 4-6 week process in individuals who are healthy. Actigraph data values may have been lower because of a delayed recovery response, or because of abnormal liver functions in this sample.

Other researchers have reported patient's anecdotal complaints of changes in sleep quality and timing associated with chemotherapy. Piper (1993b) found that the majority of women reported that they were sleeping and napping more by the third treatment. Frequent night-time awakenings, insomnia, and an increased need to sleep and nap have also been reported (Knobf, 1986; Nail et al., 1991). Wrist actigraph analysis in this study verified an increased percentage of time spent sleeping/24 hours, occurring both during the night and the day, at the time of the third treatment. Night-time awakenings ranged from means of 33-37 times/night at treatment times to 22-29 times/night at cycle mid-points; verifying anecdotal reports of frequent awakenings at night.

Mormont et al. (1996) proposed that the relationship between quality of life indicators, particularly fatigue, and activity/rest cycles deserved exploration, and that results may lead to increased use of the non-invasive actigraph in clinical studies. This non-invasive biologic instrument has provided important information for oncology health care team members that increased understanding of the relationship between activity/rest cycles, chemotherapy protocols and fatigue.

Research Question 2: To what extent do health and functional status, chemotherapy protocols, physical activity behaviors, activity/rest cycles, nutrition behaviors and status, stress management behaviors, interpersonal relations behaviors, symptom distress patterns and reaction to the diagnosis of cancer explain fatigue 48 hours after each of three chemotherapy treatments?

Path analyses were used to determine the relative weight of study variables in explaining fatigue at the three treatment times. Activity/rest cycles were omitted from this analysis

because of incomplete or missing actigraph data from numerous subjects. The relationship between these variables and fatigue was analyzed and presented separately.

Symptom distress, comprised of difficulty sleeping, nausea, and mood severity, offered the strongest direct explanation for perceived fatigue 48 hours after each chemotherapy treatment, with ß's ranging from .54 to .62 ($p<0.001$). Symptom distress has previously been recognized as contributing to a secondary fatigue state, described as the common denominator of acute symptom distress (Winningham, et al. 1992). Research examining fatigue and nausea in cancer patients receiving chemotherapy has reported the two symptoms occurring simultaneously (Ehlke, 1988). Fatigue has been correlated with depressed mood and difficulty concentrating in two studies of women with breast cancer (Knobf, 1986; Piper, 1993b). Attention needs to be directed toward "teasing" out the differences between fatigue, mood/depression, and other symptoms associated with cancer treatment. The mental health subscale of the MOS-36 was used to screen subjects for the presence of psychological morbidity in this study. This subscale did not identify any extreme cases or outliers that may have reported signs and symptoms of depression that might have mimicked fatigue in this sample. This study reinforces the belief that fatigue and severity of other symptoms accompany each other. Revision of the study model to include all four symptoms including fatigue, nausea, difficulty sleeping and mood as the dependent variables will allow other independent variables to demonstrate an influence on fatigue.

Additional direct influences at the first treatment included more toxic chemotherapy protocols and fewer interpersonal relations behaviors. Women who received intravenous Adriamycin and Cytoxan containing regimens reported higher levels of fatigue intensity at

the first treatment. Although oncology clinic nurses would not be surprised by this finding, research to date has reported no significant differences in either the number or the intensity of fatigue symptoms related to whether or not Adriamycin was included in the treatment regimen (Greene et al, 1994, Piper, 1993b). At subsequent treatment times, factors other than the regimen itself were stronger influences on fatigue.

Women who reported fewer interpersonal relations behaviors, and who reported lower social function scores on the MOS-36, reported higher levels of fatigue at some time points in this study. Feeling close to and accepted by another who will listen may decrease the psychological burden of this crisis, and women who lack this dimension in their lives may experience increased fatigue perceptions. Nine of the 12 women who withdrew from the study were not presently married, and the analysis did not include data from them. Results might be different if the entire sample had completed the study and that data entered into the path analyses. Most withdrawals occurred prior to the second chemotherapy treatment. Fewer IPR behaviors and lower social functioning did not contribute significantly to perceptions of fatigue at later times.

A stronger confronting initial response to the diagnosis of cancer was indirectly related to fatigue through IPR behaviors at the first treatment. A weaker confronting response was indirectly related to fatigue through symptom distress at the first treatment. The reaction to the diagnosis of cancer has not been previously tested in a model examining factors influencing fatigue. Frank-Stromborg (1990) reported that the confronting response was among the strongest predictors of variance in health-promoting lifestyle among 385 ambulatory cancer patients. This relationship was not supported in Berger's pilot study

(N=29), perhaps due to the small sample size and the timing of the measurement of health-promoting lifestyle behaviors (1995d). Women in the current study who had a confronting, "I can beat this", attitude were more likely to engage in all four healthy lifestyle behaviors at later treatments. At the second treatment, the direct influence of fewer physical activity behaviors explaining fatigue tied in with the finding that increased number of physical activity behaviors are performed by those who confront the diagnosis. No other relationships among the reaction to diagnosis, lifestyle behaviors and fatigue were found in this study. Reaction to the diagnosis of cancer appeared to play an important role in influencing health-promoting lifestyle behaviors, and may explain fatigue in both direct and indirect paths in future studies that examine these relationships over longer periods of time.

In conclusion, symptom distress, defined as the severity of symptoms that are distressing to women receiving adjuvant breast cancer chemotherapy, dominated the variables in explaining fatigue at treatment times. Adjusting the model to include symptom distress with fatigue as dependent variables may allow other study variables to demonstrate their contribution to variance in overall symptom distress, and specifically fatigue. Chemotherapy protocol was important at the time of the first treatment, but other factors influenced fatigue perceptions at the time of other treatments. Lower levels of both physical activity and interpersonal relations behaviors explained higher levels of fatigue at some times. A stronger confronting reaction to the diagnosis of cancer was indirectly related to fatigue through health-promoting lifestyle behaviors. Mesor and amplitude values obtained by actigraphs in women receiving adjuvant breast cancer chemotherapy were significantly below norms

established by healthy individuals at all three treatment times. There are many implications for clinical practice as a result of these findings.

Research Question 3: To what extent do health and functional status, chemotherapy protocols, physical activity behaviors, activity/rest cycles, nutrition behaviors,and status, stress management behaviors, interpersonal relations behaviors, symptom distress patterns and reaction to the diagnosis of cancer predict fatigue at the midpoints of each of three chemotherapy treatment cycles?

Path Analyses

Path analyses were used to determine the relative weight of study variables in predicting fatigue at the three mid-point recovery times, as illustrated in Figures 11, 12, and 13. Activity/rest cycles were omitted from these analyses because of incomplete and missing actigraph data from numerous subjects. The relationship between these variables and fatigue was analyzed separately.

Conclusions from these analyses were that symptom distress again offered the strongest prediction for perceived fatigue at the cycle midpoints during the first (ß=.43, p=0.002) and second (ß=.33, p=0.022) cycles of chemotherapy. Management of symptom distress duration, as well as severity, is critical to modification of fatigue at cycle mid-point recovery times. Severity of symptom distress with treatments was a strong predictor of higher levels of fatigue at mid-points, resulting in interference with numerous role obligations. This cumulative process may be a fore-runner of chronic complaints of fatigue.

Health and functional status measurements reflecting pre-diagnosis baseline were strong influences on the fatigue experienced by women at the mid-points of the treatments.

Repeating health and functional status measurements at the third treatment may also assist oncology clinicians to identify additional women with current "low" health status scores, as these scores may predict risk for experiencing further decline in health status and increasing levels of fatigue. Severity of fatigue and overall health status appeared to be reciprocally related in women with breast cancer receiving chemotherapy. Interventions could be designed and tested to assist in promoting health and meeting role obligations in "at-risk" individuals.

A lower score on the confronting initial reaction to the diagnosis of cancer was also a strong direct predictor of increased fatigue through symptom distress at the mid-point of the first cycle, and approached significance at the mid-point of the second cycle. Women who did not assume an "I can beat this" confronting attitude at the time of diagnosis experienced more intense fatigue at that time. The timing of this relationship is of interest, as by this time in the study, most women had returned to work and may have resumed major roles in families. Women may have had fewer offers of assistance, requiring more highly developed interpersonal relations behaviors in relationships. Those with less confronting responses may have easily felt overwhelmed and fatigued with all the responsibilities in their lives at that time and not felt capable of seeking assistance from others. Group psychotherapy to assist in stress and symptom management has been reported to reduce overall symptom distress, including fatigue, and may have broad applicability in patients receiving adjuvant chemotherapy for breast cancer (Fawzy, 1995; Forester et al., (1993).

A confronting initial reaction to the diagnosis of cancer directly influenced physical activity and IPR behaviors at the mid-point of the first cycle, and all four health-promoting

lifestyle behaviors at the mid-points of the second and third cycles. A high distress reaction was associated with greater frequency of IPR behaviors at the mid-point of the third cycle. Assessment of reaction to diagnosis of cancer at the time of the first chemotherapy visit may identify the individual's response, and may predict those individuals who are less likely to assume healthy lifestyle behaviors during treatment. Counseling or other supportive services may offer assistance to them in addressing the physical and emotional challenges of receiving chemotherapy.

In summary, it can be concluded that symptom distress (which measured the severity of the distressing sensations of nausea, difficulty sleeping, and mood) at the time of the treatments, health and functional status variables reflecting status pre-diagnosis and after two complete cycles of treatment, IPR behaviors, and reaction to a cancer diagnosis directly predicted which women experienced the most difficulty bouncing back from fatigue at the mid-point from each treatment. Prediction of fatigue at the mid-points in this sample was more complex than explaining fatigue at treatment times. Symptom distress that was pervasive at treatment times subsided for the majority of women, and fatigue at the mid-point recovery appeared to be linked to a variety of factors. Women who experienced more severe symptom distress at treatments were predicted in this model to experience increased fatigue at the mid-point recovery, further perpetuating a cycle of increased fatigue, decreased activity and mood changes. It may be that prompt, effective relief of symptoms is the most important intervention to modify acute fatigue, and prevent development of chronic fatigue in this population.

Analysis at the mid-point of the third treatment was informative. When the analysis was performed again using measurements of health and functional status at the third treatment with recall of lifestyle behaviors prior to diagnosis, only physical function (ß= -.41) and general health (ß= -.32) were significant predictors of perceived fatigue. When health and functional status variable scores recalled from prior to diagnosis were entered into the analysis with other variables, including current lifestyle behaviors, the path analysis identified the direct influences of symptom distress (ß=.28) and physical functioning (ß= -.33) as the significant variables, with social functioning (ß= -.36, p=.115) and physical activity behaviors (ß= -.28, p=0.075) approaching significance on perceived fatigue. This cycle mid-point comparison adds weight to the value of assessing physical function prior to diagnosis and after two cycles of treatment in prediction of fatigue levels at the mid-point of the third cycle in women receiving adjuvant chemotherapy for breast cancer.

Follow-up power analyses for multiple regression were performed after cumulative R^2 values were obtained. With a level of significance set at .05, using 16 independent variables, 60 subjects, and the cumulative R_2 value for each specific time, the power for every analysis was .99-1.00, and the effect size varied from a low of .81 at Time 4 to a high of 2.45 at Time 5, with the effect size other times ranging between 1.08 and 1.50.

Follow-up of limitations of the study suggests that some sampling bias did occur as anticipated. Although the number of refusals to participate was very low, 12 women withdrew during the study, most frequently after the first treatment. Nine of the 12 women were not married, and it could be that these women experienced lower levels of support during those first few days after the initial treatment. A second limitation was that a variety

of measures (MOS-SF-36, HPLPII, RDCQ) were completed by the women at Time 1, but instructed them to recall back prior to the diagnosis and at the time of diagnosis, approximately 1-2 months previously. Validity of responses to recall items needs to be considered when interpreting the results. Although almost 300 periods of data were obtained from women wearing the wrist actigraph, complete data for all time points were only available on 17 subjects. Further analysis will determine if this group was different than the group for which data were not obtained at all times. The study was also limited by the availability of actigraphs and the difficulty in reaching women at appropriate data collection times. Finally, since this is the first study examining these influences on fatigue during chemotherapy, generalizability is limited. Further longitudinal investigations are recommended.

Recommendations for Research

The results of this study suggest that fatigue in women receiving adjuvant chemotherapy for breast cancer was significantly different over time, from higher levels at treatment times to lower levels at the mid-points between treatments in a roller-coaster fashion. Fatigue was best explained and predicted by levels of symptom severity experienced in the areas of nausea, sleeping difficulty, and mood. Fatigue was further explained and predicted by examining the overall health and functional status of women pre-diagnosis and at the time of the third treatment. The third major conclusion was that the confrontational response to diagnosis was associated with an increased frequency of one or more health-promoting lifestyle behaviors at all six times and directly influenced levels of fatigue at the mid-point of the second cycle. Recommendations for research as a result of these findings are organized

into the following focus areas: (a) Intervention studies aimed at modification of symptom distress and specifically sleep difficulty during chemotherapy, (b) instrumentation studies aimed at issues related to measurement of fatigue, (c) outcomes research aimed at maintenance of health and functional status of patients receiving out-patient chemotherapy, (d) studies using path analysis to examine the relationships between health-promoting lifestyle behaviors and fatigue in cancer patients receiving chemotherapy throughout and following treatment, and (e) model testing of a revised model for the study of fatigue in women receiving adjuvant chemotherapy for breast cancer.

Significant progress has been made in recent years in the pharmacological control of nausea associated with cancer chemotherapy. The symptom reported as most distressing in this study was sleep difficulty. Examination of sleep in patients receiving chemotherapy has been extremely limited. Now that patterns of perceived rest and activity/rest cycle variables have been identified, interventions designed to modify the sleep experience should to be developed and tested. The use of non-invasive biologic instruments such as the wrist actigraph may compliment questionnaires and strengthen these studies. Controlling the overall symptom experience may be essential to reduce the common denominator of fatigue.

Instrumentation issues are a second focal area for research. The Piper Fatigue Scale has recently been made shorter and more user-friendly (Piper, et al., 1996). Tests of alpha reliability of subscale items in this study revealed high inter-item correlations, reducing the likelihood that the tool captures various dimensions of the concept of fatigue. At the time of the third treatment, subjects became polarized into the two sub-groups of low (X PFS score < 3.0) and high (X PFS score > 6.00) fatiguers, where previously there had been wide

variability of responses along the scale. Issues of sensitivity of measurement need to be addressed. Further development of the tool is recommended.

Future studies that examine fatigue in patients undergoing cancer treatment should include an established health and functional status scale, many times also identified as a quality of life measurement. Further understanding of the influence of health and functional status on perceptions of fatigue is needed. Since an individual's baseline status can't be changed, health care researchers should identify interventions to reduce the likelihood of a negative outcome when low scores are found in one or more dimensions of the scale at the beginning of treatment. For example, it may be important to determine which interventions are most effective in preventing a negative outcome from treatment when low social functioning is identified, or when a low mental health or physical function is present. With continued emphasis on reducing health care expenditures at the national level, patients with cancer will be expected to manage themselves quite independently in increasingly challenging situations. Interventions that maintain or improve areas of health and functional status throughout treatment need to be developed and tested, and effective research findings implemented into practice.

The contribution of health-promoting lifestyle behaviors in influencing levels of fatigue during cancer chemotherapy was not significant in this study in most analyses. These behaviors may not be strong variables in explaining and predicting acute fatigue that occurs during the first few months after diagnosis and initiation of treatment. However, following study participants for the full course of chemotherapy and after completion of chemotherapy may identify significant relationships over time. Future work will determine if health-

promoting lifestyle behaviors (i.e., physical activity behaviors) can influence perceptions of physical functioning, and modify perceptions of fatigue related to cancer treatments over time. It is important to determine if any health-promoting lifestyle behaviors are associated with lower levels of chronic fatigue after chemotherapy. If relationships are found, it is recommended that cancer rehabilitation services that test and evaluate interventions to modify lifestyle behaviors be available for patients during and following treatments.

A final recommendation is to revise the conceptual model for this study, and to include fatigue and other symptom distress as dependent variables. Once symptom distress is removed from the list of factors influencing fatigue, identification of the strongest variables that influence overall symptom distress will be possible. This analysis will provide direction for future work.

Implications for Practice

This study provided new information for clinicians involved in the administration and counseling of women receiving adjuvant chemotherapy for stage I or II breast cancer. The most succinct message was: "If you want to modify fatigue, symptom severity must be minimized". Attention should be paid to teaching and counseling women who will experience nausea, difficulty sleeping, mood changes, and fatigue. Creativity in developing instructional videos, diaries and other teaching materials to promote learning is recommended prior to the first treatment. Patients should receive state-of-the art therapies to manage nausea based on their clinical response to drugs, not based on the chemotherapy protocol drugs alone. Complaints of nausea were not significantly different between the

protocols, and nausea appears to be more complex than simply based on the chemotherapy prescription.

The responses to the second and third chemotherapy treatments were similar to the first experience in this sample of women. Reported perceived fatigue, symptom distress and measures of activity/rest cycle variables did not change significantly across treatment times. Women appeared to be affected from the first day of the treatment, and to not rebound fully at any point over time in this study. Nurses can inform women that role adjustments made during the first cycle will most likely be necessary during subsequent treatments. However, an adaptational response appeared to occur over time, and women reported lower levels of symptom distress and no increases in fatigue over time, which have been commonly held perceptions.

Nurses are working at an increasingly fast pace, and cannot know individual patients as well as in the past. Clinicians need to identify the "high risk" women among those who receive chemotherapy as early as possible. This study makes a strong argument for asking patients to complete a quick and easy baseline assessment, such as the MOS SF-36, to calculate health and functional status subscale scores. Programs for analysis of pre-printed forms could be available to nurses at their work stations, and overall and subscale scores evaluated during the first appointment. If individuals are identified as"high risk" in a particular area, supportive interventions could be quickly initiated. A social service consult, a Reach to Recovery or support group consult, or a mental health evaluation might make a difference in the outcomes of treatment. The individual, the family, and society will benefit from early intervention and prevention of complications.

Assessment to determine the reaction to the diagnosis of cancer response could also be implemented in a busy office setting, and result in identifying those women who are distressed and less likely to engage in behaviors to maintain their health during the challenging course of chemotherapy. Individuals who might benefit from group psychotherapy could also be identified and referred appropriately.

Finally, although this study has provided some new information about the concept of fatigue, this researcher concurs with Sugerman and Berg (1984) who concluded by commenting that what is known about fatigue is far less than what is not known. If fatigue is an adaptational response to psychological and physiological stress, efforts to maintain the highest level of physical and mental health and wellness are indicated until further information regarding the benefit of specific interventions on fatigue are available. This study examined the influence of a variety of influences on fatigue during adjuvant chemotherapy treatments. Future longitudinal study is required to clarify the relationship between the modifiable variables of health and functional status, activity/rest cycles, symptom distress and healthy lifestyle behaviors and fatigue in patients receiving chemotherapy over time. In the meantime, clinicians can encourage patients to seek out behaviors to influence health positively and enhance perceptions of control over a very challenging life situation.

