DETERMINING LEVEL AND TRAJECTORY OF CHANGE IN REPORTED ATTENTIONAL FUNCTION IN WOMEN WITH BREAST CANCER RECEIVING CHEMOTHERAPY, A PILOT STUDY

By

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a

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ABSTRACT

Determining Level and Trajectory of Change in Reported Attentional Function in Women with Breast Cancer Receiving Chemotherapy, A Pilot Study

Background: Symptom cluster research in cancer has linked reports of cognitive problems, depression, and fatigue, along with sleep disturbance, anxiety, and pain in a psychoneurologic symptom cluster, potentially with a shared underlying inflammatory cytokine mechanism. Better understanding of the levels and trajectories of attentional function, depression, and fatigue and the relationships among these variables is needed to pursue knowledge of underlying mechanisms and to develop interventions targeted at helping to manage cancer-related symptoms. The purpose of the study was to describe how levels of attentional function, fatigue, and depression change over time and whether levels and trajectories of fatigue and depression predict levels and trajectories of attentional function in women with breast cancer being treated with chemotherapy.

Methods: This study is a secondary analysis of data from two prospective longitudinal studies of women with early stage breast cancer (Stage I – III) being treated with chemotherapy. Attentional function was measured with the Attentional Function Index (AFI), depression with Center for Epidemiologic Studies – Depression (CESD), and fatigue with two instruments: Patient-Reported Outcomes Measurement Information System – Fatigue (PROMIS) and the Schwartz Cancer Fatigue Scale (SCFS). Sample 1 (N = 24) was from the NW U.S. and Sample 2 (N = 44) was from the NE U.S. Study data was collected at clinically significant measurement times: before the first day of

chemotherapy, at mid-treatment, at the end of treatment with chemotherapy and 3 to 6 months after the end of treatment with chemotherapy. Depending on chemotherapy regimens, participants were in the study for 9 to 12 months. Assessments were timed to be just prior to a dose of chemotherapy to control for confounding medication effects. Attentional function was the primary outcome variable. Longitudinal multilevel modeling was used to accommodate exploration of time-varying covariates in a model with a time-varying primary outcome variable.

Results: Most of the participants were in their early 50s, non-Hispanic Caucasian, and married or partnered. Compared to the women in Sample 2, the women in Sample 1 were less likely to be employed full time ($p < .001$), more likely to have an income at or below U.S. median income (~$53,000) ($p < .001$), and more likely to have a high school education or less ($p < .05$). Sample 1 reported consistently worse levels of attentional function, depression, and fatigue across time. In a longitudinal multilevel model for attentional function, a fixed quadratic model fit the Sample 1 data better than a fixed linear model (χ^2 (2) = 5.14, $p = .0233$). The model adding a random slope was nonconforming. In Sample 2, a fixed quadratic model provided the best fit to the data (χ^2 (2) = 3.13, $p = .0768$) and the addition of a random slope did not improve the model fit (χ^2 (2) = 2.06, $p = .3474$). Similarly, depression and fatigue were fit to fixed quadratic models. Adding depression as a time-varying covariate to a model with attentional function resulted in a significant coefficient for depression (Sample 1, $\beta = -.76$, $SE = .19$; $z = -3.87$, $p < .001$; and Sample 2, $\beta = -.91$, $SE = .13$; $z = -6.96$, $p < .001$).

Conclusions: These results suggest that the trajectories of attentional function, depression, and fatigue in a population of women with breast cancer receiving chemotherapy each exhibit a quadratic curve such that after start of chemotherapy each symptom worsens until mid-treatment and starts to improve before the end of treatment, returning to pretreatment levels by 3 to 6 months after the end of treatment. In a model with attentional function, the trajectory of fatigue predicts the trajectory of attentional function such that a worsening of fatigue predicts a worsening of attentional function. In a model with attentional function, the trajectory of depression predicts the trajectory of attentional function such that a worsening of depression predicts a worsening of attentional function. The science of symptom management, specifically of symptom cluster science, will benefit from this new knowledge related to trajectories of and relationships between attentional function, depression, and fatigue in women with breast cancer receiving treatment with chemotherapy.

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CHAPTER 1

INTRODUCTION

Breast cancer is the most common cancer diagnosis among women in the United States with 232,240 new cases of invasive breast cancer in 2013 (ACS, 2014b). Breast cancer survivors are the largest single group (22%) of the estimated 15 million cancer survivors in the U.S. because of the high incidence rate and the success of treatment, with the 5-year relative survival rate for localized breast cancer at 99% and at 84% for breast cancer that has spread to adjacent tissue (ACS, 2013). When these survival statistics are considered in relation to the aging of the U.S. population, the number of female breast cancer survivors in the U.S. is expected to increase by 30% by the year 2030 to 4.3 million (Smith, Smith, Hurria, Hortobagyi, & Buchholz, 2009). Forty-six percent of women diagnosed with breast cancer are treated with chemotherapy, which places them at risk for persistent and late-appearing effects associated with their specific chemotherapy regimens as well as for problems associated with other treatments, such as radiation, surgery, and hormone therapy (Barcenas et al., 2014). These include acute treatment side effects, persistent fatigue, shoulder problems, lymphedema of the trunk and arm on the affected side, premature menopause, impaired sexual function, osteoporosis, and elevated fall risk (ACS, 2014a; Jaquad, 2015).

The emerging data on cognitive effects of chemotherapy suggest that there may be both acute and longer term effects on cognitive function that may have deleterious effects on quality of life. Cognitive problems, such as difficulty concentrating, have implications for quality of life in areas such as work, family responsibilities,

relationships, life satisfaction, and contributions to the community. Longitudinal observational studies assessing attentional function prior to, during, and following treatment with chemotherapy are needed to characterize subjective attentional function to determine prevalence, correlates, and trajectories of attentional function during and following breast cancer treatment.

Women with breast cancer report problems with cognitive function, such as paying attention, following diagnosis but before initial treatment, following surgery and prior to adjuvant chemotherapy, as well as during and following treatment with chemotherapy (Downie, Fan, Houede-Tchen, Yi, & Tannock, 2006; Fitch, Armstrong, & Tsang, 2008; Shilling & Jenkins, 2007; Von Ah, Habermann, Carpenter, & Schneider, 2013). The majority of the research on cognitive dysfunction in women with breast cancer has focused on women treated with chemotherapy. The prevalence of problems with cognitive function based on various self-report measures observed in these studies varies from 21% to 90% (Pullens, DeVries, & Roukema, 2010). Reviews of research on cognitive problems among people with cancer that did not involve the central nervous system and who were treated with chemotherapy have identified several conceptual and methodologic critiques of prior work. These include failure to specify the domain(s) of cognitive function being studied, cross-sectional and/or retrospective study design, lack of an adequate control or comparison condition, lack of pretreatment and post-treatment data, use of measures or instruments that are not sensitive to subtle changes in cognitive function, and failure to address heterogeneity of cancer treatment (Wefel, Saleeba, Buzdar, & Meyers, 2010; Wefel, Vardy, Ahles, & Schagen, 2011). Attentional function is

selectively impacted by cancer and cancer treatment (M. L. Chen, Miaskowski, Liu, & Chen, 2012; X. Chen et al., 2014). This study aims to describe levels and trajectories of attentional function before, during, and after chemotherapy in women with breast cancer receiving chemotherapy.

Secondary Analysis Described

The proposed study is a secondary analysis of data from two studies of women with early stage (Stage I – III) breast cancer receiving treatment with chemotherapy:

(a) Study 1: "Mechanisms of Cancer Treatment Related Symptoms," 5R01NR012479, The National Institute of Nursing Research; PI, L.J. Wood

(b) Study 2: "Cytokine response to subclinical cytomegalovirus reactivation as a cause of severe fatigue in women undergoing chemotherapy for breast cancer, BCRP W81XWH-11-1-0456. Department of Defense Breast Cancer Research Program, Collaborative Idea Award; PI, L.J. Wood

Both studies were designed with similar and clinically significant measurement times, that is, immediately prior to the first chemotherapy treatment (First Day of Chemotherapy), a measurement prior to the third dose of chemotherapy (Mid-Treatment), a measurement prior the last dose of chemotherapy (Treatment End), and a measurement between three and six months after the last dose of chemotherapy (Follow-Up). Study 2 collected data at a measurement time prior to the First Day of Chemotherapy, providing data from a total of five measurement times. Both studies used the same valid and reliable measurement tools, which provide pertinent data to answer this study's research questions.

Complexity and Implications of Treatments for Breast Cancer

Treatments

Treatment for breast cancer may involve one or a combination of the following strategies or treatments: surgery, chemotherapy, radiation therapy, monoclonal antibody therapy, and/or hormone- and HER2/Neu-based treatments. Guidelines for treatment of breast cancer are provided to oncology practitioners by the National Comprehensive Cancer Network and are based on factors that include tumor histology, clinical and pathologic characteristics of the primary tumor, axillary lymph node status, tumor hormone receptor content, tumor HER2 status, multigene testing of tumor, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status (NCCN, 2015). Surgery, considered primary treatment for breast cancer, may or may not be followed by adjuvant treatment which is designed to decrease the risk of the return of the cancer and may include chemotherapy, hormone therapy, radiation therapy, immunotherapy and/or targeted therapy. Many breast cancer treatment modalities carry risks for problems with attentional function. A major challenge of any study of cognitive problems in breast cancer patients is identifying and managing potential confounding influences, including those that arise from various treatment modalities.

After surgery, patients who received general anesthesia often exhibit a transient reversible cognitive dysfunction (Mandal, Schifilliti, Mafrica, & Fodale, 2009). The most frequent symptoms are memory loss and lack of concentration, with severe impairment producing delirium (Mandal et al., 2009). In a study of women with breast cancer, mean

scores on a self-report measure of attentional function were significantly higher (better functioning) before surgery than at the next measure taken, one month after surgery (M. L. Chen et al., 2012). However, because 65 of the 148 subjects who were treated with chemotherapy had already started treatment at one month after surgery and Chen does not present an analysis based only on those who had not initiated any adjuvant treatment at that time, the effect of surgery alone on AFI cannot be evaluated.

Radiation therapy is a critical component of the multidisciplinary management of invasive breast cancer (Jagsi, 2014). In appropriately selected patients, radiation not only improves local control, sparing patients the morbidity and distress of local recurrence, but it also improves survival by preventing seeding and reseeding of distant metastases from persistent reservoirs of locoregional disease (Jagsi, 2014). Radiation therapy for early stage breast cancer usually occurs following chemotherapy and, unlike metastatic breast cancer, is localized to the area immediately surrounding the tumor site and local lymph nodes.