References

Aistars, J. (1987). Fatigue in the cancer patient: a conceptual approach to a clinical problem. Oncology Nursing Forum, 14(6), 25-30.

American Cancer Society. (1996). Cancer Facts and Figures- 1996. Atlanta: American Cancer Society, Inc.

Antonofsky, A. (1987). Unraveling the mystery of health: How people manage stress and stay well. San Francisco: Jossey-Bass.

Ardell, D. (1986). High Level Wellness.: An alternative to doctors, drugs and disease. Berkeley, CA: Ten Speed Press.

Baker, A., Kostov, K., Miller, R. & Weiner, M. (1993). Slow force recovery after long duration exercise: metabolic and activation factors in muscle fatigue. Journal of Applied Physiology, 74(5), 2294-2300.

Barofsky, I. & Legro, M. (1991). Definitions and measurement of fatigue. Review of Infectious Diseases, 13 (Suppl), S94-98.

Bates, D., Schmitt, W., Buchwald, D., Ware, N.,Lee, J., Thoyer, E., Kornish, R. & Komaroff, (1993). Prevalence of fatigue and chronic fatigue syndrome in a primary care setting. Archives of Internal Medicine, 153, 2759-2765.

Belza, B. (1994). The impact of fatigue on exercise performance. Arthritis Care and Research, 7(4), 176-180.

Berger, A. (1993). Fatigue and quality of life in cancer patients receiving out-patient chemotherapy. Oncology Nursing Forum,20(2), 311.

Berger, A. (1994). Reaction to the diagnosis and health-promoting lifestyle in women recently diagnosed with breast cancer. Presented at Nebraska Nurses Association State Convention, September, 1994.

Berger, A. (1995a). Reaction to the diagnosis and health-promoting lifestyle in women recently diagnosed with breast cancer. Oncology Nursing Forum, 22 (2),369.

Berger, A. (1995b). Reaction to the diagnosis and health-promoting lifestyle in women recently diagnosed with breast cancer. Presented at UNMC research day, April 1995.

Berger, A. (1995c). Reaction to the diagnosis and health-promoting lifestyle in women recently diagnosed with breast cancer. Presented at Methodist Hospital research day, April 1995.

Berger, A. (1995d). Fatigue, activity, and sleep patterns in women receiving chemotherapy for early stage breast cancer. Oncology Nursing Forum, 22(2),371.

Berger, A. (1995e). Fatigue, activity, and sleep patterns in women receiving chemotherapy for early stage breast cancer. presented at Methodist Hospital research day, Omaha, NE, May.

Berger, A. (1995f). Fatigue, activity and sleep patterns in women receiving chemotherapy for early stage breast cancer. presented at Midwest Nursing Research Society, Kansas City, MO, April.

Berger, A. (1995g). A Theoretical basis for modifying fatigue in ambulatory patients with cancer. Manuscript submitted for publication.

Blesch, K., Paice, J., Wickham, R., Harte, N., Schnoor, T., Purl, S; Rehwalt, M., Kopp, P., Manson, S., Coveny, S., McHale, M. & Cahill, M. (1991). Correlates of fatigue in people with breast or lung cancer. Oncology Nursing Forum, 18(1), 81-87.

Bloom, J. (1982). Social support, accommodation to stress and adjustment to breast cancer. Social Science & Medicine, 16, 1329-1338.

Bolger, N., Vinokur, A., Foster, M. & Ng, R. (1996). Close relationships and adjustment to a life crisis: the case of breast cancer. Journal of Personality and Social Psychology, 70(2), 283-294.

Boska, M., Moussavi, R., Carson, P., Weiner, M., & Miller, R. (1990). The metabolic basis of recovery after fatiguing exercise of human muscle. Neurology, 40, 240-244.

Brazil-Neto, J., Pascual-Leone, A., Valls-Sole, J., Cammarota, A., Cohen, L., & Hallett, M. (1993). Post exercise depression of motor evoked potentials: a measure of central nervous system fatigue. Exp Brain Res, 93, 181-184.

Breetvelt, I. & VanDam, F. (1991). Underreporting by cancer patients: the case of response-shift. Social Science Medicine, 32(9), 981-987.

Brown, A., Smolensky, M., D'Alonzo, G. & Redman, D. (1990). Actigraphy: A means of assessing circadian patterns in human activity. Chronobiology International, 7(2), 125-133.

Bruera, E., Brennis, C., Michaud, M., Rafter, J., Magnan, A., Tennant, A., Hanson, J., & Macdonald, R. (1989). Association between asthenia and nutritional status, lean body mass, anemia, psychological status, and tumor mass in patients with advanced breast cancer. Journal of Pain and Symptom Management, 4(2), 59-63.

Bruera, E. & MacDonald, R. (1988). Nutrition in cancer patients: an update and review of our experience. Issues in symptom control. J. Pain-Symptom Mgmt, 3(3), 133-140.

Bureau of the Census.(1990) Census Report. Washington DC:Department of Commerce.

Cella, D. (1990). Health promotion in oncology: A cancer wellness doctrine. J of Psychosocial Oncology, 8(1), 17-31.

Cassileth, B., Lusk, E., Bodenheimer, B., Farber, J., Jochimsen, P., & Morris-Taylor, B. (1985). Chemotherapeutic toxicity- The relationship between patients pre-treatment expectations and post-treatment results. American Journal of Clinical Oncology, 8 (419-425).

Cathebras, P., Robbins, J., Kirmayer, L. & Hayton, B. (1992). Fatigue in primary care. Journal of General Internal Medicine, 7, 276-286.

Cimprich, B. (1990). Attentional fatigue in the cancer patient. Oncology Nursing Forum, 17(2), Suppl, 218.

Cimprich, B. (1993). Development of an intervention to restore attention in cancer patients Cancer Nursing, 16(2), 83-92.

Cohen, J. (1988). Statistical power analysis for the behavioral sciences. (2nd Ed.) Hillsdale, NJ: Lawrence Erlbaum Ass., Inc.

Cole, R., Kripke, D., Gruen, W., Mullaney, D. & Gillin, J. (1992). Automatic sleep/wake identification from wrist activity. Sleep, 15(5), 461-469.

Corcoran, P. (1991). Use it or lose it- the hazards of bedrest and inactivity. The Western Journal of Medicine, 154, 536-538.

Crews, D. & Landers, D. (1987). A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. Medicine and Science in Sports and Exercise, 19(5), 5114-5120.

Dean, A. (1994). Epi Info, Version 6 Manuel. Atlanta, GA:Center for Disease Control and Prevention.

Decker, T., Cline-Elsen, J. & Gallagher, M. (1992). Relaxation therapy as an adjunct in radiation oncology. Journal of Clinical Psychology, 48(3), 388-393.

DeMark-Wahnfried, W., Winer, E. & Rimer, B. (1993). Why women gain weight with adjuvant chemotherapy for breast cancer. Journal of Clinical Oncology, 11(7)0, 1418-29.

Derogatis, L. & Spencer, P. (1982). The Brief Symptom Inventory (BSI): Administration, scoring and procedures manual. Baltimore: Clinical Psychometric Research.

Dow, K. (1991). Cancer Survivorship in the 1990s. Presented at the Sixth National Conference on Cancer Nursing, American Cancer Society, Seattle Washington, July 25-27, 1991.

Duncan, J. Gordon, N. & Scott, C. (1991). Women walking for health and fitness. How much is enough? Journal of the American Medical Association, 266(23), 3295.

Edwards, R. (1981). Human muscle function and fatigue. In: Human muscle fatigue: physiological mechanisms. London: Pitman, pp. 1-18. (Ciba Foundation Symposium 82).

Eide, R. (1982a). The effect of physical activity on emotional reactions and related physiological reactions. Scandinavian Journal of Social Medicine (Supplement), 29, 109-112.

Eide, R. (1982b). The relationship between body image, self-image and physical activity. Scandinavian Journal of Social Medicine (Supplement, 109-112.

Ehlke, G. (1988). Symptom distress in breast cancer patients receiving chemotherapy in the outpatient setting. Oncology Nursing Forum, 15(3), 343-346.

Elmore, S. & Burr, R. (1993). Circadian rhythms and nursing research: methodological considerations. Journal of Nursing Measurement, 1(1), 81-100.

Farr, L. & Boen, L. (1996). Comparison of rectal and axillary temperature rhythms with activity. NASA Space Grant Consortium Symposium. Proceedings of the Nebraska Academy of Sciences. Lincoln NE.

Farr, L., Campbell-Grossman, C. & Mack, J. (1988). Circadian disruption and surgical recovery. Nursing Research, 37(3), 170-175.

Fawzy, N. 1995. A psychoeducational nursing intervention to enhance coping and affective state in newly diagnosed malignant melanoma patients. Cancer Nursing, 18(6), 427-438.

Fawzy, F., Cousins, N., Fawzy, N., Kemeny, M., Elashoff, R. & Morton, D. (1990). A structured psychiatric intervention for cancer patients. Arch Gen Psychiatry, 47, 720-725.

Feather, B. & Wainstock, J. (1989). Perceptions of post-mastectomy patients. Part I & II. Cancer Nursing, 12(5), 293-309.

Fernsler, J. (1986). A comparison of patient and nurse perceptions of patient self-care deficits associated with cancer chemotherapy. Cancer Nursing, 9(2), 50-57.

Ferrans, C. & Ferrell, B. (1990). Development of a quality of life index for patients with cancer. Oncology Nursing Forum, 17(3) Supp, 15-21.

Fessele, K. Managing the multiple causes of nausea and vomiting in the patient with cancer. Oncology Nursing Forum, 23(9), 1409-1417.

Fisher, B., Wickerham, D. & Redmond, C. (1992). Recent developments in the use of systemic adjuvant therapy for the treatment of breast cancer. Seminars in Oncology, 19(3), 263-77.

Fobair, P., Hoppe, R., Bloom, J., Cox, R., Varghese, A., & Spiegel, D. (1986). Psychosocial problems among survivors of Hodgkin's disease. Journal of Clinical Oncology, 4(5), 805-814.

Forester, B., Kornfeld, D., Fleiss, J. & Thompson, S. (1993). Group psychotherapy during radiotherapy: effects on emotional and physical distress. Am J. Psychiatry, 150(11), 1700-1706.

Frank-Stromborg, M. (1986). Health promotion behaviors in ambulatory cancer patients: fact or fiction? Oncology Nursing Forum, 13(4), 37-43.

Frank-Stromborg, M. (1989). Reaction to the diagnosis of cancer questionnaire: Development and psychometric evaluation. Nursing Research,38(6), 364-369.

Frank-Stromborg. M., Pender, N., Walker, S.,& Sechrist, K. (1990). Determinants of health-promoting lifestyle in ambulatory cancer patients. Social Science & Medicine, 31(10), 1159-1168.

Frank-Stromborg, M., Wright, M., Segalla, P. & Diekmann, J. (1984). Psychological impact of the cancer diagnosis. Oncology Nursing Forum, 11(3), 16-22.

Ganz, P., Day, R., Ware. J., Redmond, C. & Fisher, B. (1995). Base-line quality of life assessment in the national surgical adjuvant breast and bowel project breast cancer prevention trial. Journal of National Cancer Institute, 87(18), 1372-1382.

Ganz, P., Schag, C., Polinsky, M., Heinrich, R. & Black, V. (1988). Rehabilitation needs and breast cancer: the first month after primary treatment Breast Cancer Research & Treatment, 10, 243-253.

Gaskin, T., LoBuglio, A., Kelly, P., Doss, M. & Pizitz, N. (1989). STRETCH: A rehabilitative program for patients with breast cancer. Southern Medical Journal, 82(4), 467-469.

Given, C., Given, B. & Stommel, M. (1994). The impact of age, treatment, and symptoms on the physical and mental health of cancer patients. Cancer, 74, 2128-2138.

Glanz, K. & Lerman, C. (1992). Psychosocial impact of breast cancer: a critical review. Annuals of Behavioral Medicine, 14(3), 204-212.

Goodman, M. (1991). Adjuvant systemic therapy for stage I and II breast cancer. Seminars in Oncology Nursing, 7(3), 175-186.

Graydon, J. (1994). Women with breast cancer: their quality of life following a course of radiation therapy. Journal of Advanced Nursing, 19, 617-622.

Graydon, J., Bubela, N., Irvine, D., & Vincent, L. (1995). Fatigue-reducing strategies used by patients receiving treatment for cancer. Cancer Nursing, 18(1), 23-28.

Greene, D., Nail, L., Fieler, V., Dudgeon, D. & Jones, L. (1994). A comparison of patient-reported side effects among three chemotherapy regimens for breast cancer. Cancer Practice, 2(1), 57-62.

Greer, S., Morris, T., & Pettingale, K. (1979). Psychological response to breast cancer. Effect on outcome. Lancet, 2, 785-787.

Gruber, B., Hall, N., Hersh,, S. (1988). Immune system and psychological changes in metastatic cancer patients while using ritualized, relaxation, and guided imagery. Scandinavian J. of Behavioral Therapy, 17,25-46.

Gruber, B., Hersh, S., Hall, R., Waletzky, L., Kunz, J., Carpenter, J., Kverno, K. & Weiss, S. (1993). Immunological responses of breast cancer patients to behavioral interventions. Biofeedback and self-regulation, 18(1), 1-22.

Gustafson, D., Wise, M., McTavish, F., Taylor, J., Wolberg, W., Stewart, J., Smalley, R. & Bosworth, K. (1993). Development and pilot evaluation of a computer-based support system for women with breast cancer. Journal of Psychosocial Oncology, 11(4), 69-93.

Haylock, P. & Hart, L. (1979). Fatigue in patients receiving localized radiation. Cancer Nursing,2(6), 461-467.

Hegyvary, S. (1993). Patient care outcomes related to management of symptoms. Annual Review of Nursing Research, 11, 145-168.

Heinrich, R. & Schag, C. (1985). Stress and activity management: Group treatment for cancer patients and spouses. Journal of Consulting and Clinical Psychology, 53(4), 439-446.

House, J., Landis, K. & Umberson, D. (1988). Social relationships and health. Science, 241, 540-545.

Hughes, K. (1993). Psychosocial and functional status of breast cancer patients. Cancer Nursing, 16(3), 222-229.

Institute of Medicine (IOM). (1993). Strategies for managing the breast cancer research program. A report to the U.S. Army medical research and development command. Washington, D.C.: National Academy Press.

Institute of Medicine (IOM). (1990). Breast cancer: Setting priorities for effectiveness research. Washington, D.C.: National Academy Press.

Ironson, G., Antoni, M. & Lutgendorf, S. (1995). Can psychological interventions affect immunity and survival? Present findings and suggested targets with a focus on cancer and human immunodeficiency virus. Mind/Body Medicine,1(2), 85-110.

Irvine, D., Brown, B., Crooks, D. Roberts, J. & Browne, G. (1991a). Psychosocial adjustment in women with breast cancer. Cancer Nursing, 9, 256-262.

Irvine, D., Vincent, L., Bubela, N., Thompson, L., & Graydon (1991b). A critical appraisal of the research literature investigating fatigue in the individual with cancer. Cancer Nursing, 14(4), 188-199.

Irvine, D., Vincent, L., Graydon, J., Bubela, N. & Thompson, L. (1994). The prevalence and correlates of fatigue in patients receiving chemotherapy and radiotherapy. Cancer Nursing, 17(5), 367-378.

Kaplan, R. & Toshima, T. (1990). The functional effects of social relationships on chronic illnesses and disability. In B. R. Sarason, I. B. Sarason, & G. R. Pierce. (Eds.) Social support: An interactional view. (pp. 427-453). New York: John Wiley & Sons.

Kirk, J., Douglass, R., Nelson, E., Jaffe, J., Lopez, A., Ohler, J., Blanchard, C., Chapman, R., McHugo, G. & Stone, K. (1990). Chief complaint of fatigue: a prospective study. Journal of Family Practice, 30(1), 33-41.

Knobf, M. (1986). Physical and psychologic distress associated with adjuvant chemotherapy in women with breast cancer. Journal of Clinical Oncology, 4(5), 678-684.

Knobf, M. (1990). Symptoms and rehabilitation needs of patients with early stage breast cancer during primary therapy. Cancer, 66, 1392-140.

Kripke, D., Mullaney, D, Messin, S. & Wyborney, V. (1978). Wrist actigraphic measures of sleep and rhythms. Electroencephalography and Clinical Neurophysiology, 44, 674-676.

Kurtz, M., Kurtz, J., Given, C. & Given, B. (1993). Loss of physical functioning among patients with cancer. Cancer Practice, 1(4), 275-281.

Kurtzman, S., Gardner, B. & Keller, W. (1988). Rehabilitation of the cancer patient. Am J Surgery, 155, 791-803.

Lavery, J. & Clarke, V. (1996). Causal attributions, coping strategies, and adjustment to breast cancer. Cancer Nursing, 19(1), 20-28.

Lekander, M., Furst, J., Rotstein, S., Blomgren, H. & Fredrikson, M. (1996). Social support and immune status during and after chemotherapy for breast cancer. Acta Oncologica, 35(1), 31-37.

Lee, K., Lenz, M., Taylor, D., Mitchell, E. & Woods, N. (1994). Fatigue as a response to environmental demands in women's lives. Image, 26(2), 149-154.

Libbus, K., Baker, J., Osgood, J., Phillips, T., Valentine, D. (1995). Persistent fatigue in well women. Women & Health, 23(1), 57-72.

Lusk, S., Kerr, M. & Ronis, D. (1995). Health-promoting lifestyles of blue-collar, skilled trade, and white-collar workers. Nursing Research, 44 (1), 20-24.

MacVicar, M. & Winningham, M. (1986). Promoting the functional capacity of cancer patients. The Cancer Bulletin, 38(5), 235-239.

MacVicar, M., Winningham, M. & Nickel, J. (1989). Effect of aerobic interval training on cancer patients' functional capacity. Nursing Research, 38, 348-351.

Marge, M. (1988). Health promotion for persons with disabilities: Moving beyond rehabilitation. American Journal of Health Promotion, 2(4), 29-35.

Mayer, D. & O'Connor, L. (1989). Rehabilitation of the person with cancer: an ONS statement. Oncology Nursing Forum, 16(3), 433.

McCorkle, R. (1987). The measurement of symptom distress. Seminars in Oncology Nursing, 3(4), 248-256.

McCorkle, R. & Quint-Benoliel, J. (1983). Symptom distress, current concerns, and mood disturbance after diagnosis of life-threatening disease. Soc Sci Med, 17, 431-438.

McCorkle, R. & Young, K. (1978). Development of a symptom distress scale. Cancer Nursing, 1, 373-378.

McHorney, C., Ware, J., Lu, J., Sherbourne, C. (1994). The MOS 36-Item short form health survey (SF-36): III. Tests of data quality, scaling assumptions and reliability across diverse patient groups Medical Care, 32 .

McHorney, C., Ware., J., Raczek, A. (1993). The MOS-36- item short form health survey (SF-36): II. Psychometrics and clinical tests of validity in measuring physical and mental health constructs. Medical Care, 31, 247-263.

McNair, D., Lorr, M., Droppleman, L. (1971). Profile of Mood States. San Diego: Education & Industrial Testing Service.

Meyerowitz, B., Sparks, F. & Spears, I. (1979). Adjuvant chemotherapy for breast carcinoma- psychosocial implications. Cancer, 43, 1613-1618.

Meyerowitz, B., Watkins, I. & Sparks, F. (1983). Quality of life for breast cancer patients receiving adjuvant chemotherapy. American Journal of Nursing, 83(2), 232-235.

Miller, B., Ries, L., Hankey, B. et al. (1994). SEER Cancer Statistics Review: 1973-1991 (NIH Pub. 94-2789). Bethesda, MD: National Cancer Institute.

Miller, J. (1982). Categories of self-care needs of ambulatory patients with diabetes. Journal of Advanced Nursing, 7, 25-31.

Minotti, J., Pillay, P., Chang, L., Wells, L. & Massie, B. (1992). Neurophysiological assessment of skeletal muscle fatigue in patients with congestive heart failure. Circulation, 86, 903-908.

Mock, V., Burke, M., Sheehan, P., Creaton, E., Winningham, M., McKenney-Tedder, S, Powel, L. & Liebman, M. (1994). A Nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. Oncology Nursing Forum, 21(1), 899-907.

Mooney, K., Ferrell, B., Nail, L., Benedict, S., & Haberman, M. (1991). 1991 Oncology Nursing Society research priorities survey. Oncology Nursing Forum, 18(8), 1381-1388.

Mor, V., Laliberte, L., Morris, J., & Wiemann, M. (1984). The Karnofsky Performance Status Scale. Cancer, 53, 2002-2007.

Mormont, M. & De Prins, J. (1995). Assessment of circadian activity rhythms by wrist actigraphy in patients with colo-rectal cancer. Biological Rhythm Research, 6(4), 423.

Mormont, M., Levi, F., Depres-Brummer, P., Giachetti, S., Gruia, G., Bleuzen, P., Jasmin, C., Misset, J. (March, 1996). Rest-activity circadian rhythm: an objective measure for performance status (PS) and a strong indicator for quality of life (QL). Proceedings of ASCO, 15, 508.

Morris, M. (1982). Tiredness and fatigue. In C. Norris (Ed.) Concept clarification in nursing. Rockville, MD: Aspen Systems.

Morris, T., Blake, S. & Buckley, M. (1985). Development of a method for rating cognitive responses to a diagnosis of cancer. Social Science and Medicine, 20, 795-802.

Mullaney, D., Kripke, D., & Messin, S. (1980). Wrist-actigraphic estimation of sleep time. Sleep, 3(1), 83-92.

Munkres, A., Oberst, M., & Hughes, S. (1992). Appraisal of illness, symptom distress, self-care burden, and mood states in patients receiving chemotherapy for initial and recurrent cancer. Oncology Nursing Forum, 19(8), 1201-1209.

Nail, L., Jones, L., Greene, D., Schipper, D. & Jensen, R. (1991). Use and perceived efficacy of self-care activities in patients receiving chemotherapy. Oncology Nursing Forum, 18(5), 883-887.

National Institute of Health. (1990). Treatment of early-stage breast cancer, consensus development conference statement. June, 18-21.

Nebraska Department of Health. (1994). Cancer incidence and mortality in Nebraska. Lincoln: Department of Health.

Nelson, D., Friedman, L., Baer, P., Lane, M. & Smith, F. (1989). Attitudes to cancer: psychometric properties of fighting spirit and denial. Journal of Behavioral Medicine, 12(4), 341-355.

Nelson, J. (1991). Perceived health, self-esteem health habits, and perceived benefits and barriers to exercise in women who have and who have not experienced stage I breast cancer. Oncology Nursing Forum, 18(7), 1191-1197.

Nerenz, J., Levanthal, H., & Love, R. (1982). Factors contributing to emotional distress during cancer chemotherapy. Cancer, 50(5), 1020-1027.

Neuberger, G., Kasal, S., Smith, K., Hassanein, R. & DeViney, S. (1994). Determinants of exercise and aerobic fitness in outpatients with arthritis. Nursing Research, 43(1), 11-17.

Northhouse, L. (1989). The impact of breast cancer on patients and husbands. Cancer Nursing, 12(5), 276-284.

Northhouse, L. & Swain, M. (1987). Adjustment of patients and husbands to the initial impact of breast cancer. Nursing Research, 36, 221-225.

Norusis, M. (1990). SSPS advanced statistics user's guide. Chicago, IL: SPSS, Inc.

Ott, C., Sivarajan, E., Newton, K., Almes, M., Bruce, R., Bergner, M., & Gilson, B. (1983). A controlled randomized study of early cardiac rehabilitation: The Sickness Impact Profile as an assessment tool. Heart & Lung, 12(2), 162-170.

Pearce, S. & Richardson, A. (1994). Fatigue and cancer: a phenomenological study. Journal of Clinical Nursing, 3, 381-382.

Pearson, R. & Byars, G. (1956). The development and validation of a checklist for measuring subjective fatigue. Randolph AFB, Texas School of Aviation Medicine, USAF.

Pender, N. (1982). Health promotion in nursing practice. Norwalk,CT: Appleton-Century Crofts.

Pender, N. (1987). Health promotion in nursing practice. (2nd ed.). Norwalk, CT: Appleton-Lange.

Perkins, D., Leserman, J., Stern, R., Baum, S., Liao, D., Golden, R. & Evans, D. (1995). Somatic symptoms and HIV infection: Relationship to depressive symptoms and indicators of HIV disease. American Journal of Psychiatry, 152(12), 1776-1781.

Pettingale, K., Morris, T., Greer, S., & Haybittle, J. (1985). Mental attitudes to cancer: an additional prognostic factor. Lancet, March 30, 750.

Pickard-Holley, S. (1991). Fatigue in cancer patients. Cancer Nursing,14(1), 13-19.

Pierce E. & Pate, D. (1994). Mood alterations in older adults following acute exercise. Perceptual and Motor Skills, 79, 191-194.

Piper, B. (1986). Fatigue. In V. Carrieri, A. Lindsey, & C. West. Pathophysiological Phenomena in Nursing- Human Responses to Illness. Philadelphia: W.B. Saunders, 219-234.

Piper, B. (1993a). Fatigue and cancer: inevitable companions? Support Care Cancer, 1, 285-286.

Piper, B. (1993b). Subjective fatigue in women receiving six cycles of adjuvant chemotherapy for breast cancer. (Doctoral dissertation, University of California, San Francisco, 1992). Dissertation Abstracts International, 9303553.

Piper, B., Dibble, S. & Dodd, M. (1996). The Revised Piper Fatigue Scale: Confirmation of its multidimensionality and reduction in number of items in women with breast cancer. Oncology Nursing Forum, 23(2), 352.

Piper, B., Dibble, S. & Dodd, M. (1991). Fatigue patterns and theoretical model testing in cancer patients receiving chemotherapy. Oncology Nursing Forum, 18(2), 348.

Piper, B. Friedman, L., Hartigan, K., Post, B., Smith, J., Coleman, C., Gilman, N., Dodd, M., Lindsey, A. & Paul, X. (1989b). Fatigue patterns over time in women receiving CMF chemotherapy for breast cancer. Oncology Nursing Forum, 16(2), 217.

Piper, B., Lindsey, A. & Dodd, M. (1987). Fatigue mechanisms in cancer patients: developing nursing theory. Oncology Nursing Forum, 14(6), 17-23.

Piper, B. Lindsey, A., Dodd, M., Ferketich, S., Paul, S. & Weller, S. (1989a). The development of an instrument to measure the subjective dimension of fatigue. In S. Funk, E. Tournquist, M. Champagne, L. Copp, & R. Weise (Eds.). Key aspects of comfort: Management of pain, fatigue, and nausea(pp. 199-208). New York:Springer.

Piper, B., Rieger, P., Brophy, L., Haeuber, D., Hood, L., Lyver, A. & Sharp, E. (1989c). Recent advances in the management of bio-therapy-related side effects: Fatigue. Oncology Nursing Forum, 16(6), suppl, 27-34.

Polinsky, M. (1994). Functional status of long-term breast cancer survivors: demonstrating chronicity. Health and Social Work, 19(3), 165-173.

Polit, D. & Hungler, B. (1987). Nursing Research: Principles and methods. (3rd ed.). St. Louis, MO: J.B. Lippincott Company.

Reardon, K. & Aydin, C. (1993). Changes in lifestyle initiated by breast cancer patients: who does and who doesn't? Health Communications, 5(4), 263-282.

Redmond, D. & Hegge, F. (1985). Observations on the design and specification of a wrist-worn human activity monitoring system. Behavior Research Methods, Instruments & Computers, 17(6), 659-669.

Reid, M., Grubwieser, G., Stokic, D., Koch, S. & Leis, A. (1993). Development and reversal of fatigue in human tibialis anterior. Muscle & Nerve, 16, 911-921.

Rhodes, V., Watson, P. & Hanson, B. (1988). Patients descriptions of the influence of tiredness and weakness on self-care abilities. Cancer Nursing, 3, 186-194.

Richards, K. (1987). Techniques for measurement of sleep in critical care. Focus on Critical Care, 14, 34-40.

Richardson, A. (1995). Fatigue in cancer patients: a review of the literature. European Journal of Cancer Care, 4 20-32.

Roberts, C., Cox, C., Shannon, V. & Wells, N. (1994). A closer look at social support as a moderator of stress in breast cancer. Health and Social Work, 19,(3), 157-164.

St. Pierre, B., Kasper, C. & Lindsey, A. (1992). Fatigue mechanisms in patients with cancer: effects of tumor necrosis factor and exercise on skeletal muscle. Oncology Nursing Forum, 19(3), 419-425.

Sarna, L. (1993). Fluctuations in physical function: adults with non-small lung cancer. Journal of Advanced Nursing, 18 714-724.

Silberfarb, P., Maurer, L., & Crouthamel, C. (1980). Psychosocial aspects of neoplastic disease: I. Functional status of breast cancer patients during different treatment regimens. American Journal of Psychiatry, 137, 450-455.

Simmons, S. (1993). Explaining health-promoting lifestyles of navy personnel. Military Medicine, 158(9), 594-598.

Smets, E., Garssen, B., Schuster-Uitterhoeve, A. & de Haes, J. (1993). Fatigue in cancer patients. British Journal of Cancer, 68, 220-224.

Spiegel, D. (1990). Facilitating emotional coping during treatment. Cancer, 66, 1422,1426.

Spiegel, D., Bloom, J., Kraemer, H., & Gottheil, E. (1989). Effect of psychosocial treatment on survival of patients with metastatic breast cancer. Lancet, 888-891.

Spiegel, D., Bloom, J. & Yalom, I. (1981). Group support for patients with metastatic cancer: A randomized prospective outcome study. Archives of General Psychiatry, 38(5), 527-533.

Spitzer, R., Endicott, J., Fleiss, J., Cohen, J. (1970). The psychiatric status schedules. Archives of General Psychiatry, 23, 41-55.

Stanton, A. & Snider, P. (1993). Coping with a breast cancer diagnosis: a prospective study. Health Psychology, 12(1), 16-23.

Sugarman, J. & Berg, A. (1984). Evaluation of fatigue in a family practice. Journal of Family Practice, 19(5), 643-647.

Stuifbergen, A. & Becker, H. (1994). Predictors of health-promoting lifestyles in persons with disabilities. Research in Nursing & Health, 17, 3-13.

Tait, N. & Aisner, J. (1989). Nutritional concerns in cancer patients. Seminars in Oncology Nursing, 5(2), Suppl 1, 58-62.

Taylor, S., Lichtman, R. & Wood, J. (1984). Attributions, beliefs about control, and adjustment to breast cancer. J Per Soc Psychol, 46(3), 489-502.

Tiesinga, L., Dassen, T. & Halfens, R. (1996). Fatigue: A summary of the definitions, dimensions, and indicators. Nursing Diagnosis, 7(2), 51-62.

Travis, J. & Ryan, R. (1988). Wellness Workbook for Health Professionals, (2nd Ed.), Berkeley, CA: Ten Speed Press.

Tulman, L. & Fawcett, J. (1990). A framework for studying functional status after diagnosis of breast cancer. Cancer Nursing, 13(2), 95-99.

United States Department of Health and Human Services. (1991). Healthy People 2000: National health promotion and disease prevention objectives. Washington, D.C: U.S. Government Printing Office.

Vachon, M. (1986). A comparison on the impact of breast cancer and bereavement: Personality, social support, and adaptation. In S. Hobfoll (ed.) Stress, social support and women. Washington: Hemisphere Publ. Inc., 187-205.

Walker, S. & Hill-Polerecky, D. (1996). Psychometric evaluation of the revised Health-Promoting Lifestyle Profile. Manuscript submitted for publication.

Walker, S., Sechrist, K. & Pender, N. (1987). The health-promoting lifestyle profile: development and psychometric characteristics. Nursing Research, 36(2), 76-81.

Ware, J., & Sherbourne, C. (1992). The MOS-36 item short form health survey (SF-36). I. Conceptual framework and item selection. Medical Care, 30(6), 473-483.

Watson, P. (1990). Cancer Rehabilitation. Cancer Nursing, 13(1), 2-12.

Watson, M., Greer, S., Young, J., Inayat, Q., Burgess, C., & Robertson, C. (1988). Development of a questionnaire measure of adjustment to cancer, the MAC scale. Psychological Medicine, 18, 203- 209.

Waxler-Morrison, N., Hilsop, T., Mears, B., & Kan, L. (1991). Effects of social relationships on survival for women with breast cancer: a prospective study. Social Science & Medicine, 33(2), 177-183.

Webster, J., Kripke, D., Messin, S., Mullaney, D. & Wyborney, G. An activity-based sleep monitor system for ambulatory use. Sleep, 5(4), 389-399.

Williams, J. & Klug, G. (1995). Calcium exchange hypothesis of skeletal muscle fatigue: a brief review. Muscle & Nerve, 18, 421-434.

Winningham, M. (1996). Fatigue. In S. Groenwald, M Frogge, M Goodman, & C. Yarbo (Eds.), Cancer Symptom Management (pp. 42-58). Boston:Jones and Bartlett Publishers.

Winningham, M. (1992). How exercise mitigates fatigue: implications for people receiving cancer therapy. In R. Johnson (Ed.) The Biotherapy of Cancer-V. Oncology Nursing Press, Inc.

Winningham, M,. & MacVicar, M. (1988). The effects of aerobic exercise on patient reports of nausea. Oncology Nursing Forum, 15, 447-450.

Winningham, M., MacVicar, M. & Bondac, M., Anderson, J. & Minton, J. (1989). Effect of aerobic exercise on body weight and composition in patients with breast cancer on adjuvant chemotherapy. Oncology Nursing Forum, 16(5), 683-689.

Winningham, M., MacVicar, M. & Nickel, J. (1989). Effects of aerobic interval training on cancer patients' functional capacity. Nursing Research, 38, 348-351.

Winningham, M., Nail, L., Burke, M., Brophy, L., Cimprich, B., Jones, L., Pickard-Holley, S., Rhodes, V., St. Pierre, B., Back, S., Glass, E., Mock, V., Mooney, K., & Piper, B. (1994). Fatigue and the cancer experience: The state of the knowledge. Oncology Nursing Forum, 21(1), 23-36.

Wortman, C. (1984). Social support and the cancer patient: Conceptual and methodological issues. Cancer, 53, 2339-2360.

Young-McCaughan, S. & Sexton, D. (1991). A retrospective investigation of the relationship between aerobic exercise and quality of life in women with breast cancer. Oncology Nursing Forum, 18, 751-757.

Zeman, F. & Ney, D. (1988). Applications of Clinical Nutrition. Englewood Cliffs, NJ: Prentice Hall.

Appendix A

Piper's Integrated Fatigue Model

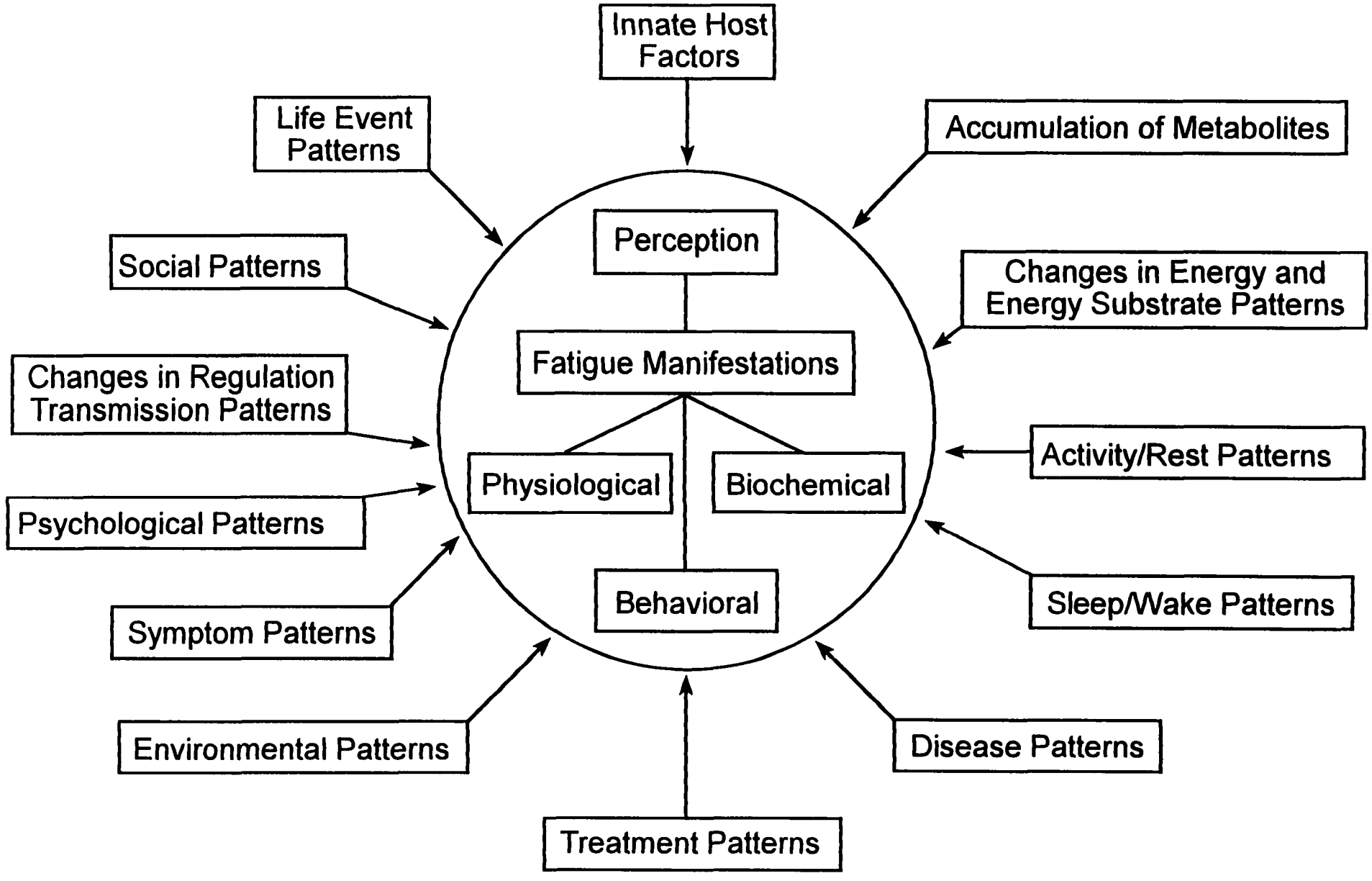


Figure 2. Fatigue framework for the conceptualization of fatigue in healthy and in clinical populations (Piper, B., Lindsey, A. & Dodd, M. (1987) Oncology Nursing Forum 14(6), 17-23.)