Approximately, two-thirds of breast cancer tumors overexpress estrogen receptors and/or progesterone receptors. These tumors, referred to as hormone receptor positive, tend to grow more slowly than non-overexpressing breast cancer tumors (Blows et al., 2010). Younger women (less than 40 years of age) with breast cancer have a higher prevalence of hormone receptor negative disease and therefore tend to have more aggressive tumors (Anders, Johnson, Litton, Phillips, & Bleyer, 2009; Fredholm et al., 2009). For women with estrogen-positive breast cancer, estrogen suppression therapy may be started before or after surgery but generally is started after both surgery and

chemotherapy have been completed (NCCN, 2015). Almost 25% of newly diagnosed breast cancer in the U. S. occurs in premenopausal women (Jemal, Siegel, Xu, & Ward, 2010) and more than one-half of premenopausal women experience chemotherapy-induced amenorrhea (Di Cosimo et al., 2004; Perez-Fidalgo et al., 2010). As loss of estrogen at midlife (menopause) may contribute to mood problems and cognitive deficits (Greendale, Derby, & Maki, 2011), breast cancer treatments designed to treat cancer by reducing estrogen in the body may negatively affect cognition (Bender, Paraska, Sereeika, Ryan, & Berga, 2001; Bender et al., 2006; Simmons, 2009).

The human epidermal growth factor receptor 2 (HER2, sometimes call the HER2/neu receptor) is overexpressed in one in five cases of breast cancer (ACS, 2014a). Breast cancer tumors found to overexpress HER2 proteins on the cell surface tend to grow and spread faster than cancers without these receptors (ACS, 2014a). Trastuzumab (Herceptin, a targeted monoclonal antibody) blocks the function of the HER2 protein in tumors whose HER2 gene is stuck on overdrive and can significantly improve survival. Women with HER2-positive breast cancers may receive HER2 blockers singularly or in combination with other therapies**.** Anecdotal reports of cognitive problems while taking trastuzumab are noted, especially for those age 50 years and older (eHealthMe, 2015).

In patients with invasive breast cancer, cyclic cytotoxic chemotherapy significantly increases survival rates (Jemal et al., 2010). The National Comprehensive Cancer Network (NCCN) currently lists 16 anti-cancer regimens for HER2-negative cancers and an additional 13 regimens for HER2-positive cancers (NCCN, 2015). Regimens usually comprise a two-part sequence of cyclic cytotoxic drugs. The first

agents usually are from two classes of drugs, anthracyclines (e.g., doxibrubicin, epirubicin.) and alkylating agents (e.g., cyclophosphamide) (NCCN, 2015) (administered over 8 to 24 weeks). The second part of the sequence usually involves a taxane (paclitaxel or docetaxel) (administered over 8 to 12 weeks). In some regimens the taxane is given in the first part of the sequence. If the tumor is HER2 positive then a monoclonal antibody (trastuzumab or pertuzumab) is included in the regimen in the first part of the sequence (8 to 12 weeks), the second part of the sequence (12 to 40 weeks), or both, and usually continues for an additional period of time (40 to 43 weeks) after completion of the cyclic cytotoxic sequence of the regimen. Alternative or additional cytotoxic drugs in the first part of the sequence are 5-fluorouracil, carboplatin, and methotrexate. However, 5-fluorouracil, epirubicin, and cyclophosphamide may be given in the second half of the sequence in the setting of neoadjuvant (before surgery) treatment. In addition to the 29 chemotherapy regimens listed by the NCCN as standard treatment for invasive breast cancer, an additional 11 study protocols brings the number of NCCN regimens to 40. Dosing schedules vary between regimens. For example, "Dose-dense AC" is Adriamycin (doxorubicin) and Cytoxan (cyclophosphamide) given every 2 weeks (rather than every 3 weeks) for four doses followed by Taxol (paclitaxel) every 2 weeks for four doses. Additionally, a regimen may be adapted or changed to a different regimen for an individual who is experiencing unacceptable side effects from a particular regimen. Controlling for the complexity and heterogeneity of chemotherapy drug regimens is difficult in a clinical study. A description of the participants' chemotherapy regimens is provided in Chapter 4.

Rare occurrences of substantial neurological toxicity resulting from a chemotherapeutic agent have been characterized (Wefel, Collins, & Kayl, 2008), and these include a variety of nonspecific neurologic syndromes (acute encephalopathy characterized by a confusional state, insomnia, and often agitation; chronic encephalopathy characterized by cognitive dysfunction consistent with "subcortical dementia," incontinence, and gait disturbance; leukoencephalopathy; a cerebellar syndrome with symptoms ranging from ataxia to a pancerebellar syndrome; and a variety of peripheral neuropathies) (Wefel et al., 2008). These rare encephalopathies and extreme peripheral neuropathies are noteworthy in that they are highly distressing for patients and families, they usually have an identifiable etiology, and they are distinct from problems with attentional function reported by many women receiving chemotherapy for breast cancer, sometimes known as "chemobrain," Self-reported problems with attentional function are the focus of this study.

Potential mechanisms that might contribute to problems with attentional function reported by women with breast cancer receiving chemotherapy are metabolic abnormalities, alterations in excitatory neurotransmitters, anemia, hormonal dysfunction, indirect chemical toxicity and oxidative stress, microvascular injury, direct neurotoxic injury to cerebral parenchyma, cerebral atrophy, CNS organ toxicity, shared genetic risk factors for the development of cancer and cognitive problems—including low efflux pumps, deficits in DNA repair mechanisms and/or deregulated immune response—genetically modulated reduction of capacity for neural repair and neurotransmitter activity, and reduced antioxidant capacity associated with treatment-induced reduction in

estrogen and testosterone levels (Wefel et al., 2008). It is likely that a combination of mechanisms underlie cognitive dysfunction associated with chemotherapy. Results of this study may help scientists around the world who are studying underlying mechanisms of cognitive dysfunction associated with chemotherapy by providing information about pretreatment levels of attentional function and changes that take place during and following treatment with chemotherapy.

Depression and Fatigue

Women with breast cancer report physical, psychological, social and spiritual distress (Budin, Cartwright-Alcarese, & Hoskins, 2008). Chemotherapy regimens produce symptoms that may continue for five or more years after therapy (Byar, Berger, Bakken, & Cetak, 2006; Ganz, Castellon, & Silverman, 2002). Fatigue is the most common unrelieved and distressing symptom related to cancer chemotherapy (Byar et al., 2006; Downie et al., 2006). Reports of prevalence of depression in people with cancer vary widely and occur in a broad spectrum from sadness to major affective disorder (Massie, 2004). Previous reports found that higher preoperative levels of psychological distress were associated with poorer psychological outcomes after breast cancer surgery (Barez, Blasco, Fernandez-Castro, & Viladrich, 2007; Dean, 1990; Dean & Surtees, 1989; Gallagher, Parle, & Cairns, 2002; Kissane, Clarke, & Ikin, 1998). Fatigue and depression are selected for inclusion in the proposed study as they are prevalent and distressing factors that may be related to attentional function in women with breast cancer receiving chemotherapy.

Demographic and Clinical Factors

Demographic and clinical variability add to the complexity associated with attentional function, depression, and fatigue during treatment for breast cancer. Demographic variability (including age, ethnicity, marital status, education, and employment status) may influence the meaning the symptom experience has for the life of a woman with breast cancer, and, subsequently, may influence distress (Goodell & Nail, 2005). In addition to demographic variability, consideration must be given to the potential influence of clinical variables, such as stage of cancer, days between study measurement visits, type and sequence of chemotherapy treatment, and adjunct medications.

Study Purpose

The purpose of the study was to describe how levels of attentional function, fatigue, and depression change over time and whether levels and trajectories of fatigue and depression predict levels and trajectories of attentional function in women with breast cancer being treated with chemotherapy. The revised theory of unpleasant symptoms (TUS) provides a theoretical foundation for the study. TUS proposes that three categories of factors—physiologic, psychological, and situational—affect one's predisposition to or manifestation of a given unpleasant symptom (Lenz, Suppe, Gift, Puch, & Milligan, 1995). Each symptom can vary in duration, intensity, quality, and distress. In addition, the level and nature of the symptom experience are proposed to affect the patient's performance, which includes functional status, cognitive functioning, and physical

performance (Lenz et al., 1995). In relation to the proposed study, TUS will be described in greater detail in Chapter 2.

Aims and Hypotheses

1. To examine and describe how levels of attentional function, fatigue, and depression change over time (pretreatment, baseline, during treatment, and three to six months after completion of chemotherapy) in women with breast cancer.
    a. Hypotheses
        i. Women with breast cancer receiving chemotherapy experience a decrease or worsening in levels of attentional function from the time before start of chemotherapy to the end of treatment with chemotherapy, and then attentional function increases or improves during the six months following the end of chemotherapy treatment.
        ii. Women with breast cancer receiving chemotherapy experience an increase or worsening in levels of fatigue from the time before start of chemotherapy to the end of treatment with chemotherapy, and then fatigue decreases or improves during the six months following the end of chemotherapy treatment.
        iii. Women with breast cancer receiving chemotherapy experience an increase or worsening in levels of depression from the time before start of chemotherapy to the end of treatment with chemotherapy,

and then depression decreases or improves during the six months following the end of chemotherapy treatment.

2. To investigate whether levels of fatigue and depression predict baseline levels and trajectories of attentional function in women with breast cancer being treated with chemotherapy.
    a. Hypotheses
        i. At baseline, higher levels of fatigue predict lower levels or worse attentional function in women with breast cancer before initiation of treatment with chemotherapy.
        ii. At baseline, higher levels of depression predict lower levels or worse attentional function in women with breast cancer before initiation of treatment with chemotherapy
        iii. Trajectories of fatigue predict trajectories of attentional function in women with breast cancer during treatment with chemotherapy and up to six months following the end of treatment with chemotherapy, such that as levels of fatigue increase or worsen, levels of attentional function decrease or worsen; and as levels of fatigue decrease or improve, levels of attentional function increase or improve.
        iv. Trajectories of depression predict trajectories of attentional function in women with breast cancer during treatment with chemotherapy and up to six months following the end of treatment with chemotherapy, such that as levels of depression increase of

worsen, levels of attentional function decrease or worsen; and as levels of depression decrease or improve, levels of attentional function increase or improve.

Research Problem and Need for Study

In studies of women with breast cancer receiving chemotherapy, patients report problems with attentional function, depression, and fatigue. What is missing is an understanding of the level and rate of change in attentional function, depression, and fatigue during treatment with chemotherapy, which has implications for treatment, patient education, and scientific inquiry.

Significance

Millions of women in the United States and around the world are survivors of breast cancer. These women and their families live with cancer- and treatment-related symptoms during and following treatment. Problems with attentional function that emerge during treatment with chemotherapy can have a significant impact on quality of life, interfere with the ability to function in daily activities, and affect educational and career choices (Ahles & Saykin, 2002). In a web survey, women with breast cancer (N = 1071) ranked the ability to concentrate as one of the four most important of 21 factors related to quality of life (Hollen et al., 2009). Little is known about the level and trajectory of change of attentional function reported by women with breast cancer receiving chemotherapy for breast cancer, and this lack of information has implications for informed consent, assessment, preparatory information for patients, and safety. Currently, treatments for cognitive deficits acquired during treatment for cancer are being

investigated. These treatments include cognitive behavioral therapy (Ferguson, Riggs, Ahles, & Saykin, 2007), support groups (J. Myers & Sloma, 2009), acupuncture (Johnston et al., 2007), and yoga (Galantino et al., 2012). Better understanding of the initial levels and trajectories of attentional function, depression, and fatigue will help inform studies of mechanisms underlying cognitive problems that arise during cancer treatment, targeted intervention studies, and may help to improve the lives of women with breast cancer receiving treatment with chemotherapy.