Appendix B

Piper Fatigue Scale

PIPER FATIGUE SCALE

TIME NOW: _____/_____
(Hours) (Minutes)

Directions: For each of the following questions, circle the number which best describes the fatigue you are experiencing now. Please make every effort to answer each question to the best of your ability. Thank you very much!

1. How long have you been feeling fatigued? (Check one response only)

   a. _____minutes
   b. _____hours
   c. _____days
   d. _____weeks
   e. _____months
   f. _____other (*please describe*): _____

2. To what degree is the fatigue you are feeling causing you distress?

No Distress **A great deal of distress**

0 1 2 3 4 5 6 7 8 9 10

3. To what degree is the fatigue you are feeling interfering with your ability to complete your work or school activities?

None **A great deal**

0 1 2 3 4 5 6 7 8 9 10

4. To what degree is the fatigue you are feeling interfering with your abillity to visit or socialize with your friends?

None **A great deal**

0 1 2 3 4 5 6 7 8 9 10

5. To what degree is the fatigue you are feeling interfering with your ability to engage in sexual activity?

None **A great deal**

0 1 2 3 4 5 6 7 8 9 10

6. Overall how much is the fatigue, which you are experiencing now, interfering with your ability to engage in the kind of activities you enjoy doing?

None **A great deal**

0 1 2 3 4 5 6 7 8 9 10

7. How would you describe the degree of intensity or severity of the fatigue which you are experiencing now?

Mild **Severe**

0 1 2 3 4 5 6 7 8 9 10

To what degree would you describe the fatigue which you are experiencing now as being:

8. **Pleasant** **Unpleasant**

0 1 2 3 4 5 6 7 8 9 10

9. **Agreeable** **Disagreeable**

0 1 2 3 4 5 6 7 8 9 10

10. **Protective** **Destructive**

0 1 2 3 4 5 6 7 8 9 10

11. **Positive** **Negative**

0 1 2 3 4 5 6 7 8 9 10

12. **Normal** **Abnormal**

0 1 2 3 4 5 6 7 8 9 10

People feeling fatigued may experience certain feelings/sensations which indicate to them that they are fatigued. For each of the following questions, circle a number that best indicates the degree to which each feeling/sensation is being experienced by you now.

13. To what degree are you now feeling:

Strong **Weak**

0 1 2 3 4 5 6 7 8 9 10

14. To what degree are you now feeling:

Awake **Sleepy**

0 1 2 3 4 5 6 7 8 9 10

15. To what degree are you now feeling:

Lively **Listless**

0 1 2 3 4 5 6 7 8 9 10

16. To what degree are you now feeling:

Refreshed **Tired**

0 1 2 3 4 5 6 7 8 9 10

17. To what degree are you now feeling:

Energetic **Unenergetic**

0 1 2 3 4 5 6 7 8 9 10

18. To what degree are you now feeling:

Patient **Impatient**

0 1 2 3 4 5 6 7 8 9 10

19. To what degree are you now feeling:

Relaxed **Tense**

0 1 2 3 4 5 6 7 8 9 10

20. To what degree are you now feeling:

Exhilarated **Depressed**

0 1 2 3 4 5 6 7 8 9 10

21. To what degree are you now feeling:

Able to concentrate **Unable to concentrate**

0 1 2 3 4 5 6 7 8 9 10

22. To what degree are you now feeling:

Able to remember **Unable to remember**

0 1 2 3 4 5 6 7 8 9 10

23. To what degree are you now feeling:

Able to think clearly **Unable to think clearly**

0 1 2 3 4 5 6 7 8 9 10

24. Overall, what do you believe is most directly contributing to or causing your fatigue?

_____

_____

_____

25. Overall, the best thing you have found to relieve your fatigue is:

_____

_____

26. Is there anything else you would like to add that would describe your fatigue better to us?

_____

_____

_____

27. Are you experiencing any other symptoms right now?
No _____
Yes _____ Please describe _____

_____

_____

_____

_____

TIME NOW: _____/_____
(Hours) (Minutes)

Appendix C

MOS-SF-36 Survey

Subject No. 193

THE MOS 36-ITEM SHORT-FORM HEALTH SURVEY (SF-36)

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health 2 months ago was:

(circle one)

Excellent 1

Very good 2

Good 3

Fair 4

Poor 5

2. Compared to 2 months ago, how would you rate your health in general now?

(circle one)

Much better now than 2 months ago 1

Somewhat better now than 2 months ago 2

About the same as 2 months ago 3

Somewhat worse than 2 months ago 4

Much worse than 2 months ago 5

(Acute)

3. The following items are about activities you might do during a typical day. Did your health 2 months ago limit you in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking several blocks	1	2	3
i. Walking one block	1	2	3
j. Bathing or dressing yourself	1	2	3

4. Two months ago, did you have any of the following problems with your work or or other regular daily activities as a result of your physical health?

(circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

Subject No._____

5. Two months ago, did you have any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious?

(circle one number on each line)

	YES	NO
a. Cut down the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. Two months ago, to what extent did your physical health or emotional problems interfere with your normal social activities with family, friends, neighbors, or groups?

(circle one)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

7. How much bodily pain did you have two months ago?

(circle one)

None 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

(Acute)

8. Two months ago, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

9. These questions are about how you feel and how things were 2 months ago. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time 2 months ago_

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. Two months ago, how much of the time did your physical health or emotional problems interfere with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

11. How TRUE or FALSE was each of the following statements for you 2 months ago?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Appendix D

Chemotherapy Protocols

Chemotherapy Protocols

Protocol	Dosages	Days in Cycle/Midpoint
#1a cyclophosphamide (Cytoxan) methotrexate 5-FU	 600 mg/M^2 IV day 1 40 mg/M^2 IV day 1 600 mg/M^2 IV days 1+8	 21 days/ 10,11,12
#1b cyclophosphamide (Cytoxan) methotrexate 5-FU	 100 mg/M^2 po days 1-14 40 mg/M^2 IV day 1+8 600 mg/M^2 IV days 1+8	 28 days/ 16,17,18
#2 cyclophosphamide (Cytoxan) doxorubicin (Adriamycin) 5-FU	600 mg/M^2 IV day 1 60 mg/M^2 IV day 1 600 mg/M^2 IV days 1+8	28 days/ 13,14,15
#3 cyclophosphamide (Cytoxan) doxorubicin (Adriamycin)	 500 mg/M^2 IV day 1 50 mg/M^2 IV day 1	 21days/ 10,11,12

* Regimens are classified as:
non-intravenous Adriamycin/Cytoxan (#1a & #1b) and
intravenous Adriamycin/Cytoxan (#2 & #3)

5/25/95
revised 11/13/96

Appendix E

Health-Promoting Lifestyle Profile II

IRECTIONS: *This questionnaire contains statements about your present way of life or personal habits.* lease respond to each item as accurately as possible, and try not to skip any item. Indicate the frequency ith which you engage in each behavior by circling:

N for never, S for sometimes, O for often, or R for routinely	NEVER	SOMETIMES	OFTEN	ROUTINELY
I. Discuss my problems and concerns with people close to me.	N	S	O	R
2. Choose a diet low in fat, saturated fat, and cholesterol.	N	S	O	R
3. Report any unusual signs or symptoms to a physician or other health professional.	N	S	O	R
4. Follow a planned exercise program.	N	S	O	R
5. Get enough sleep.	N	S	O	R
6. Feel I am growing and changing in positive ways.	N	S	O	R
7. Praise other people easily for their achievements.	N	S	O	R
8. Limit use of sugars and food containing sugar (sweets).	N	S	O	R
9. Read or watch TV programs about improving health.	N	S	O	R
10. Exercise vigorously for 20 or more minutes at least three times a week (such as brisk walking, bicycling, aerobic dancing, using a stair climber).	N	S	O	R
11. Take some time for relaxation each day.	N	S	O	R
12. Believe that my life has purpose.	N	S	O	R
13. Maintain meaningful and fulfilling relationships with others.	N	S	O	R
14. Eat 6-11 servings of bread, cereal, rice and pasta each day.	N	S	O	R
15. Question health professionals in order to understand their instructions.	N	S	O	R
16. Take part in light to moderate physical activity (such as sustained walking 30-40 minutes 5 or more times a week).	N	S	O	R
17. Accept those things in my life which I can not change.	N	S	O	R
18. Look forward to the future.	N	S	O	R
19. Spend time with close friends.	N	S	O	R
20. Eat 2-4 servings of fruit each day.	N	S	O	R
21. Get a second opinion when I question my health care provider's advice.	N	S	O	R
22. Take part in leisure-time (recreational) physical activities (such as swimming, dancing, bicycling).	N	S	O	R
23. Concentrate on pleasant thoughts at bedtime.	N	S	O	R
24. Feel content and at peace with myself.	N	S	O	R
25. Find it easy to show concern, love and warmth to others.	N	S	O	R
26. Eat 3-5 servings of vegetables each day.	N	S	O	R

27.	Discuss my health concerns with health professionals.	N	S	O	R
28.	Do stretching exercises at least 3 times per week.	N	S	O	R
29.	Use specific methods to control my stress.	N	S	O	R
30.	Work toward long-term goals in my life.	N	S	O	R
31.	Touch and am touched by people I care about.	N	S	O	R
32.	Eat 2-3 servings of milk, yogurt or cheese each day.	N	S	O	R
33.	Inspect my body at least monthly for physical changes/danger signs.	N	S	O	R
34.	Get exercise during usual daily activities (such as walking during lunch, using stairs instead of elevators, parking car away from destination and walking).	N	S	O	R
35.	Balance time between work and play.	N	S	O	R
36.	Find each day interesting and challenging.	N	S	O	R
37.	Find ways to meet my needs for intimacy.	N	S	O	R
38.	Eat only 2-3 servings from the meat, poultry, fish, dried beans, eggs, and nuts group each day.	N	S	O	R
39.	Ask for information from health professionals about how to take good care of myself.	N	S	O	R
40.	Check my pulse rate when exercising.	N	S	O	R
41.	Practice relaxation or meditation for 15-20 minutes daily.	N	S	O	R
42.	Am aware of what is important to me in life.	N	S	O	R
43.	Get support from a network of caring people.	N	S	O	R
44.	Read labels to identify nutrients, fats, and sodium content in packaged food.	N	S	O	R
45.	Attend educational programs on personal health care.	N	S	O	R
46.	Reach my target heart rate when exercising.	N	S	O	R
47.	Pace myself to prevent tiredness.	N	S	O	R
48.	Feel connected with some force greater than myself.	N	S	O	R
49.	Settle conflicts with others through discussion and compromise.	N	S	O	R
50.	Eat breakfast.	N	S	O	R
51.	Seek guidance or counseling when necessary.	N	S	O	R
52.	Expose myself to new experiences and challenges.	N	S	O	R

Appendix F

Modified Symptom Distress Scale

Symptom Distress Scale

Subject Code _____ Watch on: Date/Time_____
Date _____ Time Now: _____

Please fill out between 2 and 6 p.m.

Time you first turned off the light to fall asleep last night. LIGHTS OFF: ____ : ____
Time you awakened and turned the light on this morning. LIGHTS ON: ____ : ____

Directions: Place a circle around the number that best indicates the severity of your symptoms.

How severe is the fatigue you are experiencing now ?											
"I am not tired at all"	0	1	2	3	4	5	6	7	8	9	10	"I am totally exhausted"
I would describe my sleep last night as:											
"A good night's sleep"	0	1	2	3	4	5	6	7	8	9	10	"A bad night's sleep"
How severe is the nausea you are experiencing now?											
"I do not feel sick at all"	0	1	2	3	4	5	6	7	8	9	10	"I feel as sick as I could possibly be"
I would describe my mood today as:											
"Could not feel happier"	0	1	2	3	4	5	6	7	8	9	10	"Could not feel more miserable"

General Comments about your day's activities, symptoms you have experienced, and medications taken for them:

_____

_____

_____

_____

_____

_____

BERGER\MODSYMP.595.5/23/95/AB:dk

Appendix G

Reaction to the Diagnosis of Cancer Questionnaire

REACTION TO THE DIAGNOSIS OF CANCER QUESTIONNAIRE

DATE OF DIAGNOSIS:_____

DIRECTIONS: A number of statements which people have used to describe their reaction to the diagnosis of cancer are given below. Read each statement and then circle the letter to the right of the statement to indicate HOW YOU FELT WHEN FIRST TOLD YOU HAD CANCER. There is no right or wrong answers. Please respond to each item even if you feel it doesn't apply to you.

	No, I did not feel that way.	Yes, I felt that way a little.	Yes, I felt that way moderately.	Yes, I felt that way quite a bit.	Yes, I felt that way extremely.
I was angry.	A	B	C	D	E
I refused to feel sorry for myself.	A	B	C	D	E
I was numbed.	A	B	C	D	E
I decided to make the best of it.	A	B	C	D	E
I refused to accept the diagnosis.	A	B	C	D	E
I decided to beat the cancer.	A	B	C	D	E
I felt despair.	A	B	C	D	E
I decided cancer wouldn't get the best of me.	A	B	C	D	E
I was upset.	A	B	C	D	E
I was stunned.	A	B	C	D	E
I was scared.	A	B	C	D	E
I knew I was going to die.	A	B	C	D	E
I decided that cancer wouldn't change my life.	A	B	C	D	E
I refused to believe it.	A	B	C	D	E

		No, I did not feel that way.	Yes, I felt that way a little.	Yes, I felt that way moderately.	Yes, I felt that way quite a bit.	Yes, I felt that way extremely.
15.	I was depressed.	A	B	C	D	E
16.	I was worried about the future.	A	B	C	D	E
17.	I accepted it.	A	B	C	D	E
18.	"Why me?"	A	B	C	D	E
19.	I could not understand why I had cancer.	A	B	C	D	E
20.	I cried.	A	B	C	D	E
21.	I was uncertain about the future.	A	B	C	D	E
22.	I knew I was doomed.	A	B	C	D	E
23.	I was optimistic about how things would turn out.	A	B	C	D	E
24.	I felt helpless.	A	B	C	D	E
25.	I felt the diagnosis was a mistake.	A	B	C	D	E
26.	I decided to conquer the cancer.	A	B	C	D	E
27.	I felt there was nothing to worry about.	A	B	C	D	E
28.	I began to hope.	A	B	C	D	E

Appendix H

Background Characteristics

BACKGROUND DATA AT ENTRY

SUBJECT/NUMBER_____ DATE___/___/____ AGE _____

Marital Status (Circle One) single, married, separated, divorced, widowed

Employment (Circle One) full-time, part-time, homemaker, retired

Number of Dependents and ages at home_____ away _____

Education _____(grades completed, degrees earned)

Household Income (Circle One) less than $20,000 $20,000 - 40,000 over $40,000

Residence (Circle One) own home rent home rent apartment Other_____

Ethnic/Racial Background (Circle One)

American Indian/ Alaskan Native | Asian or Pacific Islander | Black, not of Hispanic Origin | Hispanic | White, not Hispanic Origin

Current Medications (drug, dose, frequency)

_____
_____
_____
_____

Chronic Illnesses: (list all) _____
_____
_____

Date of cancer diagnosis _____ Surgery Date _____

Surgical Procedure (Circle One) Modified Mastectomy Lumpectomy Reconstruction

Radiation Treatment Date(s) _____

Cancer Location & Stage _____

Lymph Node Status _____

Estrogen/Progesterone Receptor Status _____

Menopausal Status (Circle One) pre-menopause, peri-menopause, post-menopause

Start of Chemotherapy Date _____ Chemotherapy Protocol _____

Karnofsky Performance Score (see chart) _____

BERGER\BACKDATA.AB
Revised: 5/11/95:AB:dlk

BACKGROUND DATA
AT STUDY COMPLETION

SUBJECT/NUMBER_____ DATE___/___/_____ AGE _____

Current Employment Status (Circle One)

full-time part-time homemaker retired

Explain if there has been a change since beginning chemotherapy and why:

_____
_____
_____

Current Medications (drug, dose, frequency):

_____
_____
_____
_____

Menopausal Status: (Explain if there has been a change since beginning chemotherapy):

_____
_____
_____

Support Services used during last 3 months: (Mark all that apply):

American Cancer Society Reach to Recovery:_____
Breast Cancer Support Group:_____ # times attended:_____
Counselor/Therapist:_____ # times:_____

Other - Describe:_____
_____
_____

In your own words, compare your health and well-being now in comparison to the way you felt before your diagnosis of breast cancer:

BERGER\BACKDATA.AB
5/11/95:AB:dlk

Appendix I

Institutional Review Board Authorization Letters

University of Nebraska
Institutional Review Board
For the Protection of
Human Subjects

University of Nebraska Medical Center
Eppley Science Hall 3018
600 South 42nd Street
Box 986810
Omaha, NE 68198-6810
(402) 559-6463
Fax (402) 559-7845

October 18, 1995

Ann Berger, RN-C, MSN
College of Nursing
UNMC 2445

IRB # 045-94

TITLE OF PROPOSAL Fatigue and Lifestyle During Breast Cancer Chemotherapy

Dear Ms. Berger:

The Institutional Review Board for the Protection of Human Subjects has completed its review of your Request for Change in Protocol and/or consent form modifications submitted in your letter to the IRB dated October 17, 1995.

This letter constitutes official notification of the approval of the protocol and/or consent form change. You are therefore authorized to implement this change accordingly.

Sincerely,

[redacted]

Ernest Prentice, Ph.D.
Vice Chairman, IRB

EDP/lmc

CREIGHTON UNIVERSITY

Institutional Review Board
Grants Administration

July 3, 1995

Ann Berger, RN, MSN
Clinical Nurse Specialist in Oncology
University of Nebraska Medical Center
[redacted]

RE: IRB # 1921 - Fatigue and Lifestyle During Breast Cancer Chemotherapy

Dear Ms. Berger:

Thank you for your letter of June 28, 1995. The changes summarized in your letter and contained in the revised protocol and proposed flier appear to satisfy the concerns of the IRB as indicated to you in my letter of June 22, 1995. Accordingly, this study is approved and HHS Form 310, certifying IRB review and approval of the revised protocol and informed consent document for a one year period is enclosed.

[redacted]

David L. Dworzack, M.D.
Chairman, Institutional Review Board

DLD/bd

Enclosure

Bergan Mercy
MEDICAL CENTER
7500 Mercy Road
Omaha, NE 68124
398-6060

March 20, 1995

Ann Berger, MSN, RN-C
University of Nebraska Medical Center
[redacted]

RE: Fatigue and Lifestyle During Breast Cancer Chemotherapy

Dear Ms. Berger:

The above-mentioned protocol and informed consent was reviewed and approved by the Bergan Mercy Medical Center Institutional Review Committee at their meeting on March 20, 1995. The protocol has been assigned IRC #432.

Please plan to present a yearly update to the committee on progress and notify the committee at the time of closure of this study.

This information will be filed accordingly.

[redacted]
Samuel H. Mehr, MD
Chairman
Institutional Review Committee

vh

METHODIST HOSPITAL

THE NEBRASKA METHODIST HOSPITAL
8303 DODGE STREET
OMAHA, NEBRASKA 68114-4199
(402) 354-4000

May 9, 1995

Ann Berger, MSN, RN-C
Doctorate in Nursing Candidate
University of Nebraska Medical Center
[redacted]

Dear Ms. Berger,

This letter is to inform you that your study "Fatigue and Lifestyle during Breast Cancer Chemotherapy" was presented to the Executive Committee on May 2, 1995 with a recommendation for approval by the Human Experimentation Committee of the Medical Staff.

Action was taken to approve the study at Methodist.

Sincerely,

[redacted]

Cindy Hamilton, CMSC
Medical Staff Coordinator

cjh

MIDLANDS COMMUNITY HOSPITAL

11111 SOUTH 84TH STREET
PAPILLION, NEBRASKA 68046
(402) 593-3000
AFFILIATED WITH COLUMBIA HEALTH GROUP, INC.

November 7, 1995

Ann Berger, MSN, RN-C
College of Nursing
UNMC - 5330
[redacted]

Dear Ms Berger:

The Institutional Review Committee has approved the protocol and medical consent form that was presented at the 11/7/95 meeting entitled:

UNMC 045-94 Fatigue and Lifestyle During Breast Cancer Chemotherapy

The Institutional Review Committee will be required to review all data once the study has been finalized. However, should any adverse reactions or changes in the protocol develop, please notify me immediately, and a special meeting can be scheduled.

[redacted]
Blaine Y. Rothman, M.D.
Chairman, Institutional Review Committee

BUILDING ON THE LEGACY

Clarkson Hospital
4350 Dewey Avenue
Omaha, Nebraska
68105-1018
402-552-2000

December 20, 1995

Ann M. Berger, MSN, RN-C
CNS General Oncology
University of Nebraska Medical Center
[redacted]

Dear Ms. Berger:

This letter constitutes official notification from the Institutional Review Board (IRB) of Clarkson Hospital of the approval, through expedited review, of the protocol and informed consent, Fatigue and Lifestyle During Breast Cancer Chemotherapy.

You are responsible for keeping the Board informed of any changes to the protocol or consent form. The Board will request yearly reports of progress and results.

[redacted]

James E. Call, M.D.
Chairman
Institutional Review Board

CAE:bae

Alegent Health

Alegent Health
Immanuel Medical Center
6901 North 72nd Street
Omaha, Nebraska 68122-1799
Phone (402) 572-2121
Fax (402) 572-3177

February 8, 1996

Joseph D. Verdirame, M.D.
The Cancer Center
[redacted]

RE: **IRC # 0001.96**

Fatigue and Lifestyle During Breast Cancer Chemotherapy; in conjunction with UNMC (#045-94)

Dear Dr. Verdirame:

On January 31, 1996, the Immanuel Institutional Review Committee thoroughly reviewed the above protocol and informed consent and unanimously voted approval for participation.

This letter, therefore, serves as notification of approval for participation.

In order to conform to guidelines set forth by this committee, a review of this study will be requested at six-month intervals. You will be notifed when these reviews are due. When corresponding with the IRC regarding this study, please refer to the IRC number indicated above.

[redacted]

Edgar H. Smith, M.D.
Chairman
Institutional Review Committee

EHS/as

Appendix J

Letters of Permission from Physicians

University
of Nebraska
Medical Center

Department of Internal Medicine
Section of Oncology and Hematology
600 South 42nd Street
Box 983330
Omaha, NE 68198-3330
(402) 559-5520
Fax: (402) 559-6520

November 16, 1994

Ann Berger, RN-C, MSN
Doctoral Student
University of Nebraska College of Nursing
[redacted]

Dear Ann,

I received your letter requesting permission to use the University of Nebraska Clinical Cancer Center as a site for your proposed dissertation research entitled "Fatigue and Lifestyle during Breast Cancer Chemotherapy". I understand that you need to demonstrate adequate sample size and support within the Omaha area in order to complete the study.

I am interested in your study which examines the distressing symptom of fatigue during treatment with adjuvant chemotherapy. I offer you access to my patients who meet the study criteria. I look forward to working with you on this project in the future.

Sincerely,
[redacted]
Elizabeth C. Reed, M.D.
Assistant Professor of Medicine
Director, Breast Cancer Program

ECR/las

CREIGHTON UNIVERSITY

Creighton Cancer Center

November 30, 1994

Ms. Ann Berger, RN-C, MSN
[redacted]

Dear Ms. Berger:

I have reviewed your letter with regard to your dissertation research on "Fatigue and Lifestyle During Breast Cancer Chemotherapy". The number of breast cancer patients seen in clinic are as follows: Crieghton Cancer Center 20%, Bergan Oncology Clinic 20%, Missouri Valley Oncology Clinic 5%, and Onawa Oncology Clinic 5%.

Best of luck to you on your doctoral work and on the National Research Service Award. If we can be of any further assistance, do not hesitate to contact me.

[redacted]

James A. Mailliard, M.D., F.A.C.P.
Professor of Medicine
Chief, Medical Oncology Service

JAM/wt

Cancer Center Clinic Saint Joseph Hospital 601 North 30th Street Omaha, NE 68131 (402) 280-4364
Administrative Offices Criss III, Room 353/358 2500 California Plaza Omaha, NE 68178 (402) 280-2338

ROBERT M. LANGDON, JR., M.D.
MARGARET BLOCK, M.D., F.A.C.P.
PETER M. TOWNLEY, M.D.

Langdon & Block, P.C.

MEDICAL ONCOLOGY AND HEMATOLOGY

November 29, 1994

Ann Berger, RN-C MSN
[redacted]

Dear Ann:

I am wrtiting in response to your planned dissertation study entitled "Fatigue and Life Style during Breast Cancer Chemotherapy". I would be happy to make available to you patients whom would be interested in participating. This practice sees a large number of women per year for breast cancer chemotherapy. I would be happy to meet with you in regards to the mechanics of completing this study.

[redacted]

Robert M. Langdon, Jr., M.D.

RML:jss

9300 Underwood Avenue
Suite 550
Omaha, Nebraska 68114
402.393.3110
Fax 402.393.5732

Methodist Cancer Center
8303 Dodge Street
Suite 275
PO Box 24608
Omaha, Nebraska 68114
402.390.5818
Fax 402.390.3998

Midlands Cancer Center
401 East Gold Coast Road
Suite 103
Omaha, Nebraska 68046
402.593.3141
Fax 402.593.3145

ROBERT M. LANGDON, JR., M.D.
MARGARET BLOCK, M.D., F.A.C.P.
PETER M. TOWNLEY, M.D.

Langdon & Block, P.C.

MEDICAL ONCOLOGY AND HEMATOLOGY

November 24, 1994

Ann Berger, RN-C MSN
Doctoral Student
[redacted]

Dear Ann:

I am writing in response to your planned dissertation study entitled "Fatigue and Life Style during Breast Cancer Chemotherapy". Our office sees a large number of women for breast cancer chemotherapy each year. I would be most happy to make any information available to you.

Sincerely,

[redacted]

Margaret Block, M.D., F.A.C.P.

MB:jss

9300 Underwood Avenue
Suite 550
Omaha, Nebraska 68114
402.393.3110
Fax 402.393.5732

Methodist Cancer Center
8303 Dodge Street
Suite 275
PO Box 24608
Omaha, Nebraska 68114
402.390.5818
Fax 402.390.3998

Midlands Cancer Center
401 East Gold Coast Road
Suite 103
Omaha, Nebraska 68046
402.393.3141
Fax 402.393.3145

MIDLANDS CANCER Care CENTER

November 29, 1994

Ann Berger, RN-C, MSN
Doctoral Student
[redacted]

Dear Ann:

I am writing this letter in support of your project entitled "Fatigue and Lifestyle during Breast Cancer Chemotherapy". We see a large number of patients with Stage I or II breast carcinoma. I think the questions you are asking are important ones. I would be most happy to cooperate and make any information available to you.

Thank you again for your interest.

[redacted]

Peter M. Townley, M.D.

Midlands Cancer Care Center • 11111 South 84th Street
Papillion, Nebraska 68046 • (402) 292-2273

ONCOLOGY HEMATOLOGY WEST, P.C.

225

Medical Oncology
Hematology

Margaret Block, M.D., F.A.C.P.
Robert M. Langdon, Jr., M.D.
David A. Silverberg, M.D.
Peter M. Townley, M.D.

Ann M. Berger RN-C, MSN
Doctoral Student
University of Nebraska College of Nursing
[redacted]

November 29, 1994

Dear Ann,

I received your request to have access to the patients I care for in my practice who are receiving chemotherapy for stage I or II breast cancer. I am interested in your study examining fatigue patterns in these women as they receive treatment, entitled "Fatigue, Lifestyle and Breast Cancer Chemotherapy". I offer you access to my patients who meet your study criteria.

As you know, Methodist Hospital and out-patient services are seeing approximately 160 new cases of breast cancer each year, with a good percentage of women receiving adjuvant chemotherapy. I feel we can assist you in obtaining your desired sample size (70) within a year's time.

Let me know how I can assist you when you are ready to start your study.

[redacted]

Embassy Towers
9300 Underwood Avenue, Suite 550
Omaha, Nebraska 68114
402-393-3110
402-393-5732 fax

Methodist Cancer Center
8303 Dodge St. Suite 250
Omaha, Nebraska 68114-4123
402-354-8124
402-354-8127 fax

Midlands Cancer Center
401 East Gold Coast Road, Suite 103
Papillion, Nebraska 68046
402-593-3141
402-593-3145 fax

CLARKSON HOSPITAL

BUILDING ON THE LEGACY

Storz Cancer Institute
4350 Dewey Avenue
Omaha, Nebraska
68105-1018
402-552-3948

Clarkson Cancer Institute
at Shenandoah Memorial Hospital
300 Pershing
Shenandoah, Iowa
51601-2397
712-246-1230, Ext. 300

Douglas R. Jones, M.D.
Medical Director
Storz Cancer Institute

Charles A. Enke, M.D.
Medical Director
Radiation Oncology

Robert B. Thompson, M.D.
Radiation Oncology

James M. Merfeld, M.D.
Radiation Oncology

Kara D. Griffith, M.D.
Cancer Liaison Physician

Marc R. Hapke, M.D.
Cancer Committee Chairman

Robyn K. Tweedy, M.H.A.
Administrative Director
Storz Cancer Institute

Ann Yager, B.S.R.T.
Manager
Radiation Oncology

Diane Lepley, R.N., B.S.N.
Manager, Ninth Floor

Rita Armendariz, R.N., B.S.N.
Oncology Research Associate

Gladys Pierce, R.N.
Cancer Care Coordinator

December 18, 1995

James E. Call, M.D.
Chairman, Institutional Review Board
Clarkson Hospital
[redacted]

Dear Dr. Call:

We have reviewed the attached protocol and agree to allow eligible patients from our practice to participate in the study.

Sincerely,
[redacted]
Douglas R. Jones, M.D.
Medical Director
Storz Cancer Institute
[redacted]
Bruce M. Boman, M.D., Ph.D
Director
Cancer Research & Hereditary Tumors

DRJ:bae

Attachment

Heartland
Oncology & Hematology

John A. Okerbloom, M.D.
Robert W. Warner, M.D.

October 1, 1995

To Whom It May Concern:

This letter is written to acknowledge consent for patients in my practice to participate in the nursing research study entitled "Fatigue & Lifestyle During Breast Cancer Chemotherapy" (IRB#045-94). The study has been fully explained to me and I am aware of the potential benefit to participants and society. I grant permission to Patti Higginbotham to contact patients in my practice who meet eligibility requirements.

[redacted]

801 Harmony
Suite 201
Council Bluffs, Iowa 51503
712/322-4136

One Edmundson Place
Suite 100
Council Bluffs, Iowa 51503
712/322-4136

Appendix K

Adult Consent Form

University
of Nebraska
Medical Center
College of Nursing

600 South 42nd Street
Box 985330
Omaha, NE 68198-5330
Fax #: (402) 559-7570

IRB # 045-94
ADULT INFORMED CONSENT FORM
FATIGUE AND LIFESTYLE DURING BREAST CANCER CHEMOTHERAPY

INVITATION TO PARTICIPATE

You are invited to participate in this research study. The following information is provided in order to help you make an informed decision whether or not to participate. If you have any questions please do not hesitate to ask.

BASIS FOR SUBJECT SELECTION

You are eligible to participate because you are an adult woman, between the ages of 30-69, newly diagnosed with Stage I or II breast cancer, and will soon begin intravenous chemotherapy (cancer drugs through the vein) treatments. You are not eligible if you are diagnosed with congestive heart failure, chronic obstructive pulmonary disease, insulin-dependent diabetes or neuro-muscular diseases or on long-term steroid therapy.

PURPOSE OF THE STUDY

The purpose of this study is to learn more about the patterns of fatigue and the relationship between the reaction to the diagnosis of cancer, lifestyle behavior patterns and fatigue patterns in women with breast cancer during the first three cycles of intravenous chemotherapy.

EXPLANATION OF PROCEDURES

You will be asked to complete questionnaires six times, at approximately 10-14 day intervals according to your chemotherapy schedule. You will be able to complete the following written questionnaires in your home at the specific time points: a baseline Background Data Sheet (time #1), a General Health Survey (MOS-36)(times #1 and 5), a baseline Reaction to the Diagnosis of Cancer Questionnaire (time #1), a questionnaire called the Piper Fatigue Scale (time #1-6), a Lifestyle Profile (time #1,3,5), and a Symptom Distress Scale (time #1-6). Blood work (hematocrit) and height and weight will be obtained from your chart as available. You will be asked to wear a special wrist watch for 3-4 days at times #1-6 which can detect your arm motion. The watch stores information about your activity and rest patterns.

_____ subject's initials

There are no known risks or discomforts associated with this research. It is possible that you may feel uncomfortable with the watch on initially, but it is expected that you will get used to it quickly.

POTENTIAL BENEFITS TO SUBJECT-

There are no direct benefits to you as a subject.

POTENTIAL BENEFITS TO SOCIETY-

The knowledge gained from this study may assist nurses in caring for patients who are receiving chemotherapy and feeling fatigued.

ASSURANCE OF CONFIDENTIALITY-

Any information obtained during the study will be kept strictly confidential. The information obtained in the study may be published in scientific journals or presented at scientific meetings, but your identity will be kept strictly confidential.

RIGHTS AS A RESEARCH SUBJECT-

Your rights as a research subject have been explained to you. If your have any additional questions concerning your rights, you may contact the University of Nebraska Institutional Review Board (IRB), telephone [redacted].

VOLUNTARY PARTICIPATION AND WITHDRAWAL

You are free to decide not to participate in this study or to withdraw at any time without adversely affecting your relationship with the investigator or the hospital. Your decision will not result in any loss of benefits to which you are otherwise entitled.

DOCUMENTATION OF INFORMED CONSENT

YOU ARE VOLUNTARILY MAKING A DECISION WHETHER OR NOT TO PARTICIPATE IN A RESEARCH STUDY. YOUR SIGNATURE CERTIFIES THAT YOU HAVE DECIDED TO PARTICIPATE HAVING READ AND UNDERSTOOD THE INFORMATION PRESENTED. YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

_____ _____

SIGNATURE OF SUBJECT **DATE**

IN MY JUDGEMENT THE SUBJECT IS VOLUNTARILY AND KNOWINGLY GIVING INFORMED CONSENT TO PARTICIPATE IN THIS RESEARCH STUDY.

_____ _____

SIGNATURE OF INVESTIGATOR **DATE**

IDENTIFICATION OF INVESTIGATORS

PRINCIPAL INVESTIGATOR ANN M. BERGER RN-C,MSN [redacted]

SECONDARY INVESTIGATORS: PATTI HIGGINBOTHAM RN, MS, OCN Off: [redacted]

SUSAN NOBLE WALKER RN, EdD, FAAN [redacted]

Appendix L

Letters of Permission for Use of Instruments

PERMISSION FORM

I plan to use the *Health-Promoting Lifestyle Profile II* in a research or evaluation project entitled:
Patterns of Fatigue and Factors Influencing Fatigue During Adjuvant Breast Cancer Chemotherapy

I am enclosing a check for ten dollars ($10.00) payable to the University of Nebraska Medical Center College of Nursing.

Ann M. Berger
Print Name

[redacted]
Signature

Clinical Nurse Specialist-Gen. Onc.
Position

[redacted] (H)
Area Code Telephone #

[redacted]
Mailing Address
Omaha, NE 68132

Permission is granted to the above investigator to copy and use the *Health-Promoting Lifestyle Profile II* for non-commercial data collection purposes such as research or evaluation projects provided that content is not altered in any way and the copyright/permission statement at the end is retained. The instrument may be reproduced in the appendix of a thesis, dissertation or research grant proposal without further permission. Reproduction for any other purpose, including the publication of study results, is prohibited without specific permission.

[redacted]

11/12/96
Date

Please send two signed copies of this page to:

Susan Noble Walker, Ed.D., R.N., F.A.A.N.
University of Nebraska Medical Center
College of Nursing
[redacted]

NORTHERN ILLINOIS
UNIVERSITY
1895 - 1995

SCHOOL OF NURSING
1240 NORMAL ROAD
DEKALB, ILLINOIS 60115-2894
(815) 753-1231
FAX (815) 753-0814

November 8, 1996

Ann Berger, RN-C, MSN, PhD candidate
[redacted]

Dear Ann:

You have my permission to use the 28 item Reaction to the Diagnosis of Cancer Questionnaire in your study.