CHAPTER 2

REVIEW OF LITERATURE AND THEORETICAL FRAMEWORK

This review of literature provides a background for the study of self-reported attentional function, depression, and fatigue before, during, and after treatment with cyclic cytotoxic chemotherapy in women with early stage breast cancer (Stage I – III). Limitations of existing research include studies that are cross-sectional in design, the recruitment of samples of people months and years after treatment, and the problem of heterogeneity of treatment received by subjects (Wefel et al., 2011). While women with breast cancer report problems with thinking, little is known about the levels and trajectories of change of attentional function, depression, and fatigue that occur in women with breast cancer being treated with chemotherapy. Initial levels, trajectories, and relationships among attentional function, depression, and fatigue will now be discussed in the context of the revised theory of unpleasant symptoms.

The Revised Theory of Unpleasant Symptoms

The revised theory of unpleasant symptoms (TUS) proposes that three categories of factors—physiological, psychological, and situational—affect one's predisposition to or manifestation of a given unpleasant symptom (Lenz et al., 1995). Each symptom can vary in duration, intensity, quality, and distress. In addition, the theory proposes that the level and nature of the symptom experience affect the patient's performance, which includes functional status, cognitive functioning, and physical performance (Lenz et al., 1995).

The TUS has been revised (Lenz, Pugh, Milligan, Gift, & Suppe, 1997), taking the theory from a purely linear model to a more interactive one and

allowing for the experience of multiple symptoms simultaneously (Lenz et al., 1997). The assumption behind the theory is that there are sufficient commonalities among symptoms to warrant a theory that is not limited to one symptom, but can explain and guide research and symptoms (Lenz et al., 1997). For example, the TUS attempts to achieve parsimony by proposing that some of the same factors may influence the experience of a number of different symptoms; consequently, similar interventions may be effective in alleviating more than one symptoms (Lenz et al., 1997). Symptoms can occur alone or in combination with other symptoms and can interact with one another. Feedback loops are included to show that antecedents can influence one or more symptoms, symptoms can influence performance, and performance can in turn affect both antecedents and further symptoms (Brant, Beck, & Miaskowski, 2010). A feedback loop provides some sense of the temporal nature of symptoms and the possibility for symptom recurrence. A representation of the TUS (Lenz et al., 1997) is presented in Figure 1. Current study concepts as they relate to the TUS are described below and are presented in the context of the TUS in Figure 2.

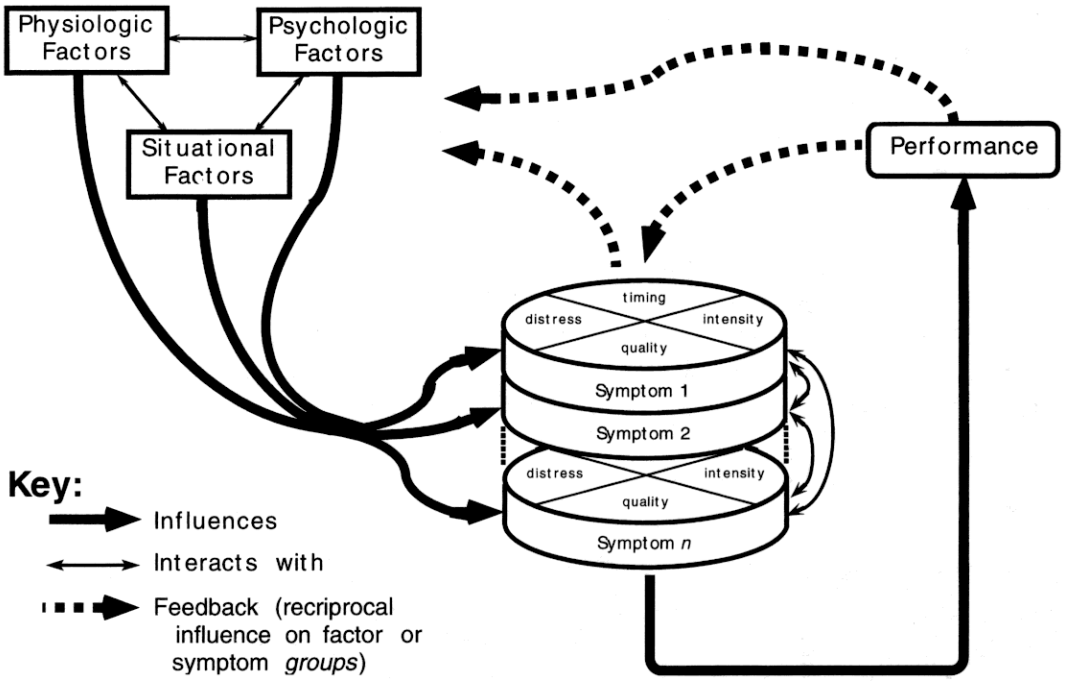


Figure 1. Revised theory of unpleasant symptoms. Adapted from "The middle-range theory of unpleasant symptoms: An update." By E.R. Lenz, K. R. Pugh, R. A. Milligan, A. G. Gift, and F. Suppe, F. ,1997, *Advances in Nursing Science, 19*(3), p.p. 14-27.

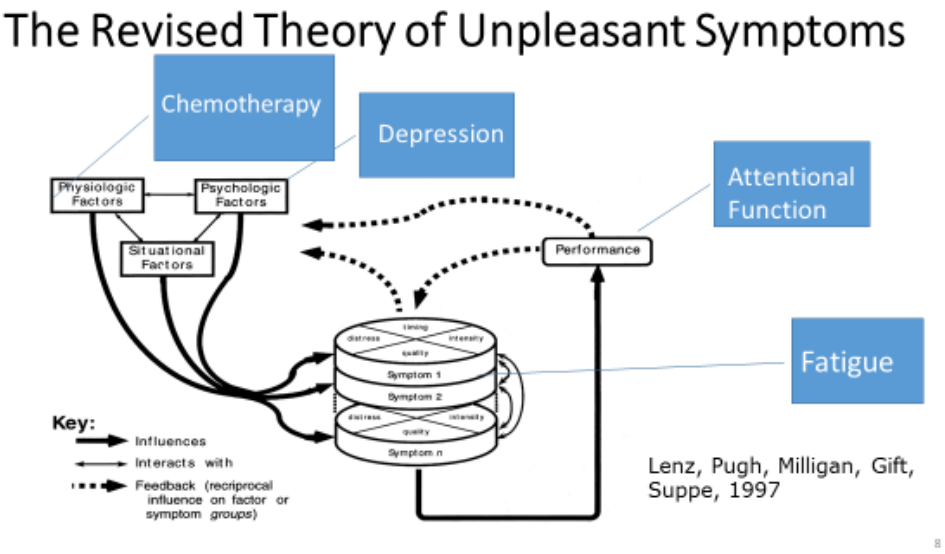


Figure 2. Proposed study concepts illustrated in the revised theory of unpleasant symptoms. "The middle-range theory of unpleasant symptoms: An update." By E.R. Lenz, K. R. Pugh, R. A. Milligan, A. G. Gift, and F. Suppe, F. ,1997, *Advances in Nursing Science, 19*(3), p.p. 14-27.

Performance – Attentional Function

In the TUS, *performance* is the outcome component. In the proposed study, attentional function is identified as the performance component. Performance is conceptualized to include functional and cognitive activities (Lenz et al., 1997). It has been demonstrated with a variety of symptoms that people with more numerous or more severe symptoms tend to have lower functional health status, less effective role performance, lower cognitive functioning, lower quality of life, and lower physical performance capabilities (Fawcett, Tulman, & Myers, 1988; Graydon, Ross, Webster, Goldstein, & Avendano, 1995; Lenz et al., 1997; Pugh & Milligan, 1995).

Ninety percent of women undergoing treatment with chemotherapy for breast cancer reported at least mild problems with attentional function (Downie et al., 2006). Following treatment with chemotherapy, 55% reported problems with attention and concentration (Von Ah et al., 2013). Attentional function is involved in centralizing brain or mental activities and the allocation of psychological resources (X. Chen et al., 2014; Cimprich, Visovatti, & Ronis, 2011; Lezak, Howieson, & Loring, 2004). There are both automatic processes—"bottom up" influence of ascending reticular activating system (ARAS)—and controlled aspects—"top down" influence of the cerebral cortex—of attentional function (Lezak et al., 2004; Mesulam, 2000). The ARAS stays in monitoring mode while the cerebral cortex prioritizes the work of the brain. A salient characteristic of the attentional system is its limited capacity. Attentional function requires mental effort such that engagement of the system in processing one attentional task calling on controlled attentional function can interfere with a second task having similar processing requirements (Cimprich et al., 2011; Kaplan, 1995; Lezak et al., 2004). When attentional deficits occur, all other cognitive functions may be intact and the person experiencing an attentional deficit may even be capable of some high-level performances, yet overall cognitive productivity suffers (Lezak et al., 2004). High levels of attentional function serve as the foundation for effective cognitive function. Thus, attentional function is an important outcome variable in the proposed study.

Symptoms – Fatigue

In the TUS, each symptom is considered a multidimensional experience, which can be conceptualized and measured separately or in combination with other symptoms. Although symptoms differ from one another, several dimensions are common across

symptoms and clinical populations: intensity (strength or severity), timing (duration and frequency of occurrence), level of distress perceived (degree of discomfort or bothersomeness), and quality (the way in which symptoms are manifest). Quality attributes tend to be specific to a given symptom; they portray its unique and essential nature (Lenz et al., 1997). These dimensions are assumed to be separable but related to one another (Lenz et al., 1997).

Cancer-related fatigue is defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (Berger et al., 2010). Fatigue is the most common unrelieved and distressing symptom related to cancer and cancer chemotherapy (Byar et al., 2006; Downie et al., 2006; Patrick et al., 2004). Estimates of the percentage of people who experience persistent fatigue for months and years following the completion of cancer treatment range from 10% to 38%; most studies are of women with breast cancer (Broeckel, Jacobsen, Balducci, Horton, & Lyman, 1998; Byar et al., 2006; Jacobsen et al., 1999; Servaes, Verhagen, & Bleijenberg, 2002). As many as 99% of women with breast cancer being treated with cancer chemotherapy experienced some level of fatigue during the course of treatment, and more than 60% rate the level of fatigue as moderate to severe (Bower et al., 2000; Byar et al., 2006; Jacobsen et al., 1999).