You may have copies made from the form that is enclosed. Content should not be altered in any way and the copyright/permission statement at the end must be produced.

There is no charge for approved research use, but I would appreciate receiving a complete report of your study for our files. We are particularly interested in information about scores (range, mean and standard deviation) on the RDCQ, reliability coefficients, and correlations with other measured variables.

Please feel free to contact me if you have any questions.

Best of luck on your research.

Sincerely,
[redacted]

Marilyn Frank-Stromborg, EdD, JD, ANP, FAAN
Professor and Chair

MFS/si

Enclosures

UNIVERSITY of PENNSYLVANIA

Center for Advancing Care in Serious Illness

Ruth McCorkle, PhD, FAAN
Director
Barbara Lowery, EdD, FAAN
Co-Director

School of Nursing
420 Guardian Drive
Philadelphia, PA 19104
Tel: (215) 898-9134
Fax: (215) 898-1868

November 8, 1996

Ann M. Berger, RN.C, MSN
[redacted]

Dear Ann:

This letter is to verify that I gave you permission to use the Symptom Distress Scale. Your original correspondence was dated February 3, 1993 and the permission continues to be in effect from that time.

Please let me know if you need any additional assistance. We are in the process of developing a user's manual and hope to have it available in February, 1997.

Sincerely,
[redacted]
Ruth McCorkle, PhD, FAAN
Professor

Enclosure

RM/srj

Appendix M

Analysis of Activity/Rest Cycles Data from Actigraphs

Activity-Rest Cycles

Examination of means, standard deviations and plots of activity/rest variable data revealed a wide range of values. Further exploration to identify relationships between activity/rest cycles and other study variables lead to One-way analysis of variance of the relationship between activity/rest cycle variables and the chemotherapy protocols.

All subjects for whom data were available were examined. Subjects were divided into two groups; one group did not receive an Adriamycin-based regimen, and the second group did receive an Adriamycin-based regimen; a division consistent with other comparisons between activity and adjuvant chemotherapy protocols for breast cancer. Mean scores and standard deviations for both groups fluctuated over time in similar tri-modal patterns. However, means of activity/rest cycle variables were considerably lower for the group receiving the Adriamycin-containing drugs. Table 25 presents results from pairwise comparisons of these activity/rest cycle variables by chemotherapy regimen. Results demonstrate significantly lower mesor scores for the Adriamycin-based group at all 6 times and on day high 3 at each time, and significance at some time points between groups on amplitude scores. Day 3 was selected for comparison because it coincides with the time when fatigue was measured, 48-72 hours after treatment. Figure 14 illustrates the values and patterns of activity/rest cycles that are clearly different from norms established in healthy, middle aged, mostly female subjects by Farr and Boen (1996), and also are different depending on the chemotherapy protocol. Women receiving Adriamycin-based regimens had lower mesor and amplitude scores than women receiving the non-

Table 25.

One-Way ANOVA Comparisons[a] Between Non-Adriamycin/Adriamycin Based Regimens[b] and Activity-Rest Cycle Variables at Each Time

Variable	Non-Adriamycin/Adriamycin Regimens[d]					
	Time					
	1	2	3	4	5	6
Mesor for Entire Time[c]						
F	33.85	6.70	8.10	4.07	5.53	5.58
p	.000	.015	.007	.052	.024	.024
df	(1,45)	(1,28)	(1,39)	(1,32)	(1,35)	(1,35)
Amplitude for Entire Time[c]						
F	13.15	-1.86	2.65	3.07	2.64	2.48
p	< .001	.184	.111	.089	.112	.125
df	(1,45)	(1,28)	(1,39)	(1,32)	(1,35)	(1,34)
Mesor Plus Amplitude (Day High 3)						
F	18.69	5.23	4.83	5.62	7.67	11.74
p	< .001	.031	.035	.024	.009	.002
df	(1,40)	(1,26)	(1,36)	(1,29)	(1,32)	(1,32)

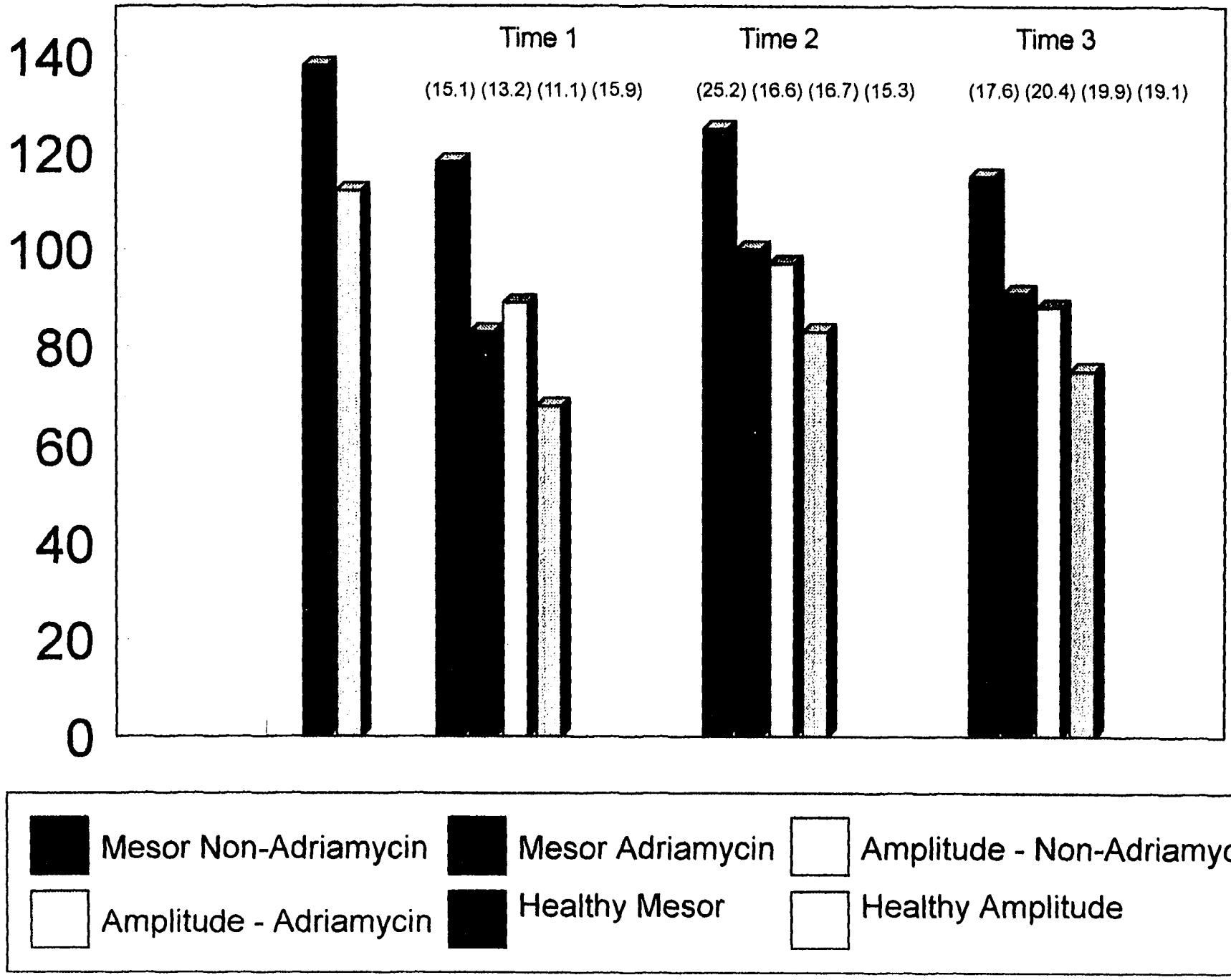
[a]Pairwise comparisons (n ranged from 27 to 46).

[b]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

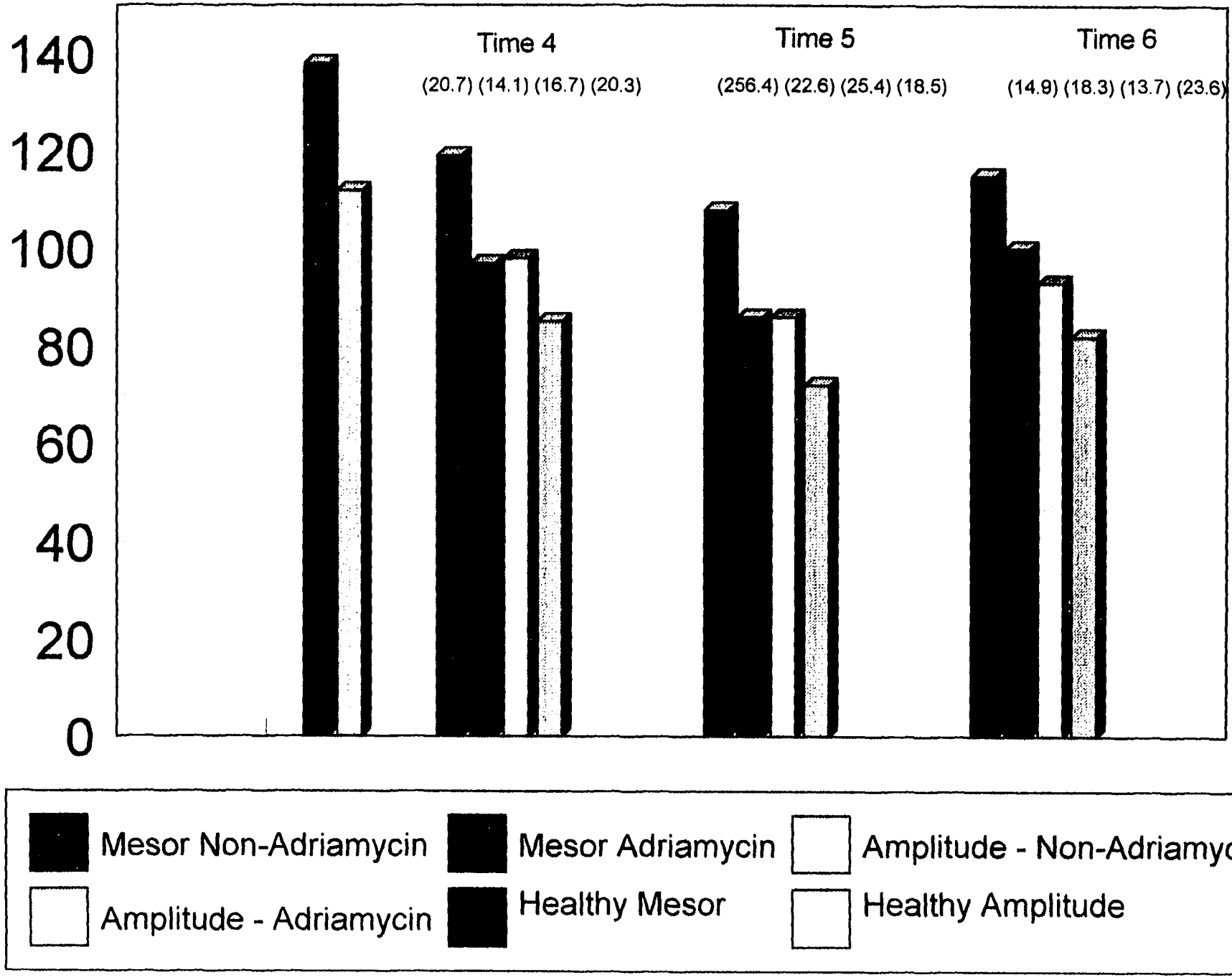
[c]Entire time = 96' at Times 1, 3, & 5; 72' at Times 2, 4, & 6.

Figure 14 Illustration of Mean Activity-Rest Cycle Variables in Women Receiving Adjuvant Chemotherapy for Breast Cancer and Healthy Norms. Activity events per minute are illustrated for the mesor and amplitude for each three or four day measurement time in both chemotherapy groups. Times 1,3, and 5 are the chemotherapy treatment days, and Times 2,4, and 6 are the mid-point recovery periods.

Activity Events Per Minute



Activity Events Per Minute



Adriamycin-based protocols at both treatment times and at mid-points as shown in Tables 26, 27, and 28. Figures 15 and 16 visually plot a "typical" subject on each regimen using output files from the Action-3 software analysis program. Intensity of motion both at night and during the daytime is easy to visually inspect in these figures.

All actigraph data available from subjects at any time points (pairwise comparisons) were examined to determine the relationship between activity/rest cycle variables and fatigue intensity at each of the 6 times. Lower mean (mesor) and peak (amplitude) activity variables were correlated with higher perceptions of fatigue at all six times. Activity/rest cycle variables were then compared in relationship to chemotherapy regimens. The activity/rest cycle variables of mesor and day high 3 reflected more activity and less night-time restlessness in women not receiving Adriamycin-based protocols than in those containing Adriamycin at all six data collection times. Baseline values for individuals were not obtained in this study, since the subject was not contacted until a few days before treatment. However, norms on healthy subjects have been established and documented (Farr & Boen, 1996). Values obtained in this study were below these norms at the treatments and midpoint recovery times for the oral Cytoxan group, and more significantly for the intravenous Adriamycin and Cytoxan group. These differences could be explained by the argument that activity/rest cycle values changed from the very first day of chemotherapy, and remained below healthy norms throughout the study. These results indicate that women receiving adjuvant chemotherapy experience decreases in activity/rest cycle parameters that may be associated with perceptions of fatigue, and that these parameters are affected significantly more by Adriamycin-based

Table 26

Analysis of Variance of Activity/Rest Cycle Variables Obtained by Actigraph[a] Across Time in Women[b] With Stage I or II Breast Cancer Receiving Adjuvant Chemotherapy[c] (N=17)[d]

Variable	Time							
	1	2	3	4	5	6	F	p
	X, (SD)	X, (SD)	X, (SD)	X, (SD)	X, (SD)	X, (SD)		
Mesor								
Entire sample	104.14 (22.77)	119.22 (21.45)	103.61 (17.65)	112.98 (20.17)	100.50 (22.64)	110.55 (14.29	3.72	.029
Non-adriamycin group	118.64 (13.83)	130.17 (18.77)	110.31 (15.10)	120.81 (20.82)	106.08 (28.87)	115.56 (14.29)		
Adriamycin group	83.44 (15.65)	103.57 (14.58)	93.31 (16.79)	101.79 (13.65)	92.54 (22.72	103.39 (21.86)		
Amplitude								
Entire sample	81.46 (19.02)	93.31 (13.93)	82.55 (18.14)	93.51 (19.17)	80.45 (23.64)	87.58 (21.79)	2.54	.097
Non-adriamycin group	92.99 (9.98)	99.84 (8.04)	83.92 (18.22)	97.84 (15.48)	81.77 (27.73	92.26 (14.28)		
Adriamycin group	64.98 (16.60)	83.99 (15.75)	80.58 (19.21)	87.31 (23.34)	78.57 (18.16)	80.90 (29.53)		
Mesor plus Amplitude (Day Hi 3)								
Entire group	189.75 (48.24)	231.19 (48.24)	192.77 (57.21)	211.63 (33.55)	179.86 (61.05)	205.56 (42.25)	3.83	.032
Non-adriamycin group	210.02 (40.28)	243.47 (24.39)	201.29 (69.37)	220.84 (33.88)	186.34 (73.09)	224.90 (22.25)		
Adriamycin group	160.78 (42.92)	213.66 (41.82)	180.59 (34.85)	198.48 (30.62)	170.66 (41.91)	177.93 (50.04)		
Awakenings at night								
Entire sample	35.82 (15.61)	27.18 (15.97)	32.35 (16.07)	22.41 (14.34)	33.59 (17.40)	25.13 (14.05)	3.93	.007
Non-adriamycin group	36.20 (12.18)	25.40 (16.82)	30.20 (11.99)	22.90 (13.92)	35.60 (17.85)	24.20 (12.31)		
Adriamycin group	35.29 (20.65)	29.71 (15.75)	35.43 (21.49)	21.71 (16.04)	30.71 (17.70)	26.43 (17.19)		

[a]Mesor, Amplitude, Mesor plus Amplitude (Day High 3), Awakenings at night.

[b]Only women for whom complete data were available at all 6 times were entered into this analysis.

[c]Non-Adriamycin group=10, Adriamycin group=7.

[d]Healthy adult norms: Mesor = 138.20 (8.377); Amplitude = 112.35 (4.93) (Farr & Boen, 1996)

Table 27

Analysis of Variance of Activity/Rest Cycle Variables Obtained by Actigraph[a] Across Treatment Times in Women[b] With Stage I or II Breast Cancer Receiving Adjuvant Chemotherapy[c] (N=29)[d]

Variable	Time							
	1	2	3	4	5	6	F	p
	X, (SD)		X, (SD)		X, (SD)			
Mesor								
Entire sample	100.01 (22.35)		102.96 (22.29)		96.76 (26.56)		1.83 (1,3,5)	.171
Non-adriamycin group	117.95 (15.05)		115.20 (17.55)		108.27 (26.40)			
Adriamycin group	83.37 (13.18)		91.53 (20.44)		85.98 (22.61)			
Amplitude								
Entire sample	78.61 (17.25)		81.35 (20.26)		78.60 (22.94)		.42 (1,3,5)	.616
Non-adriamycin group	89.46 (11.09)		87.97 (19.94)		86.18 (25.45)			
Adriamycin group	68.48 (15.92)		75.18 (19.16)		71.52 (18.47)			
Mesor plus Amplitude (Day Hi 3)								
Entire group	179.09 (52.45)		181.96 (51.68)		172.18 (63.50)		.55 (1,3,5)	.582
Non-adriamycin group	218.08 (25.28)		211.77 (30.78)		204.26 (43.07)			
Adriamycin group	136.08 (39.52)		158.40 (48.83)		143.99 (67.05)			
Awakenings at night					175.33 (62.71)			
Entire sample	34.51 (15.80)		36.17 (17.73)		34.76 (19.95)		.10 (1,3,5)	.880
Non-adriamycin group	37.29 (16.05)		35.28 (17.14)		32.71 (16.30)			
Adriamycin group	31.93 (15.68)		37.00 (18.84)		36.67 (23.26)			

[a]Mesor, Amplitude, Mesor plus Amplitude (Day High 3), Awakenings at night.

[b]Oly women for whom complete data were available for times 1, 3, & 5 were included in this analysis.

[c]Non-Adriamycin group=14, Adriamycin group=15.

[d]Healthy adult norms: Mesor = 138.20 (8.377); Amplitude = 112.35 (4.93) (Farr & Boen, 1996).