Fatigue experienced as a side effect of cancer treatment differs from acute fatigue in that the feelings of weakness and tiredness are not fully relieved by rest (Byar et al., 2006; D. Cella, Davis, Breitbart, & Curt, 2001). The intensity and duration of fatigue experienced by women with breast cancer undergoing treatment and women who have

completed breast cancer treatment are significantly greater than healthy controls (Andrykowski, Curran, & Lightner, 1998; Jacobsen et al., 1999). Higher levels of fatigue are associated with lower quality of life (Andrykowski et al., 1998; Byar et al., 2006; Curt, Breitbart, & Cella, 1999; Jacobsen et al., 1999).

Fatigue has been found to increase significantly after the first cycle of cancer chemotherapy and remain elevated during the following cycles of treatment (Byar et al., 2006; Donovan et al., 2004; Jacobsen et al., 1999). The most common pattern for daily fluctuations in fatigue is a sharp increase in the first 24 to 48 hours after chemotherapy; however, some women deviate from that pattern (Schwartz, 2000). Longitudinal studies designed to understand level and trajectory of fatigue during treatment with chemotherapy are needed.

Fatigue is significantly associated with depression (Bower et al., 2006; Bower et al., 2000; S. H. Kim et al., 2008; Meeske et al., 2007; Prue, Rankin, Allen, Gracey, & Cramp, 2006; Schultz et al., 2011; Stone & Minton, 2008). Fatigue and depression both are heterogeneous constructs with physical, cognitive and emotional dimensions and a high degree of overlap across the dimensions (Brown & Kroenke, 2009). In a review of 59 studies in cancer patients Brown and Kroenke (2009) found the average correlation between fatigue and depression weighted by sample size was 0.56. Longitudinal studies of fatigue and depression in people with cancer demonstrate that these symptoms do not exhibit the pattern that would be expected if the fatigue reported by people with cancer was a symptom of depression (Redeker, Lev, & Ruggiero, 2000; Visser & Smets, 1998). However, the results of longitudinal studies of people undergoing cancer treatment

indicate that unrelieved symptoms, including fatigue, are related to subsequent negative outcomes, such as depressed mood (Dodd, Miaskowski, & Paul, 2001).

Fatigue is associated with cognitive problems (D. Cella et al., 2001; Cull et al., 1996; Sadler et al., 2002; Servaes et al., 2002) and specifically problems with attentional function (Cull et al., 1996; Mehnert et al., 2007). Disease-free breast cancer patients with severe fatigue reported more problems with concentration and memory compared with non-severely fatigued breast cancer patients and with a group of women who had no history of breast cancer (Servaes et al., 2002). The proposed study is a novel exploration of the relationship between fatigue and attentional function before, during, and following treatment with chemotherapy.

Influencing Factors

In the TUS, there are variables identified as influencing factors. These influence the occurrence, intensity, timing, distress level, and quality of symptoms and are categorized as physiological factors, psychological factors and situational factors. The three categories relate to one another and may interact to influence the symptom experience (Lenz et al., 1997). For example, increased age, fewer years of education, and the presence of chronic illnesses have been associated with lower cognitive functioning in women newly diagnosed with breast cancer before start of treatment with chemotherapy (Cimprich, So, Ronis, & Trask, 2005).

Physiological factors. As identified by Myers (2009) in her model using the TUS to explain cognitive impairment from chemotherapy, conceptually likely significant physiological factors relevant to the proposed study include normal systems (intelligence quotient, genetic makeup, age) and pathological problems, such as chemotherapy-induced

anemia, inflammatory cytokines, low serum estradiol, low serum testosterone, comorbidities, concomitant therapies, and low levels of vitamin D. Anemia, as measured by hemoglobin levels, has been implicated in the occurrence of cognitive dysfunction after chemotherapy, but study results are inconclusive (Jacobsen et al., 2004; Tchen et al., 2003; Vearncombe et al., 2009). A few factors, such as longer treatment duration (Wieneke & Dienst, 1995) and use of adjuvant endocrine therapy (Bender et al., 2006; Castellon et al., 2004; Collins, Mackenzie, Bielajew, & Verma, 2009), are reported to be significantly associated with cognitive dysfunction following chemotherapy for breast cancer.

Situational factors. Situational factors are aspects of social and physical environments that may affect the individual's experience and reporting of symptoms. Lifestyle situational factors potentially relevant to this study include employment status, type of employment, and diet and exercise (J. S. Myers, 2009). Personal experience factors are marital status, social support, and educational level (J. S. Myers, 2009).

Psychological factors – depression. The psychological components of the TUS include the individual's mood, affective reaction to illness, and degree of uncertainty and knowledge about the symptoms and their possible meaning (Lenz et al., 1997). Research into a variety of symptoms has established that anxiety and depression contribute to their occurrence, severity, timing, distress, and quality (Dales, Spitzer, Schechter, & Suissa, 1989; Gift & Pugh, 1993; Leidy, 1990; Lenz et al., 1997; Pugh, 1990; Pugh & Milligan, 1995). Increased anxiety over the course of chemotherapy was found to significantly predict impairment in multiple cognitive measures (Vearncombe et al., 2009). Results from many studies indicate a strong positive relationship between depression and/or

anxiety and self-report of cognitive dysfunction (Castellon et al., 2004; Cimprich et al., 2005; Cull et al., 1996; Hermelink et al., 2010; Jenkins et al., 2006; Pullens et al., 2010; Van Dam et al., 1998). Depression is proposed as an influencing psychological factor in the study of changes in attentional function in women with breast cancer being treated with chemotherapy.

Reports of prevalence of depression in people with cancer vary widely and occur in a broad spectrum from sadness to major affective disorder (Massie, 2004). Major depression is reported in 0–38% of patients with cancer (referred for psychiatric evaluation) while depression spectrum syndrome (adjustment disorder with depressed mood according to DSM-III) is reported in 0%–58% (Massie, 2004). In breast cancer the prevalence is 0%–48% (Burgess et al., 2005; Massie, 2004). Lack of standardization (population studied, disease site and stage, sample size, assessment instruments, cutoff score, type of interview, and diagnostic criteria employed) contributes to the large variance in reported prevalence of depression in cancer patients (Massie, 2004). In the current study participants were screened and excluded for clinical depression (Center for Epidemiological Studies, Depression (CESD scale score > 27). It is generally accepted that depression and anxiety are more commonly found amongst cancer patients than in the general population and that the prevalence of clinically significant morbidity following treatment is in the region of 25–33% (Sellick & Crooks, 1999).

Depression has been shown to affect cognitive function, specifically attentional function and memory in the general population (Airaksinen, Larsson, Lundberg, & Forsell, 2004; Austin, Mitchell, & Goodwin, 2001) and in people with cancer (Downie et al., 2006; Kayl, Collins, & Wefel, 2012; Tarbuck & Paykel, 1995). Research in adult

disease-free lymphoma patients found that those with memory and concentration problems had significantly higher levels of depression compared to patients without such problems (Cull et al., 1996). However, findings have been mixed in breast cancer survivors. Some studies have found that self-reported cognitive impairments were significantly related to depression in breast cancer survivors (Castellon et al., 2004; Cimprich et al., 2005; Jenkins et al., 2006; Schagen et al., 1999; Van Dam et al., 1998; Von Ah, Russell, Storniolo, & Carpenter, 2009) whereas others have not (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Tchen et al., 2003). Only one study has specifically examined the relationship between self-reported attentional function, as measured by the attentional function index (AFI), and depression in patients with breast cancer (Von Ah, Russell, et al., 2009). In Von Ah's study of 184 patients with breast cancer prior to surgery, deficits in attentional function were positively related to higher depression ($r = 0.62$; $p < 0.001$) (Von Ah, Russell, et al., 2009). The relationship between attentional function and depression will be further explored in the current study.

Clinically Important Measurement Times for Attentional Function

Women with breast cancer report problems with attentional function before, during, and after treatment (X. Chen et al., 2014; Correa & Ahles, 2008; Frank, Vance, Jukkala, & Meneses, 2014). Study measurement times accomplished at clinically significant points in treatment are a strength of this study and are described below.

Prior to initiation of chemotherapy

Cimprich and colleagues (2005), who studied a sample of 184 women with early stage breast cancer, found that 50% reported moderately effective attentional functioning while 25% indicated deficits in ability to direct attentional function prior to receiving

chemotherapy. Fifty percent of 124 breast cancer patients rated themselves as having deficits in attentional function after surgery and before initiation of chemotherapy (Debess, Riis, Pedersen, & Ewertz, 2009). And in a study of 200 women with breast cancer, mean scores for self-reported attentional function dropped dramatically from levels measured before surgery to one month after surgery with a trend in improvement in attentional function up to two years after surgery (M. L. Chen et al., 2012). Lower than expected levels of attentional function measured prior to initiation of chemotherapy may be related to recent surgery, to an emotional response to a new diagnosis, to sleep dysregulation, and/or to removal of estrogen replacement therapy (Vearncombe et al., 2009). To account for wide variability in level of attentional function before initiation of chemotherapy a baseline measurement prior to initiation of chemotherapy is important for a longitudinal study of reports of attentional function during and following treatment with chemotherapy.

Mid-treatment with chemotherapy

Few studies have reported on levels of attentional function reported by women with breast cancer during the four to six months required of most chemotherapy treatment regimens. In a study of women measured before surgery and periodically for two years after surgery for breast cancer, Chen, Miaskowski, Liu & Chen (2012) (N = 200) found the mean score on the AFI (modified to a 0 to 10 scale with a higher number indicating better attentional function) prior to surgery to be 8.17, SE = .148. Statistically significant decrements in AFI scores were found from prior to surgery to one month after surgery (6.66, SE = .155, $p < .001$), two months after surgery (6.97, SE = .158, $p < .001$), three

months after surgery (7.09, SE = .161, p < .001), four months after surgery (6.89, SE = .161, p < 0 .001), five months after surgery (6.98, SE = .165, p < .001), six months after surgery (7.34, SE = .169, p < .001), eight months after surgery (7.17, SE = .179, p < .001) and 10 months after surgery (7.32, SE = .186, p < .001). Women in this sample received adjuvant treatment with some beginning chemotherapy, radiation therapy, and/or hormone therapy prior to the one month post-surgery data collection point. Except for hormone therapy, treatment was completed between four and twelve months following surgery. For measurements at 12, 18 and 24 months after surgery the mean difference from baseline is not significant, and by 24 months after surgery the mean AFI score of 8.20, SE = .189, was at the level reported prior to surgery. Chen et al. (2012) described a nonlinear model of change in attentional function with a dramatic decrease (worsening) in attentional function between the pre-surgery measure and one month after surgery and gradual return to pre-surgery baseline by 12 months after surgery.