Table 28

Analysis of Variance of Activity/Rest Cycle Variables Obtained by Actigraph[a] Across Midpoint Recovery Time in Women[b] With Stage I or II Breast Cancer Receiving Adjuvant Chemotherapy[c] (N=23)[d]

Variable	Time							
	1	2	3	4	5	6	F	p
		$\bar{X}$, (SD)		$\bar{X}$, (SD)		$\bar{X}$, (SD)		
Mesor								
Entire sample		113.29 (24.02)		109.04 (20.93)		108.26 (17.35)		
Non-adriamycin group		125.15 (24.17)		119.82 (20.70)		115.29 (14.87)	1.09 (2,4,6)	.345
Adriamycin group		100.35 (16.56)		97.27 (14.18)		100.59 (18.27)		
Amplitude								
Entire sample		90.61 (17.19)		91.78 (19.36)		88.18 (19.54)		
Non-adriamycin group		97.14 (16.73)		98.21 (16.75)		93.59 (13.77)	.71 (2,4,6)	.488
Adriamycin group		87.95 (5.50)		84.77 (20.31)		82.27 (23.62)		
Mesor plus Amplitude (Day Hi 3)								
Entire group		109.09 (34.25)		181.25 (46.50)		197.31 (59.70)		
Non-adriamycin group		204.83 (18.54)		213.98 (36.33)		214.64 (61.71)	.22 (2,4,6)	.798
Adriamycin group		173.88 (40.83)		166.24 (44.86)		178.26 (54.03)		
Awakenings at night								
Entire sample		27.80 (18.84)		22.48 (13.45)		24.48 (13.58)		
Non-adriamycin group		28.85 (21.89)		22.46 (13.39)		22.23 (11.31)	1.44 (2,4,6)	.248
Adriamycin group		26.67 (15.79)		22.50 (14.12)		26.92 (15.82)		

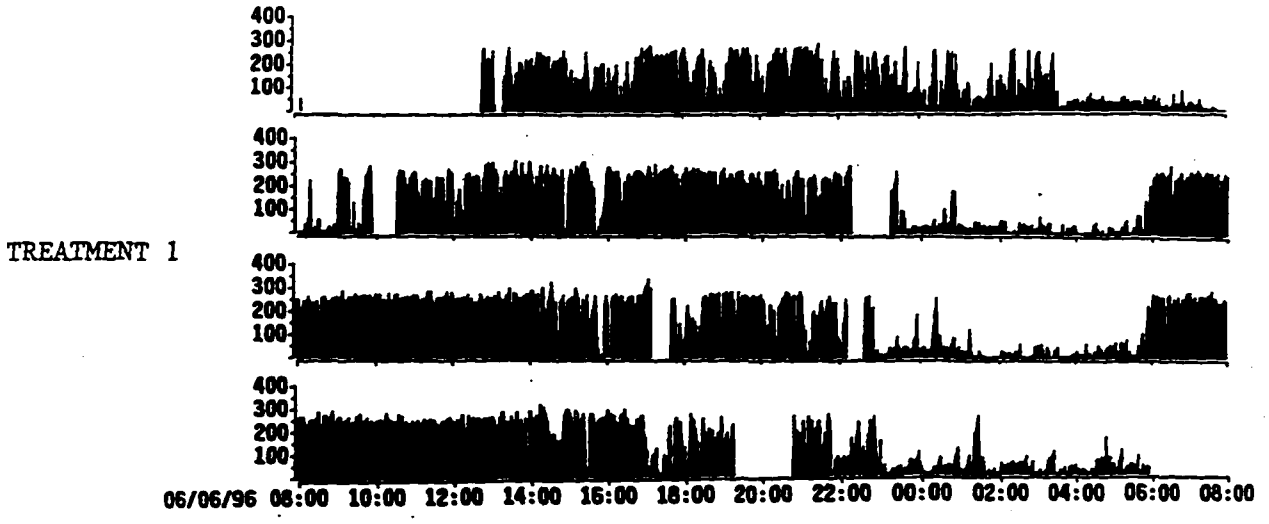
[a]Mesor, Amplitude, Mesor plus Amplitude (Day High 3), Awakenings at night.

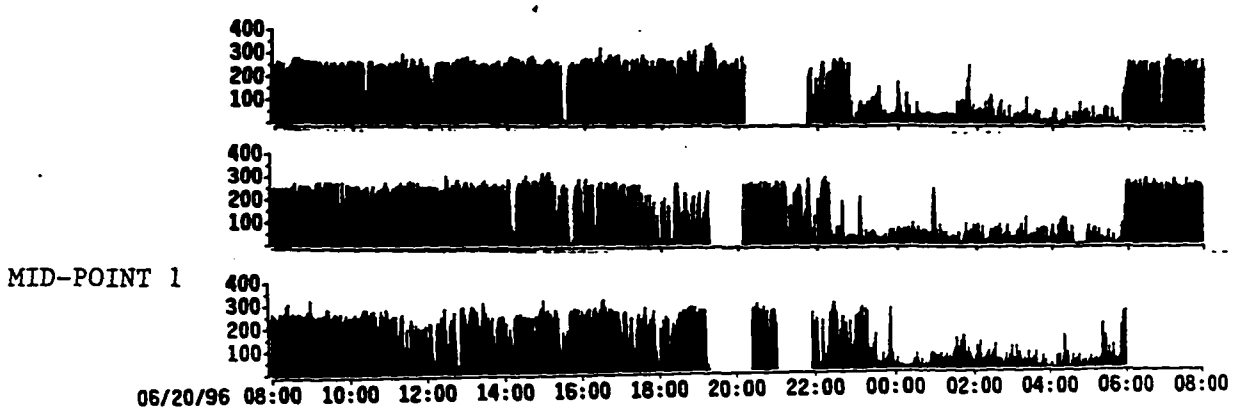
[b]Only women for whom complete data were available for times 2, 4, & 6 were included in this analysis.

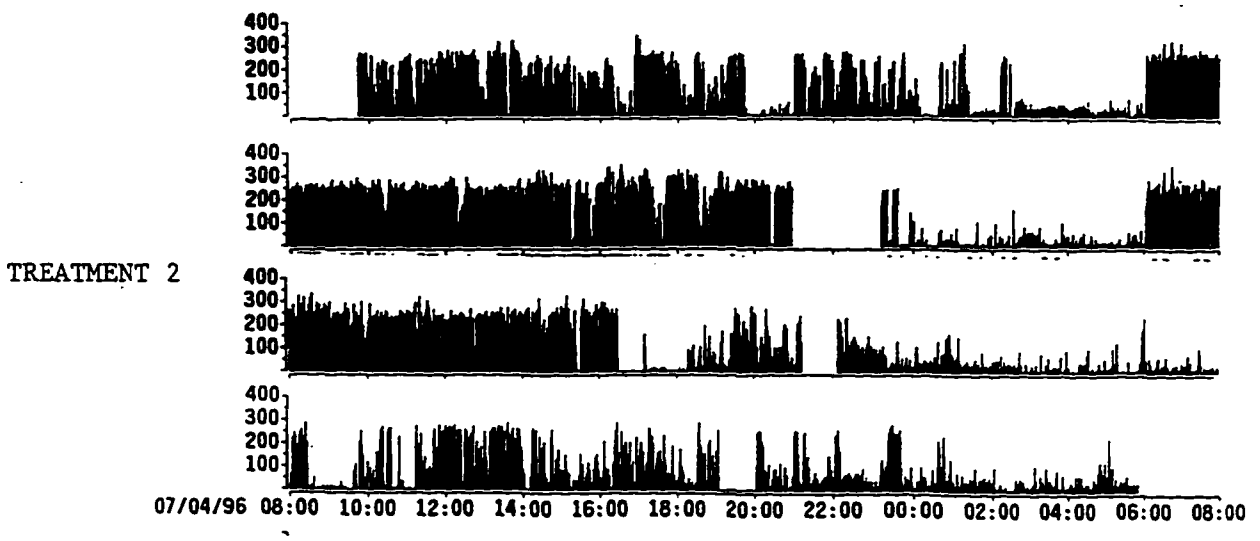
[c]Non-Adriamycin group=12, Adriamycin group=11.

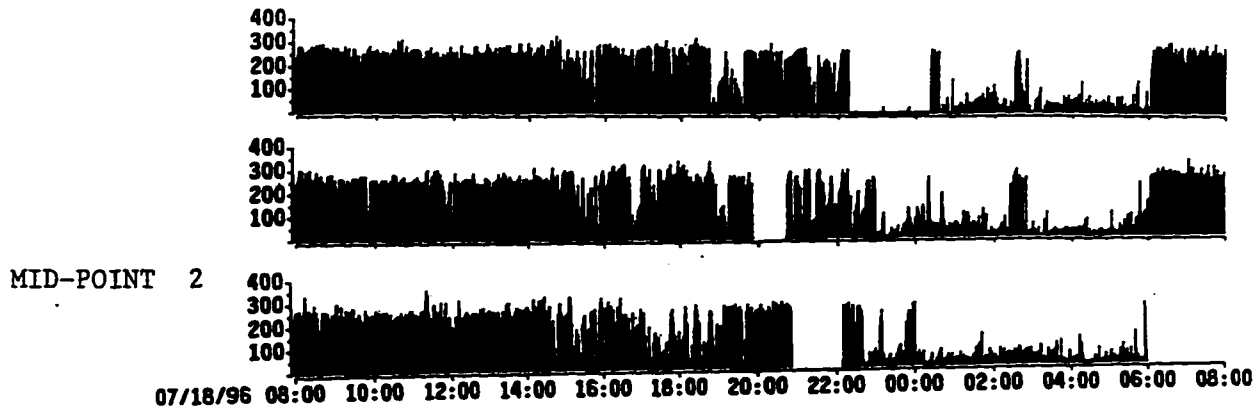
[d]Healthy adult norms: Mesor = 138.20 (8.377); Amplitude = 112.35 (4.93) (Farr & Boen, 1996)

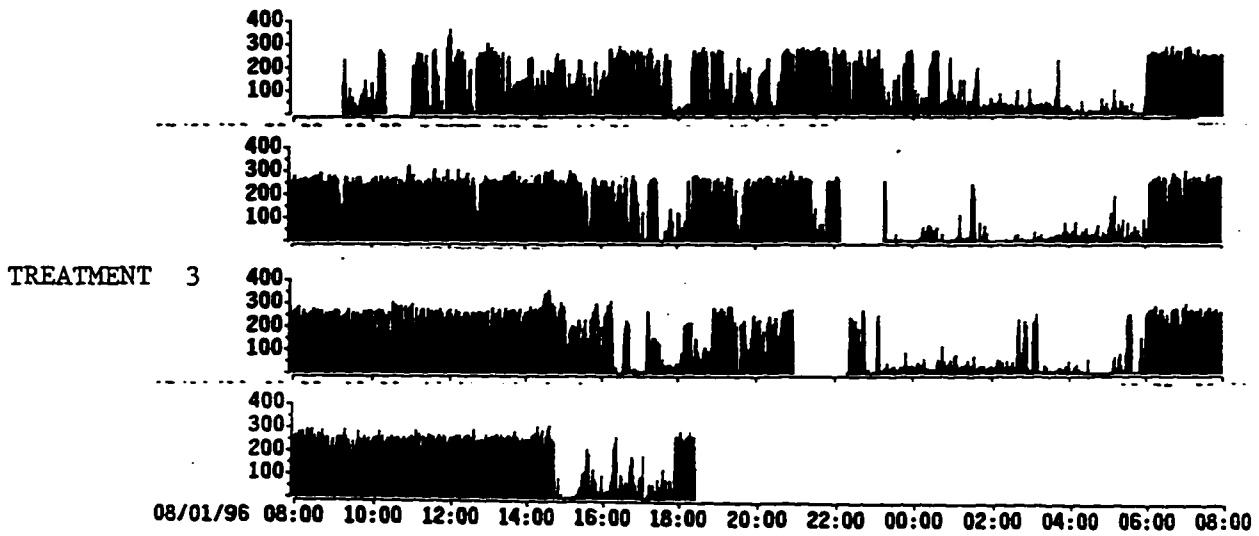
Figure 15 Activity/Rest patterns obtained by wrist actigraph from a typical subject receiving a non-Adriamycin-based regimen of chemotherapy for early breast cancer. The first 4 days after each of 3 chemotherapy treatments, and 3 mid-point days (beginning 10 to 15 days later) of each cycle were selected for analysis. Each strip represents a 24 hour period.











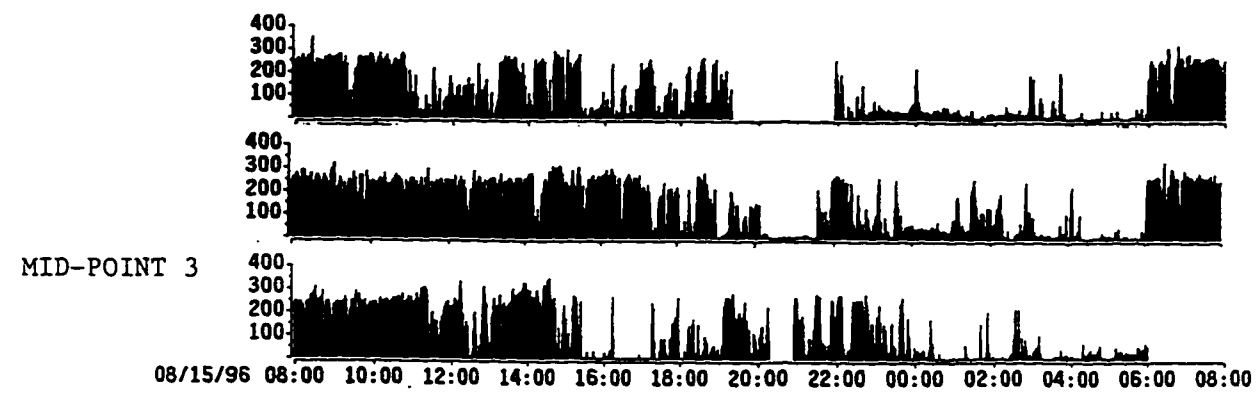
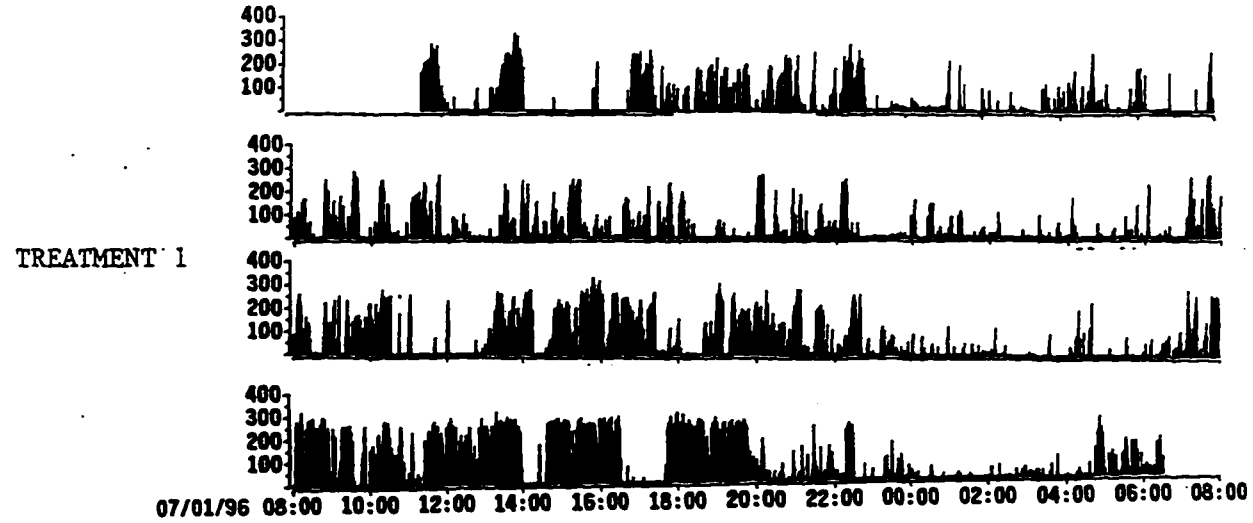
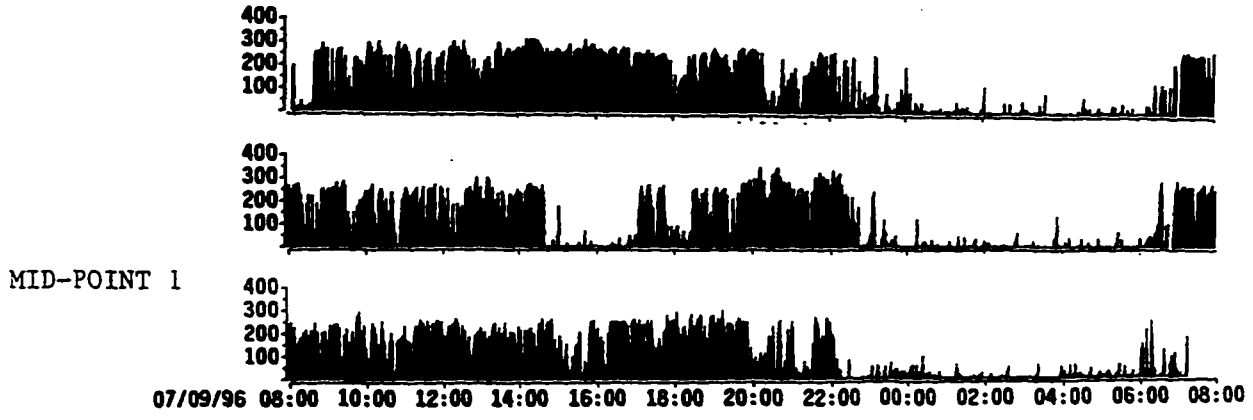
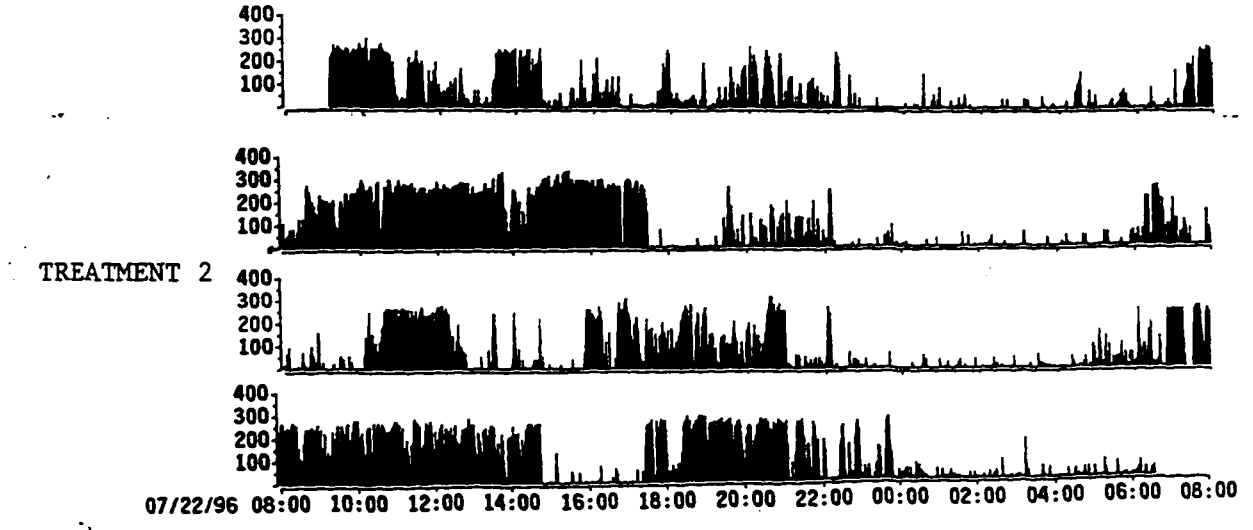
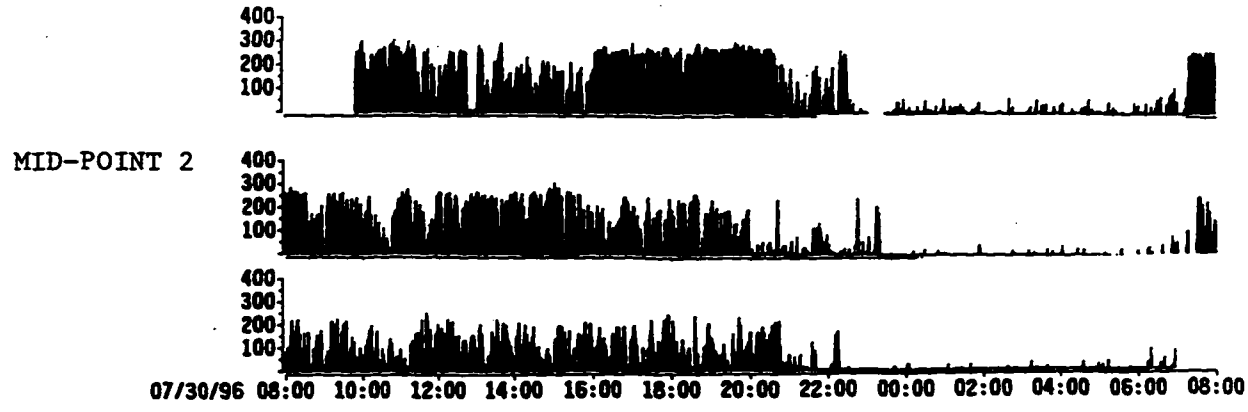