End of chemotherapy treatment

Measurements at the end of chemotherapy treatment indicate that women with breast cancer report worse attentional function than at baseline. Shortly after completion of chemotherapy, 90% of 21 breast cancer survivors reported difficulties with attentional function that affect many aspects of life (Downie et al., 2006). Nine of 18 breast cancer survivors described difficulties with attentional function after completion of treatment with chemotherapy, including difficulty focusing on the plot when reading a novel, difficulty paying bills, and trouble multitasking (J. S. Myers, 2012).

Follow-up after chemotherapy.

Of the women who report problems with attentional function during chemotherapy treatment, some return to pretreatment levels at follow-up and others do not, as demonstrated in a study by Weis, Poppelreuter & Bartsch (2009), where nine months after the end of chemotherapy treatment 32% of breast cancer survivors judged their everyday cognitive function as being very poor. Also, six years post-diagnosis, 26% of 132 women reporting on their current attentional function were categorized as having poor capacity to direct attentional function as based on previously established cutoff scores for the attentional function index (Von Ah, Harvison, et al., 2009).

Trajectories

Recent studies have begun to describe a trajectory of attentional function in women with breast cancer before, during, and after surgical treatment and radiation treatment. In a study by Chen et al. (2012) (N = 200), self-reported attentional function was assessed prior to surgery for breast cancer. Reliable change analyses indicate a decrease in attentional function in 54% of women one month after surgery and 30% of women in the study at 24 months after measurement before surgery. The reliable change index is a statistical measure of change that takes into account both the population variance and the reliability of the test, in this case the attentional function index (AFI). The baseline reliability and standard deviation of the AFI were used to calculate the reliable change index. In the Chen (2012) study, change in attentional function was determined using a 90% reliable change interval from baseline. Analysis of attentional function over time, using a mixed effects model with time as a fixed effect, indicated a significant time effect ($F = 17.58$, $p < .001$). Post-hoc tests indicated that levels of

attentional function at 1, 2, 3, 4, 5, 6, 8 and 10 months were all significant lower (worse) than at baseline. In the Chen (2012) study attentional function was significantly inversely correlated with anxiety (r = -.43 to -.70, $p < .001$), depression (r = -.53 to -.74, $p < .001$), fatigue (r = -.49 to -.74, $p < .001$) and sleep disturbance (r = -.43 to -.64, $p < .001$) at each point in time, indicating that that as anxiety, depression, fatigue, and sleep disturbance worsened, attentional function worsened. Age and menopausal status were not correlated with attentional function. Women in this study experienced a range of post-surgical anti-cancer treatments. The Chen study begins to describe levels and trajectories of attentional function, depression, and fatigue in a surgical population of women with breast cancer.

Merriman et al., (2010) in a study (N = 73) of trajectories of reported attentional function in a population of women with breast cancer receiving radiation therapy, reversed the scoring of the AFI so that higher scores indicated lower levels of attentional function. Measures were taken before, during, and after radiation treatment and analyzed with descriptive statistics and hierarchical linear modeling, Merriman et al. (2010) found the trajectory for attentional function to be a best fit in a linear model. In the unconditional (no covariates) model the estimated linear weekly rate of change in AFI scores was .022 (p = 0.003). The variance in individual change parameters estimated by the model (variance components, intercept = 1.185, $p < .0001$; linear rate = .001, $p < .0001$) suggested that substantial inter-individual differences existed in the trajectories of attentional function. Merriman et al. (2010) found that before start of radiation, worse attentional function was associated with younger age, not working, a higher number of comorbidities, and higher levels of trait anxiety. Interestingly, the only predictor of difference in the trajectory of attentional function was body mass index; the trajectory in

attentional function over time indicated improvement for women with higher BMI at baseline (Merriman et al., 2010).

In a separate study (N = 397) by Merriman et al. (2014), the initial assessment was performed a mean of 4 days prior to surgery for breast cancer with follow-up questionnaires completed each month for six months after surgery. Merriman et al. (2014) used growth mixture modeling to identify three distinct classes of attentional function (measured with AFI, not reverse coded in this study) trajectories in women with breast cancer receiving treatment. Patients in the high attentional function class (41.6%) had estimated AFI scores of 7.78 (adjusted 0–10 scale, higher score indicates better function) at enrollment that increased significantly and remained high through the study period of 6 months after surgery. Patients in the moderate attentional function class (25.4%) had estimated AFI scores of 6.58 at enrollment that decreased until the measurement at 3 months after surgery and then increased significantly but remained in the moderate class as determined by the model. Patients in the low-moderate attentional function class (33.0%) had estimated AFI scores of 5.23 at enrollment that did not change significantly during the study. Using a backwards stepwise approach, only age, comorbidities, and functional status significantly predicted class membership in multivariate models unadjusted for genotype. For each five-year increase in age, patients had a 12% decrease in the odds of belonging to a lower attentional function class. For every one-point increase in self-administered comorbidity questionnaire score (i.e., comorbidities), patients had a 14% increase in the odds of belonging to a lower attentional function class. For every 10-point increase in KPS score (increase in functional status) patient had a 30% decrease in the odds of belonging to a lower

attentional function class. The secondary aim of the Merriman et al. (2014) study was to evaluate for phenotypic and genotypic characteristics associated with latent class membership. Controlling for age, comorbidities, functional status, and population stratification due to race/ethnicity, the model fit for IL1R1 rs949963 (interleukin reception type 1) remained significant ($p < .001$). The final model explained 7.5% of variance in class membership ($p < .001$). Controlling for covariates, carrying the rare A allele (i.e., GA or AA genotype) was associated with a twofold increase in the odds of belonging to a lower attentional function class. Women in the Merriman et al. (2014) study had breast cancer stage 0–IV and experienced a range of postsurgical treatments (adjuvant chemotherapy, radiation therapy, estrogen receptor positive, progesterone receptor positive, HER2/neu positive and hormone replacement therapy before diagnosis). In the Merriman study, staging and treatment factors were not statistically significant predictors of group membership.

There is mounting evidence describing and explaining trajectories of change of attentional function during treatment for breast cancer. Chen et al. (2012) found a dramatic decrease in attentional function one month after surgery with a gradual return to baseline, while Merriman et al. found subtler gradual increases following before-surgery (2014) and a before-start-of-radiation (2010) measurement of attentional function. All three studies found a wide inter-individual variability and some interesting relationships with demographic and clinical factors, as noted above. The current study assessed the level of trajectory of attentional function at measurement times tied to chemotherapy treatment landmarks, rather than to surgery, radiation, or calendar-driven intervals of time.

Measurement of Attentional Function in Relation to Timing of Delivery of Chemotherapy.

The current study measurements were taken before administration of each relevant cycle of chemotherapy (i.e., First Day of Chemotherapy, Mid-treatment, and Treatment End). The precise timing is significant as it differs from prior studies when precise timing of assessment is not reported. Our timing minimizes the potential influence of medications given in conjunction with administration of chemotherapy, such as anti-emetics, anti-anxiety drugs, and steroids, all of which may be related to reported attentional function. The feasibility of measuring attentional function and other variables immediately prior to delivery of chemotherapy is limited as it requires high diligence on the part of the research team and the study participants. This secondary analysis of two existing datasets that include data with specific timing of data collection that minimizes confounds seen in other studies maximizes the contributions made by the work of the original team of investigators and the study subjects.

Symptom Clusters

Patients rarely present with a single symptom. Lenz's et al. (1997) TUS asserts the presence of multiple symptoms that influence one another. Symptom cluster research examines complex interrelationships between multiple concurrent symptoms and their mechanisms (Aktas, 2013). Evidence points to a cluster of psychoneurological symptoms—depressive symptoms, cognitive disturbance, fatigue, sleep disturbance, and pain (H. J. Kim, Barsevick, Beck, & Dudley, 2012; H. J. Kim, Barsevick, Fang, & Miaskowski, 2012; Moskowitz, Feuerstein, & Tood, 2013; So et al., 2009)—that may

have an underlying inflammation and neural signaling mechanism (H. J. Kim, Barsevick, Fang, et al., 2012; Wood & Weymann, 2013).

The science of symptom management has evolved from a focus on single symptoms to the exploration of symptom clusters. A systematic review of 18 studies showed that 30% of cancer patients experienced more than five concurrent symptoms (Esther, Dodd, & Aouizerat, 2009). It has been proposed that consistent clusters are those that have similar *core* symptoms over time (Aktas, 2013). Research has also shown that a *sentinel* symptom can predict the presence of other relevant symptoms within a cluster (Aktas, 2013). Lagged symptom changes were examined using a latent change score model approach to evaluate the proposed symptom cluster of sleep disturbance, fatigue, and depressed mood in patients treated with chemotherapy (Jim, Phillips, Roberts, & Small, 2013). The study's findings suggest that sleep disturbance, fatigue, and depressed mood occur in a cascade pattern during chemotherapy, in which increases in sleep disturbance contribute to fatigue, which, in turn, contributes to depressed mood (Jim et al., 2013). Studying the complex symptoms of oncology patients will yield increased understanding of the patterns of association, interaction, and synergy of symptoms (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006).

Significance and Summary

Prior studies have had methodological problems including use of cross-sectional design, inclusion of heterogeneous cancer diagnoses and heterogeneous treatment regimens, and lack of consistent definition of cognitive impairment. The current study addresses shortcomings of prior studies and moves the science forward by looking at clinically relevant points in time in the treatment trajectory, including a measurement

time prior to start of chemotherapy, by recognizing the sensitivity of reported attentional function to the effects of chemotherapy, by examining trajectories of change in attentional function over time in women with breast cancer being treated with chemotherapy, and by assessing relationships between initial level and trajectory of change in attentional function, fatigue, and depression.

CHAPTER 3

RESEARCH DESIGN AND METHODS

This pilot study examined how ratings of attentional function, depression, and fatigue change during treatment with chemotherapy in women with breast cancer and how ratings of attentional function, depression, and fatigue are related to one another. This study is a secondary analysis of data provided by two studies of women with early stage (Stage I–III) breast cancer receiving treatment with chemotherapy. Lisa Wood, PhD, is the principal investigator of both studies. Study 1 provides data for Sample 1, and Study 2 provides data for Sample 2:

(a) Study 1: "Mechanisms of Cancer Treatment Related Symptoms," 5R01NR012479, The National Institute for Nursing Research;

(b) Study 2: "Cytokine response to subclinical cytomegalovirus reactivation as a cause of severe fatigue in women undergoing chemotherapy for breast cancer," BCRP W81XWH-11-1-0456. Department of Defense Breast Cancer Research Program, Collaborative Idea Award

The studies were designed to further understanding of the molecular mechanisms underlying the initiation and perpetuation of cancer treatment-related symptoms, specifically fatigue. Of particular interest was the cytokine response to subclinical cytomegalovirus (CMV) reactivation as a possible cause of severe fatigue in women undergoing chemotherapy for breast cancer. Related to primary and secondary parent-study aims, the following data were collected: clinical and demographic information, lifetime traumatic events, caloric intake, fall history, depression, well-being, attentional

function, fatigue, biomarkers for CMV, use of complementary and alternative medicine, body composition, and physical activity. From these studies, data on clinical and demographic information, as well as depression, fatigue, and attentional function over time were used in the current study.

In this chapter the study design and methods will be described, including the setting, sample, and data collection methods. The limitations and benefits of doing a secondary analysis will be discussed. Finally, the planned statistical approach will be presented, explaining how multilevel modeling is well suited for characterizing initial levels and trajectories of attentional function, depression, and fatigue.

Research Methods

Study Design

This study utilized a prospective longitudinal study design which included data collection at four (Sample 1) or five (Sample 2) clinically significant points in time: before the first dose of chemotherapy (First Day of Chemotherapy), during treatment with chemotherapy (Mid-Treatment), at the end of treatment with chemotherapy (End of Treatment), and three to six months after the end of treatment with chemotherapy (Follow-Up). Sample 2 has an additional measurement time before the first dose of chemotherapy (Prior to Chemotherapy). The research questions are: 1) How do levels of self-reported attentional function, fatigue, and depression change over time from before initiation of chemotherapy to three to six months after completion of chemotherapy in women with breast cancer? 2) Do levels of fatigue and depression predict levels of attentional function in women with breast cancer being treated with chemotherapy?

Subjects were enrolled over a four-year period, 2009 to 2013, for Sample 1 and through 2014 for Sample 2. Sample 1 provides data on 25 participants (one participant withdrew after the first measurement time), measured at four times. Sample 2 provides data on 44 participants measured at five times.

Secondary Analysis. Secondary analysis is the use of existing databases to investigate research questions other than those for which the data were originally gathered. The principal investigator in a secondary analysis is not involved in data gathering, cleaning, and storage in the original study (Stewart & Kamins, 1993). Analyzing data from an existing database may be a viable, and perhaps preferable, option (Nicoll & Beyea, 1999) to answer research questions compared to designing and implementing a new study. Advantages of a secondary data analysis are that it may be more cost-effective and a more efficient use of time than gathering and analyzing primary data (Nicoll & Beyea, 1999). A secondary analysis may generate new insights, different from the original intent and scope of the parent study. For the proposed study, performing a secondary analysis takes advantage of pertinent data collected at a clinically significant time, using valid, reliable and sensitive instruments, and using already-collected data, which decreases the burden of collecting data in another prospective study on the breast cancer population.

For this study, the feasibility of conducting a secondary analysis was first addressed by determining that the research questions could be answered using the data from the parent study. This was accomplished by careful review of the parent study proposal. Also, the appropriateness of the measurement instruments used in the parent

study to answer research questions in the proposed study was established. A detailed discussion of measurement instruments is provided below.

Longitudinal data. Measurement of study variables over time provides points of comparison to baseline (i.e., before the start of chemotherapy). The second important aspect of time in the proposed study is the change over time of attentional function as compared with change in fatigue and change in depression. In the parent study, fatigue and depression were measured at the same points in time as was attentional function, and thus provide data for the study of change in fatigue and depression before, during, and after chemotherapy as well as data for the study of relationships among depression, fatigue, and attentional function.

Sample and Setting. Sample 1 and Sample 2 are both convenience samples of women with early breast cancer (Stages I–III) who were scheduled to receive chemotherapy. Women were recruited from Oregon Health & Science University (OHSU) Knight Cancer Institute (Sample 1) or Massachusetts General Hospital (Sample 2) either before or after primary treatment with surgery but before receiving chemotherapy. Women were referred by their oncologists to a study coordinator for assessment of eligibility to participate in the study. Inclusion criteria were women 18–80 years of age with stage 0–III breast cancer whose treatment would minimally include chemotherapy and granulocyte stimulating factor (GCSF) at two- or three-week intervals. Exclusion criteria for the parent study were patients with inflammatory breast cancer, women who were pregnant or became pregnant during the study, women who had received chemotherapy, radiation, or certain other medications for cancer in the past

twelve months, those who rated their pretreatment fatigue levels as 10 on a 1–10 scale, and those who scored above 27 on the Center for Epidemiologic Studies Depression Scale (CESD) (Radloff, 1977). Patients experiencing level 10 of fatigue before the start of the study have no variability left to measure in the study, and a score above 27 on the CESD reliably detects clinically depressed patients (Thomas, Jones, Scarinci, Mehan, & Brantley, 2001; Zich, Attkisson, & Greenfield, 1990).

Data collection. Potential study participants were approached, and those who agreed provided written informed consent and completed baseline data collection prior to receiving any chemotherapy. Data collection was accomplished at the time of regularly scheduled appointments with the treating oncologist in the outpatient oncology clinic immediately prior to administration of chemotherapy. All data collection was done by research associates who were part of the study team. There were no additional data collected for this study.

Measurement Instruments

The measurement instruments and detailed information on each tool to be used in the proposed study is provided in Table 1.

Table 1

Description of Measurement Instruments, Reliability and Validity

Concept	Instrument	Reliability	Validity
Attentional Function	Attentional Function Index (AFI), 13-item, 100 mm visual analogue scale measuring perceived effectiveness in daily activities "at this time." Mean scale scores 0 – 100. Higher scores indicate better functioning.	Internal consistency α = .92 total scale	Convergent: total AFI and concentration item SDS (r = -.58, p < .01) and total CFQ (r = -.60, p < .01) Divergent: Total AFI and confusion subscale, POMS-SF (r = -.*59*, p < . 01) Predictive: mental fatigue on SDS [F (3, 167) = 33.27, p < .001). AFI did not predict physical fatigue, SDS
Fatigue, feelings	Schwartz Cancer Fatigue Scale (SCFS), 6-item, 1-5 scale in past "2-3 days" Scale scores total 6 – 30. Higher scores indicate worse fatigue.	Internal Consistency α = .80	Content: panel of patients and nurses Convergent: POMS, LFS, MAF Divergent: significant differences those in cancer treatment versus those who had completed treatment and exercisers versus non-exercisers
Fatigue, impact on quality of life	PROMIS, 8-item, 1-5 scale, "past 7 days" items #1-6 fatigue experience, items #7-8 interference. Scale scores total 8 – 40. Higher scores indicate worse fatigue.	Measurement precision along the continuum, r > .91 for scores ranging from 2 SD < the mean to 4 SD > the mean	Convergent: FACIT-FS (r = .95) Divergent: SF-36 vitality scale, (r = -.89)
Depression	Center for Epidemiological Studies – Depression (CESD), 20-item, "during the past week." Scale scores total 0 – 60. Higher score	Internal consistency α > .85 Test retest reliability: treatment group .57, p < .001 versus healthy control .51, p < .001	Construct: Patients versus healthy controls (Time 1, F = 4.71, p < .05 and Time 2, F = 11.72,p < .001); fatigue (POMS-F, r = .66, p < .001), anxiety

Concept	Instrument	Reliability	Validity
	indicates worse depression.		(STAI-S, $r = .77$, $p < .001$), and global mental health functioning (SF-36 MHSS, $r = .6$, $p < .001$)

A copy of each measure is provided in Appendices A, B, and C. Below is a brief description of measurement instruments used to collect data for the secondary analysis.

Attentional function. Attentional function was measured by the 13-item attentional function index (AFI) (Cimprich et al., 2011). The AFI uses 100 mm horizontal line visual analogue scales for each of the 13 items. Each item has a possible score of 0–100. The first nine items of the AFI ask for responses to the prompt, "Place a mark through the line at whatever point best describes how you are doing in each area at present" for such items as "Getting started on activities (tasks, jobs) you intend to do." The visual analog scales are anchored with "Not at all" and "Extremely well." The last 4 questions ask for responses to the prompt, "At this time, how would you rate yourself on:" items such as "How hard you find it to concentrate on details." Anchors for the last 4 questions are "Not at all" and "A great deal." The first 9 questions are positively worded. The respondent is then given a new set of directions for responding to the last 4 questions, which are negatively worded. Scores on the last 4 items are reversed so that higher scores indicate better attentional function. The total score on the instrument is computed by averaging responses on the 13 items.

The AFI measures perceived effectiveness in daily activities, "at this time," that require attentional function and working memory to be performed well (Cimprich et al., 2011). The first 9 items were derived from Lezak's (Lezak et al., 2004) four components of executive functioning, including goal formulation, planning, carrying out activities, and monitoring effective performance (Cimprich et al., 2011). The last 4 items of the AFI were formulated to assess behavioral and affective responses associated with a lowered capacity to direct attentional function, including making mistakes, forgetting, irritability, and impatience (Cimprich, 1993).The AFI provides insight into the loss of personal effectiveness resulting from problems with attentional function and working memory. The AFI has three subscales: (1) The effective action subscale includes seven items assessing an individual's perceived effectiveness in carrying out basic activities in daily living that require focused attentional function; (2) the attentional function lapses subscale includes three items measuring perceived difficulties in directing attentional function in daily tasks; and (3) the interpersonal effectiveness subscale includes three items reflecting perceived ability to interact in a deliberate manner that depends on attentional or inhibitory effort. The proposed study will use the AFI total score of the AFI based on all thirteen items.

Reliability of the AFI was evaluated in the samples for this study this study by computing an internal consistency coefficient (Cronbach's α) for the total scale at each measurement time. (See results in Chapter 4.) Prior studies reported internal consistency reliability for the 13-item scale at 0.92 and at 0.80 to 0.92 for the three subscales (Cimprich et al., 2011), which is above the acceptable range of 0.70–0.80 (Nunnally &

Bernstein, 1994). The AFI demonstrated strong item-total correlations, indicating a good ability to discriminate between high and low scores (Cimprich et al., 2011).

Factor analysis, specifically principal exploratory component analysis, was used to determine construct validity for the 13-item instrument (Cimprich et al., 2011). In a sample of 172 women with breast cancer, evaluated after diagnosis had been revealed to them and before surgery for breast cancer treatment, findings indicate a significant Bartlett's test [χ^2 (78, N = 172) = 1581.94, p = < .001], a Kaiser-Meyer-Olkin (KMO) measure of 0.89 and item communalities > .60. Bartlett's test of sphericity tests the hypothesis that all of the variables are uncorrelated. The significant value for this analysis leads us to reject the null hypothesis and conclude that there are correlations in the dataset that are appropriate for factor analysis. The KMO is a measure of sampling adequacy (.80–.90 great) (Cerny & Kaiser, 1977). The amount of variance in each variable that can be explained by the retained (three) factors is represented by the communalities (Carless, 2004). These factors become the three subscales: (a) The effective action subscale (b) The attention lapses subscale and (c) The interpersonal effectiveness subscale

Convergent validity of the AFI was tested in a sample of 172 women, newly diagnosed with breast cancer (Cimprich et al., 2011) by: (a) assessing the correlation between the total score of the AFI and the scores on the concentration item in the Symptom Distress Scale (SDS), an instrument which is widely used as a symptom measure in studies of people with cancer (McCorkle & Young, 1978)). A significant negative correlation was found between the AFI total score and the SDS concentration

item (r = -0.58, p < 0.01), indicating that higher overall effectiveness in attentional function was associated with less difficulty concentrating; and (b) assessing the correlation between the total scores on the AFI and the total scores on the Cognitive Failures Questionnaire (CFQ) (Broadbent, Cooper, FitzGerald, & Parker, 1982). A significant negative correlation was found between AFI total scores and the scores on the CFQ (r = -.60, p < .01), indicating that as attentional function scores improved, reported cognitive failures decreased (Cimprich et al., 2011).