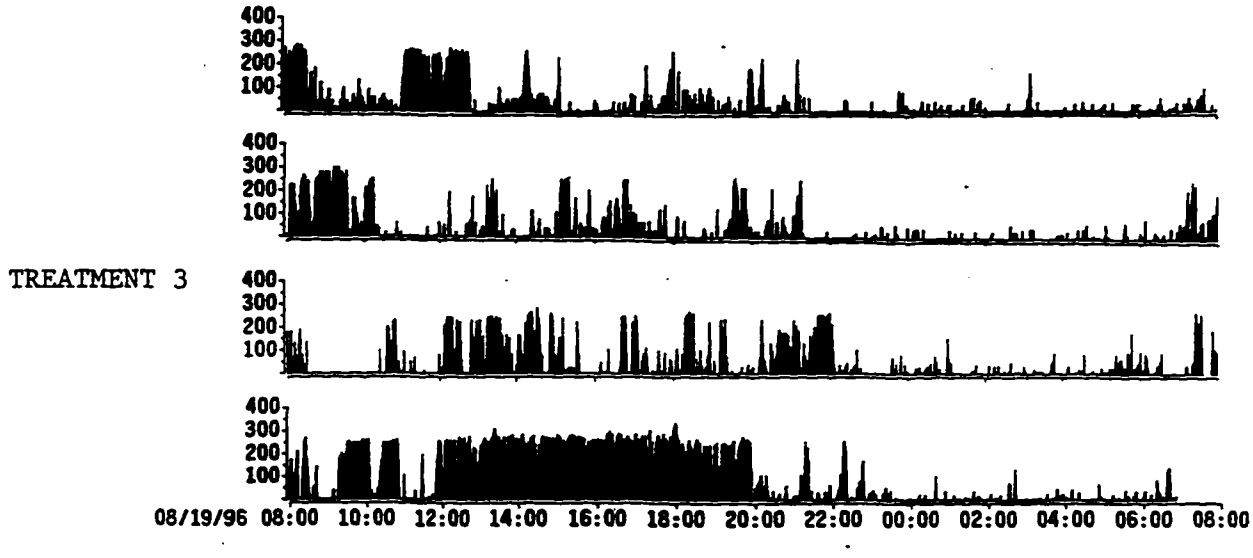
Figure 16 Activity/Rest patterns obtained by wrist actigraph from a typical subject receiving an Adriamycin-based regimen of chemotherapy for early breast cancer. The first 4 days after each of 3 chemotherapy treatments, and 3 mid-point days (beginning 10 to 15 days later) of each cycle were selected for analysis. Each strip represents a 24 hour period.

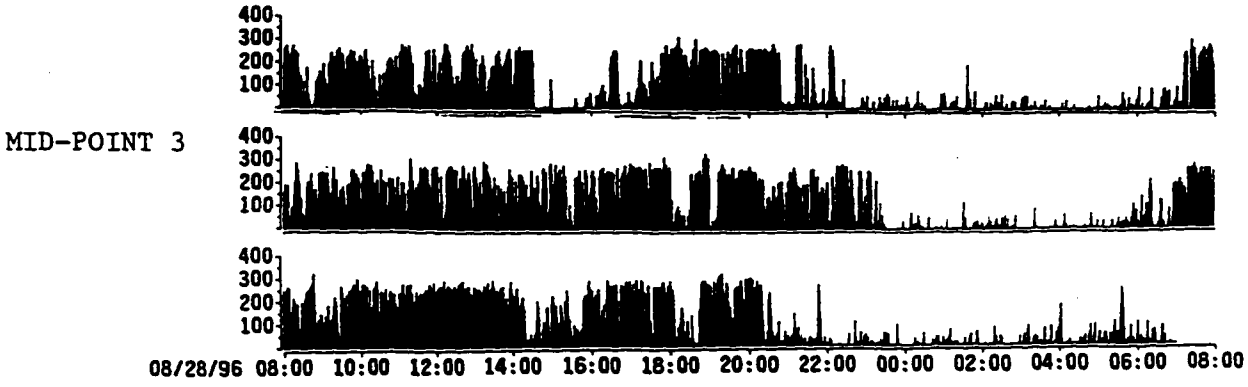












regimens beginning with the first treatment. These results have generated new knowledge that support the prevailing opinion among oncology nurses that Adriamycin regimens impact the individual's lifestyle more than non-Adriamycin regimens do.

Information on activity/rest cycle variables has been synthesized to further understanding of the patterns over time. Examination of the first treatment (T1) patterns revealed activity levels that correlated negatively with perceived fatigue scores. Women kept relatively active during the day throughout the 4 days of measurement, with mean daily activity scores equal to 134 motions per minute as compared to 200-300/minute in healthy individuals (Brown, Smolensky, D'Alonzo & Redman, 1990). Data from actigraphs suggest that women kept going at a normal pace during the daytime despite receiving their first chemotherapy treatment. However, mean scores from all subjects with available data on the activity/rest variables of mesor and amplitude for the entire 4 days were 72% and 70% of the norms established on healthy subjects by Farr and Boen (1996). Mesor and amplitude scores were also significantly lower in subjects receiving Adriamycin when protocols were examined using One-way ANOVA.

At the first cycle mid-point (T2) women displayed more adaptive activity/rest cycle variable scores. Mesor and amplitude levels correlated with subjective feelings of fatigue in these women. This may have been due to levels of fatigue driving the behavioral response, or the women deliberately adjusting their activity levels in an attempt to balance energy. Mean nighttime awakenings equaled 27 but did not correlate with fatigue scores.

Examination of actigraph data from the second chemotherapy treatment (T3) revealed that women were modifying their daytime behavior through naps and rest breaks. This could be explained by the fact that women may have known more about what to expect with the second chemotherapy treatment. As at the mid-point of the first cycle (T2), decreased mean activity levels were associated with intense fatigue. The treatment appeared to be associated with activity/rest patterns in a similar manner as at T1, and was no easier to tolerate. Awakenings at night at T3 ($\bar{X}$= 36.2) were similar to values obtained at the first treatment ($\bar{X}$=34.5), also suggesting a rationale for the daytime naps and rest breaks.

Analyses of the midpoint of cycle 2 (T4) actigraph recordings showed that activity levels did not correlate with perceived fatigue scores. Fatigue perceptions were similar to the first mid-point (T2), and mean activity levels fluctuated little. Mid-point recovery scores of fatigue ($\bar{X}$=3.7, 0-10 scale) were significantly different than at the previous treatment, a consistent findings throughout all time points.

Analysis of data at the third chemotherapy treatment (T5), revealed a polarization into low ($\bar{X}$<5.0 on total score, PFS) and high ($\bar{X}$>5.0, on total score, PFS) fatiguers in relation to activity/rest cycle variables. Significant differences were found in every activity/rest cycles variable examined between the high and low fatigue groups using One-way ANOVA. Individuals in the low fatigue group remained more active during the day, while those in the high fatigue group recorded increased daytime sleep percentage and lower daytime activity levels. Data suggest that some women may have been

establishing a pattern of lowered expectations for themselves in regard to activity with each treatment.

By the mid-point of the third chemotherapy treatment (T6), the high fatigue group again recorded increased sleep percentages during the day, and throughout the measurement period when examined by One-way ANOVA. A "couch potato" phenomena may have been developing, with a scenario of increased day time naps, decreased daytime activity, and increased overall sleep percentage determined by One-way ANOVA.

Further examination and analysis of activity/rest cycle variables throughout the full chemotherapy course (4-6 treatments) and during recovery are needed to further explain the patterns of these cycles over the course of treatment.

Appendix N

Supplemental Regression Tables

Table 29

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Treatment 1 (T1) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.485[c]	.292				
Physical Functioning			-.143	0.63	.433	-.060
Role-Physical			.211	1.73	.195	-.030
Role-Emotional			-.014	0.01	.944	.016
Social			-.051	0.04	.836	-.171
Mental Health			-.162	0.54	.468	-.242
General Health			.169	0.84	.365	-.270
Chemotherapy Protocol[d]			.303	6.03	.018	.301
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity						
Nutrition			.072	0.19	.669	-.010
Interpersonal Relations			.065	0.16	.688	-.124
Stress Management			-.419	5.32	.026	-.296
Nutrition Status[f]			.297	3.00	.090	-.124
Hematocrit						
Body Mass Index			-.064	0.24	.630	-.052
Symptom Distress[f]			-.203	2.15	.149	.046
Reaction to Diagnosis of Cancer[g]			.596	16.3	.001	.561
Distress						
Confront			-.394	0.16	.558	.070
			.072	0.21	.652	-.166

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measruement at Time 1, recall of status prior to diagnosis.

[c]Overall F = 2.53 (p = .008).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measurement at time 1, recall of lifestyle behaviors prior to diagnosis.

[f]Measured at current time (T1).

[g]Measurement at Time 1, recall of reaction to diagnosis.

Table 30

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors on Women Receiving Adjuvant Chemotherapy for Breast Cancer at Treatment 2 (T3) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.534[c]	.361				
Physical Functioning			-.045	.06	.803	-.309
Role-Physical			-.001	.00	.991	-.162
Role-Emotional			-.036	.03	.857	-.141
Social			-.116	.24	.623	-.234
Mental Health			.152	.46	.503	-.042
General Health			-.012	.01	.943	-.311
Chemotherapy Protocol[d]			.141	1.53	.224	.175
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			.091	.33	.570	-.195
Nutrition			-.066	.17	.680	.238
Interpersonal Relations			-.232	1.77	.191	-.184
Stress Management			.277	2.56	.117	-061
Nutrition Status[f]						
Hematocrit			-.111	.70	.407	-.069
Body Mass Index			-.135	1.14	.291	.113
Symptom Distress[f]			.651	24.08	.001	.623
Reaction to Diagnosis of Cancer[g]						
Distress			-.113	.59	.446	-.146
Confront			-.013	.01	.930	-.010

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement at Time 3, recall of status prior to diagnosis.

[c]Overall F = 3.08 (p = .002).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measurement at time 1, recall of lifestyle behaviors prior to diagnosis.

[f]Measured at current time (T3).

[g]Measurement at Time 1, recall of reaction to diagnosis.

Table 31

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Treatment 3 (T5) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.695[c]	.581				
Physical Functioning			-.256	4.12	.048	-.556
Role-Physical			-.135	1.35	.252	-.518
Role-Emotional			-.098	.57	.455	-.479
Social			-.107	.50	.482	-.591
Mental Health			.040	.06	.811	-.510
General Health			.133	1.38	.246	-.299
Chemotherapy Protocol[d]			.031	0.11	.746	.177
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			-.058	.21	.647	-.123
Nutrition			.007	.03	.954	-.086
Interpersonal Relations			-.066	.25	.620	-.220
Stress Management			.020	.03	.874	-.182
Nutrition Status[f]						
Hematocrit			.067	.41	.527	.136
Body Mass Index			-.093	.93	.341	.136
Symptom Distress[f]			.573	24.0	.001	.739
Reaction to Diagnosis of Cancer[g]						
Distress			..080	4.53	.504	-.086
Confront			.112	1.16	.287	-.024

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement at Time 5 (current status).

[c]Overall F = 6.11 ($p < .001$).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measurement at time 1, recall of lifestyle behaviors prior to diagnosis.

[f]Measured at current time (T5).

[g]Measurement at Time 1, recall of reaction to diagnosis.

Table 32

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Mid-point, Cycle 1 (T2) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.545[c]	.375				
Physical Functioning			-.427	6.29	.016	-.288
Role-Physical			.182	6.34	.015	-.016
Role-Emotional			.379	.37	.547	-.171
Social			-.317	1.93	.172	-.409
Mental Health			-.066	.11	.753	-.407
General Health			-.085	.24	.628	-.494
Chemotherapy Protocol[d]			.044	.14	.707	.156
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			.182	1.32	.256	-.215
Nutrition			-.161	1.12	.297	-.337
Interpersonal Relations			-.246	2.06	.157	-.360
Stress Management			.054	.11	.741	-.268
Nutrition Status						
Hematocrit[f]			.098	.62	.436	-.026
Body Mass Index			-.143	1.21	.278	.149
Symptom Distress[f]			.364	6.91	.012	.509
Reaction to Diagnosis of Cancer[g]						
Distress			.120	.64	428	-.134
Confront			.130	.77	.385	.079

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement of Time 1 - recall of status prior to diagnosis.

[c]Overall $F = 3.21$ ($p < .001$).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 1 intravenous Cytoxan & Adriamycin = 1.

[e]Measurement at time 1, recall of lifestyle behaviors prior to diagnosis.

[f]Measured at curent time (T2).

[g]Measured at Time 1 - recall of reaction to diagnosis.

Table 33

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Mid-point, Cycle 2 (T4) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.496[c]	.308				
Physical Functioning			-.216	1.36	.250	-.311
Role-Physical			.317	4.08	.049	-.025
Role-Emotional			-.113	.29	.588	-.242
Social			-.153	.39	.533	-.284
Mental Health			.386	2.73	.106	-.174
General Health			-.483	6.80	.012	-.439
Chemotherapy Protocol[d]			.048	.16	.686	.095
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			235	2.01	.163	-.096
Nutrition			-.241	2.10	.154	-.194
Interpersonal Relations			.322	3.15	.083	-.050
Stress Management			-.210	1.36	.249	-.086
Nutrition Status						
Hematocrit[f]			.138	.99	.324	018
Body Mass Index			-.048	.13	.718	.099
Symptom Distress[f]			.266	3.74	.059	.467
Reaction to Diagnosis of Cancer[g]						
Distress			-.101	.43	.514	-.064
Confront			-.364	5.65	.022	-.168

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement of Time 1 - recall of status prior to diagnosis.

[c]Overall F = 3.21 ($p < .001$).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measurement at time 1, recall of reaction to diagnosis.

[f]Measured at current time (T4).

Table 34

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Mid-point, Cycle 3 (T6) (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.604[c]	.457				
Physical Functioning			-.409	8.10	.006	-.650
Role-Physical			-.019	0.21	.885	-.329
Role-Emotional			.088	3.37	.547	-.249
Social			.015	0.01	.927	-.297
Mental Health			-.041	0.05	.832	-.386
General Health			-.320	6.15	.017	-.566
Chemotherapy Protocol[d]			-.118	1.18	.282	.110
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			-.071	.25	.616	-.321
Nutrition			-.250	2.86	.097	-.340
Interpersonal Relations			.080	0.28	.597	-.118
Stress Management			.116	0.66	.421	-.099
Nutrition Status						
Hematocrit[f]			009	0.01	.938	-.096
Body Mass Index			.041	0.14	.704	.220
Symptom Distress[f]			.184	1.93	.172	.423
Reaction to Diagnosis of Cancer[g]						
Distress			.115	0.71	.403	.031
Confront			.019	0.03	.868	-.118

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measured at T5.

[c]Overall F = 4.11 ($p < .001$).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measurement at time 1, recall of lifestyle behaviors prior to diagnosis.

[f]Measured at curent time (T6).

[g]Measured at Time 1 - recall of reaction to diagnosis.

Table 35

Regression Coefficients for Fatigue Regressed on Direct Influencing Factors in Women Receiving Adjuvant Chemotherapy for Breast Cancer at Time 6 Using Retrospective MOS-36 Scores (N = 60)

Variables	Cumulative R^2	Adjusted R^2	Univariate [a] Beta	F	p	Simple r
Health and Functional Status[b]	.542[c]	.372				
Physical Functioning			-.333	4.07	.049	-.419
Role-Physical			.191	1.61	.222	-.075
Role-Emotional			.140	.553	.461	-.236
Social			-.363	2.59	.115	-.426
Mental Health			.264	1.74	.212	-.267
General Health			-.218	1.94	.171	-.453
Chemotherapy Intensity[d]			-.094	.700	.407	.110
Health-Promoting Lifestyle Behaviors[e]						
Physical Activity			-.285	3.32	.075	-.441
Nutrition			-.182	1.53	.222	-.418
Interpersonal Relations			.089	.253	.617	-.147
Stress Management			.085	.231	.194	-.240
Nutrition Status						
Hematocrit[f]			-.037	.084	.773	-.096
Body Mass Index			-.083	.458	.502	.220
Symptom Distress[f]			.280	4.30	.044	.423
Reaction to Diagnosis of Cancer[g]						
Distress			.145	.828	.368	.031
Confront			-.015	.011	.918	-.118

[a]Univariate F reflects the importance of each variable after all have entered.

[b]Measurement at time 1, recall of status prior to diagnosis.

[c]Overall F = 2.51 (p = .008).

[d]Coded as non-intravenous Cytoxan & Adriamycin = 0, intravenous Cytoxan & Adriamycin = 1.

[e]Measurement at time 5, current.

[f]Measured at current time (T6).

[g]Measured at Time 1 - recall of reaction to diagnosis.