Divergent validity helps to establish construct validity by demonstrating that the construct of interest (attentional function) is different from other constructs that might be present in the study (fatigue and depression). Divergent validity of the AFI has been tested by: (a) assessing the correlation between total scores on the AFI and total scores on the confusion subscale of the Profile of Mood States-Short Form (POMS-SF) (McNair, Lorr, & Droppleman, 1992), and as expected, a significant negative correlation between AFI scores and POMS-SF confusion subscale total (r = - .59, p < .01) suggests that as AFI scores increased (better attentional function), confusion decreased; and (b) assessing the predictive validity of the AFI for self-ratings of mental and physical fatigue using related items on the SDS. A multiple regression analysis indicated a significant relationship between total AFI scores and scores on the SDS item of mental fatigue. The total score on the revised AFI instrument predicted mental fatigue. The AFI total score did not predict physical fatigue (results for physical fatigue are not provided). Evidence of discriminant validity is important as the proposed study is designed to investigate the relationships among attentional function, cancer-related fatigue, and depression.

Demographic and clinical variables. Relationships between conceptually significant demographic and clinical variables and attentional function were assessed as part of the preliminary data analysis of the proposed study. The questionnaire (Appendix D) includes questions about age, ethnicity, level of education attained, income and work status, relationship status, cancer type, prior and current cancer treatment (such as hormone manipulation), menopausal status (pre-, peri-, meno- and postmenopausal), use of hormone replacement therapy, use of other prescription and over-the-counter medications, co-morbidities, and use of tobacco products. While clinically significant variables with statistically significant relationships with attentional function were considered for inclusion in multivariate analyses, sample sizes limited the number of variables that could be included.

Fatigue. Fatigue was measured with two measurement instruments, the Schwartz Cancer Fatigue Scale (SCFS),(Schwartz, 1998) and the PROMIS 8a Fatigue scale (PROMIS) (D. Cella et al., 2010). The scales are complementary. The SCFS was developed as a multidimensional measure of fatigue for use with cancer patients, and PROMIS was developed to measure the impact of a chronic condition on health-related quality of life. Each scale provides a single summative result which will be assessed for significance, directionality and magnitude of relationship with attentional function..

The SCFS is a brief, six-item scale asking participants to rate, in the past two to three days, how much their fatigue has made them feel tired, have difficulty thinking, overcome, listless, worn-out, and hopeless. Participants are asked to rate their feelings on a 1–5 scale where 1 = not at all, 2 = a little, 3 = moderately, 4 = quite a bit, 5 = extremely.

Scores for the items were summed with total scores that range from 6–36 with higher score indicating greater fatigue.

Reliability of the SCFS scale was evaluated in the samples from the current study by computing an internal consistency coefficient (Cronbach's α) for the total scale at each measurement time. (See results in Chapter 4.) Previous internal consistency reliability has been established for the total scale with a Cronbach's α 0.90 (Schwartz, 1998; Schwartz & Meek, 1999).

In cancer patients, content validity of the SCFS has been established with a panel of patients and nurses (Schwartz & Meek, 1999) and also in Schwartz and Meek (Schwartz & Meek, 1999) convergent validity with Profile of Mood States fatigue Scale (POMS, (McNair et al., 1992), Lee Fatigue Scale (Lee, Hicks, & Nino-Murcia, 1991) and Multidimensional Assessment of Fatigue Scale (Smets, Gerseen, Bonke, & DeHaes, 1995). Divergent validity has been established through known group comparisons by demonstrating significant differences in the expected direction on SCFS scores of participants undergoing cancer treatment compared to scores of those who had completed treated and scores of exercisers compared to non-exercisers (Schwartz & Meek, 2000; Wilkie et al., 2001).

The PROMIS was created to measure the impact of fatigue on quality of life in the past 7 days. PROMIS is part of the National Institutes of Health Patient Reported Outcomes Measurement Information System (PROMIS). PROMIS is a system of highly reliable, precise measures of patient-reported health status for physical, mental, and social well-being, building and validating instruments that measure feelings, functions, and

perceptions applicable to a range of chronic conditions, enabling efficient and interpretable clinical research and clinical practice application of patient-reported outcomes. PROMIS utilized rigorous methodology for developing its measures and testing their validity (D. Cella et al., 2010).

Survey items for PROMIS measures have been developed using item response theory. From the PROMIS item bank previously developed, the 95-item fatigue item bank was calibrated on a sample of 21,133, measuring components of self-reported fatigue. An eight-item short form from the bank of 95 fatigue questions was developed by a team of PROMIS investigators, consisting of experts in the measurement and assessment of fatigue (D. Cella et al., 2010). A 7-day recall period was chosen for PROMIS scales based on recent studies suggesting reasonably high correspondence between real-time symptom reports and 7-day recall of the same symptoms and a correlation greater than 0.90 with a daily diary and a 2-week recall instrument, suggesting minimal recall bias (D. Cella et al., 2010).

The PROMIS Fatigue short form was created to sample from items assessing both fatigue experience and interference. For the first two questions, participants are instructed to consider the timeframe of "During the past 7 days…" and respond to the prompts, "I feel fatigued…," and "I have trouble starting things because I am tired…" using a scale of 1 to 5 where 1 = not at all, 2 = a little bit, 3 = somewhat, 4 = quite a bit, and 5 = very much. For the next four items the prompt is "In the past 7 days…" and respondents are asked to respond to the questions "How run-down did you feel on average?" "How fatigued were you on average?" "How much were you bothered by your fatigue on

average?" And "To what degree did your fatigue interfere with your physical functioning?" using the same 1–5 scale as above. Finally, in the last two questions the responses change. The prompt for the last two questions is, again, "In the past 7 days…" and the questions, "How often did you have to push yourself to get things done because of your fatigue?" and "How often did you have trouble finishing things because of your fatigue?" Respondents are asked to respond using a 1–5 scale where 1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = always. The raw score for the scale is a sum of responses to all eight items and ranges from 8 to 40 for each participant, with higher sums indicating higher fatigue.

Correlations between scores on the PROMIS 95-item fatigue bank of items and scores on the short form for fatigue were $r = .76$ (D. Cella et al., 2010). As noted previously, the fatigue short form was designed to sample across content, which includes both the fatigue experience and interference, which might explain the relatively low correlation between the larger fatigue item bank and the short form items (FACIT.ORG, 2007). Reliability, as defined by measurement precision along the continuum, was strong with a correlation of $r > .91$ for scores ranging from 2 standard deviation (SD) less than the mean to 4 SDs greater than the mean (D Cella, Jacobsen, & Orav, 1987; D. Cella et al., 2010). Reliability of the PROMIS scale was evaluated in the samples from the current study by computing an internal consistency coefficient (Cronbach's α) for the total scale at each measurement time. (See results in Chapter 4.)

Construct validity for PROMIS was supported by strong correlations with well-validated and widely accepted measures: the Functional Assessment of Chronic Illness

Therapy (FACIT)-Fatigue Scale (Webster, Cella, & Yost, 2003; Webster, Odom, Peterman, & Cella, 1999) (*r* = .95), and the SF-36 Vitality scale (Ware, Kosinski, & Keller, 1994) (*r* = -.89. Cella et al. (2010) report the relationship between PROMIS 8a Fatigue and SF-36 Vitality scale as a positive correlation. Conceptually and per an article by Bjorner et al. (2007), vitality scores on the SF-VS are negatively associated with fatigue such that as fatigue increases vitality decreases. The FACIT-Fatigue Scale comparison provides convergent validity, and SF-36 VS scale comparison provides divergent validity.

Depression. The 20-item Center for Epidemiological Studies Depression Scale (CESD, (Radloff, 1977), National Institute of Mental Health (NIMH), is commonly used to measure depressive symptomatology in studies of cancer patients. The CESD focuses primarily on cognitive and affective components of depression rather than the physical manifestations of depression (Hann, Winter, & Jacobsen, 1999). Respondents are asked to respond to the prompt: "Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week." The list contains 20 statements, such as "I thought my life had been a failure," "People are unfriendly," I felt sad," "I felt hopeful about the future," and "I enjoyed life." The response values for all 20 questions in the CESD are provided in columns with the headings: "Rarely or none of the time (less than 1 day);" "Some or a little of time (1–2 days)"; "Occasionally or a moderate amount of the time (3–4 days)"; and "Most or all of the time (5–7 days)." Responses are scored as follows: column 1 receives 0 points, column 2 =1 point, column 3 = 2 points, and column 4 = 3 points. The scoring of positive items is reversed. Possible

range of scores is zero to 60, with the higher scores indicating the presence of more depression. Reliability of the CESD was previously measured by internal consistency (Hann et al., 1999) with α coefficients > .85 for both a group of women undergoing treatment for breast cancer and a group of women with no history of cancer. Test-retest reliability coefficients for the active treatment group and healthy comparison group were 0.57 ($p < .001$) and .51 ($p < .001$), respectively. These moderate and significant correlations support the test-retest reliability of the CESD over an average of 2.5 weeks (Hann et al., 1999). Reliability of the CESD scale was evaluated in the samples from the current study by computing an internal consistency coefficient (Cronbach's α) for the total scale at each measurement time. (See results in Chapter 4.)

Validity of the CESD has been demonstrated in a number of studies. In 1999 Hann, Winter & Jacobsen were the first to validate the CESD in a cancer population. Construct validity was supported by findings indicating that patients undergoing cancer treatment reported more depressive symptomatology than healthy individuals (Time 1, $F = 4.71$, $p < .05$ and Time 2, $F = 11.72$, $p < .001$). In addition, construct validity was demonstrated by moderate to high correlations in both the group of patients undergoing cancer treatment and healthy individuals with measures of fatigue (POMS-F, Patient Time 1, $r = .66$, $p < .001$), anxiety (STAI-S (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983); Patient Time 1, $r = .77$, $p < .001$) and global mental health functioning (SF-36 mental health summary scale, Patient Time 1, $r = -.65$, $p < .001$). Moderate and significant correlations among the measures reflect that more depressive symptomatology was associated with worse fatigue, more severe anxiety, and impaired mental health

functioning. The direction and significance of the correlations were similar in the patient group and healthy comparison group (Hann et al., 1999).

Protection of Human Subjects and Ethical Considerations

OHSU Institutional Review Board (IRB) approval was obtained prior to enrolling patients. All study participants signed informed consent documents prior to study participation. Recruitment procedures were developed using guidelines for protecting the privacy of patients who were potential research subjects and in accord with IRB requirements. Participant data has been de-identified and each participant's data assigned a unique identification number for analysis purposes. Research personnel in this study did not have access to identified information. Data management and study administration will be the responsibility of the principal investigator.

Analysis

The original data collected in the parent project were entered into the SPSS software program, verified, and corrected. The existing data sets consisted of longitudinal data collected in four or five measurement times, as previously described. The de-identified data were transferred to the principal investigator by Excel spreadsheets. The principal investigator imported data to STATA IC 12 (StataCorp, 2011) statistical software for analysis.

Appropriateness of Multilevel Modeling (MLM) to the Research Questions

This study used a multilevel model (MLM) approach to estimate parameters in attentional function, depression, and fatigue over time in women receiving chemotherapy for breast cancer and to identify the extent to which fatigue and depression predict levels

and trajectories of attentional function over time. MLM involves postulating a statistical model and then fitting the model to sample data, estimating the unknown values of population parameters. Methods of estimation provide a goodness of fit for the model. If the model fits well, one can use the estimated parameter values to draw conclusions about the direction and magnitude of the hypothesized effects in the population. STATA uses the method of maximum likelihood to estimate models.

The MLM approach has many benefits for the design of the proposed study. Longitudinal data are required for causal inference—comparing actual observed responses within subjects is closer to the ideal than comparing observed responses between subjects (Rabe-Hesketh & Skrondal, 2012). The great advantage of longitudinal data as compared with cross-sectional data is that each subject can serve as his or her own control. Pooled ordinary least squares (OLS) techniques, such as ANOVA, treat longitudinal data as repeated cross-sectional data and combine them into a composite whole within- and between-comparisons. Conversely, within-subject comparisons, such as those generated by MLM, are free from such bias because subjects truly act as their own controls. MLM has a unique and inherent ability to control for the dependencies of repeated measures (Lyons, Stewart, Archibold, Carter, & Perrin, 2004). While OLS techniques assume independent observations, normal distribution, and homoscedastic variance across occasions and individuals (Kwok et al., 2008), MLM does not. It is important to note that MLM residuals are expected to meet normal distribution and homoscedasticity assumptions which will affect level-2 models (Rabe-Hesketh & Skrondal, 2012). MLM can accommodate unbalanced designs, which allows for the

analysis of data when the number and spacing of assessments vary across respondents (Raudenbush, 2001; Raudenbush & Bryk, 2002) and MLM has the ability to model individual change, which helps to identify more complex patterns of change that are often overlooked by other methods (Raudenbush, 2001; Raudenbush & Bryk, 2002).

Missing Data and Uneven Intervals between Measurement Times. Inherent in the use of longitudinal study design is the problem of missing data. Data may be missing due to dropout or attrition or may be intermittently missing (Rabe-Hesketh & Skrondal, 2012). MLM employs statistical techniques that are able to extrapolate and account for missing data during analysis. This is suggested as a way to increase precision of the estimates and the power of the statistical tests (Hox, 2010). MLM can handle variation in the number of waves of measurement, spacing of measurement and numbers of respondents in the presence of sample attrition (Raudenbush, 2001; Raudenbush & Bryk, 2002). These characteristics of MLM are an advantage when random missing data occur in longitudinal data (Hox, 2010).

Preliminary Analysis

A preliminary analysis of the data was conducted to explore data distribution and look for normality and outliers of data for attentional function, fatigue, and depression in all measurement times main variables of data and baseline values of time invariant variables. A series of zero-order correlations between study variables was performed to evaluate strength of relationships between variables. Time invariant variables, such as work and marriage status, age, and educational level as measured at baseline, found to be significantly correlated with attentional function at baseline were considered for

inclusion. However, constraints of sample size restricted inclusion of all but the theoretically determined variable of age, which was included in modeling with attentional function, depression, and fatigue.

Combining of the two data sets, Sample 1 and Sample 2, would have provided a much larger sample for analysis, but decisions about clinically significant similarities needed to be made before the samples could be merged. Of primary interest was whether the number of days elapsed between measurement times was significantly similar in the two samples to consider merging them. A variable of days since last study visit was created using data on study visit dates. Intervals in days between study visits were compared between samples using t-tests. These results were used to make the decision to not combine Sample 1 and Sample 2 data for further analyses. (See Chapter 4 for further explication.)

Primary Analyses

Aim 1. To examine how level and trajectory of attentional function, fatigue, and depression change from the time before initiation of chemotherapy to three to six months after completion of chemotherapy in women with breast cancer. Similar analyses were run separately for attentional function, depression and fatigue.

MLM was used to examine trajectories. MLM is useful for exploring and explaining average trends as well as individual differences by allowing subject-specific relationships to vary randomly around average relationships (Rabe-Hesketh & Skrondal, 2012). MLM involves modeling at two levels, Level-1 and Level-2. Level-1 (repeated measures within individuals) represents individual change in attentional function

experienced by each member of the population during a year under study (Singer & Willett, 2003). Level-2 (the variations between individuals) codifies the relationship between inter-individual differences in the change trajectories and predictors (Singer & Willett, 2003). All of the tests are similar in that they test the evidence concerning the null hypothesis that the parameter's population value is 0 against the alternative that it is not (Singer & Willett, 2003).

Evaluation of the unconditional (without covariates) intra-class correlation coefficient (ICC) revealed how much of the variance of attentional function over time was variance between individuals and how much was variance within individuals across time. Substantial intra-individual variation around the average intercept and slope in attentional function, indicated that a Level-2 (between individuals) model was warranted. If the ICC was not significant then there would be insufficient intra-individual variability for multi-level modeling and use of alternative statistical procedures such as repeated measures analysis of variance would be indicated. Scale means for AFI, CESD, PROMIS, and SCFS at each measurement time were tabulated. Spaghetti plots of individual trajectories of attentional function, depression, and fatigue using raw data were visually inspected for variability and trends.

MLM estimates in both samples were prepared for fixed linear, fixed quadratic, random linear, and random quadratic models for attentional function, for depression, and for fatigue; and models were compared using likelihood ratio testing and information criteria. Fixed linear and fixed quadratic models were compared to determine the best fit

for a trajectory and a fixed quadratic model was compared with a random quadratic model to determine whether addition of a random slope would improve the model.

Aim 2. To investigate whether initial levels of fatigue predict initial levels of attentional function and whether initial levels of depression predict initial levels of attentional function in women with breast cancer being treated with chemotherapy.

Pearson's Product Moment correlational analyses between scale scores of attentional function (AFI) and depression (CESD) and between attentional function (AFI) and fatigue (PROMIS and SCFS) were used to assess for significant relationships on the First Day of Chemotherapy to determine whether depression significantly predicted initial levels of attentional function and whether fatigue significantly predicted levels of attentional function.

Aim 3. To investigate whether trajectories of fatigue predict trajectories of attentional function and whether trajectories of depression predict trajectories of attentional function in women with breast cancer being treated with chemotherapy.

In MLM, time varying variables (fatigue and depression) are included as random coefficients in Level-1. Time invariant variables, such as age, are added in Level-2 to allow for the effect of these variables to vary between subjects. Once the best fit model of attentional function was determined, data from depression across time was added to Level-1 of the model and age was added to Level-2 of the model. Model coefficients were assessed for statistical significance in the model to determine predictive effects.

Power Analysis

Conceptually, MLM estimates are those guesses for the values of the unknown population parameters that maximize the probability of observing a particular sample of data (Singer & Willett, 2003); they are asymptotic—or approximated. As sample size increases MLM estimates have three desirable properties: They are consistent, their sampling distributions are approximately normal with known variance, and their standard errors are smaller than those derived by other methods (Singer & Willett, 2003). No one knows how large a sample size is large enough (Singer & Willett, 2003). Power analyses are evaluated on what aspect of the MLM model is being evaluated. The sample size that matters most is the sample size at the level where the effect is being measured. For measuring effect over time, the greater the number of points in time the less important the sample size at each point in time.

CHAPTER 4

RESULTS

The data were analyzed using STATA 12 (1996–2015 StataCorp,LP, CollegeTown, TX, USA.). The results of the descriptive analysis are presented first, followed by the multivariable analysis. An alpha level of .05 was used in all tests of significance.

Samples

Demographic and clinical characteristics of the two samples are presented in Table 2.

Table 2

Demographic and Clinical Characteristics of Samples 1 and 2 and Statistical Comparisons between Samples (frequency unless otherwise noted)

Characteristics	Sample 1	Sample 2	*p*-value
Demographic Characteristics			
Age in years (*M, SD*)	53.76, 12.41	51.0, 9.90	.330
Non-Hispanic Caucasian[a]	24 (96%)	37 (84.1%)	.137
Married or partnered[b]	17 (70.8%)	34 (79.1%)	.448
Less than or equal to U.S. median income[c]	14 (63.6%)	11 (25.6%)	.003
Less than or equal to 2 in household[d]	14 (56.0%)	21 (48.8%)	.569
Employed full- or part-time[e]	12 (48.0%)	35 (81.4%)	.004
High school education or less[f]	13 (52.0%)	11 (25.6%)	.028
Clinical Characteristics			
Stage of Breast Cancer			.332
Stage I	7 (33.3%)	11 (29.7%)	
Stage II	9 (42.9%)	22 (59.5%)	
Stage III	5 (23.8%)	4 (10.8%)	
Number of days since prior study visit			
Mid-Treatment since Day of Chemo (*M, SD*)	50.4, 15.90	52.3, 18.70	.6748
Treatment End since Mid-Treatment (*M, SD*)	58.0, 20.28	37.5, 20.81	.0003
Follow-Up since Treatment End (*M, SD*)	92.5, 33.00	39.13, 17.82	.0001
Menopausal status			
Premenopausal	--	19 (45.2%)	
Peri- and menopausal	--	5 (11.9%)	
Postmenopausal	--	18 (42.9%)	

Characteristics	Sample 1	Sample 2	*p*-value
Weeks between chemo treatment: ≤ 2[g]	10 (41.7%)	19 (44.2%)	.842
Chemotherapy Agents and Sequencing			
First agent			
Anthracycline[h]	10 (40.0%)	19 (44.2%)	.736
Taxane[h]	13 (52.0%)	21 (48.8%)	.801
Trastuzumab[h]	4 (16.7%)	7 (16.3%)	.967
Pertuzumab/T-DM1[h]	0	6 (13.9%)	.050
Second agent			
Taxane[h]	9 (36.0%)	18 (41.9%)	.634
Trastuzumab[h]	7 (28.0%)	5 (11.63%)	.088
Anthracycline[h]	5 (20.0%)	2 (4.6%)	.045
Surgery, after Chemotherapy	13 (56.5%)	--	
Radiation, after Chemo	5 (21.7%)	--	
Adjunct Medications			
Dexamethasone[h]	--	41 (93.2%)	
Diphenhydramine[h]	--	16 (38.4%)	
Benzodiazepine[h]	--	18 (40.9%)	

Notes. -- = not measured. Chi-square tests were used for categorical variables and t-tests for continuous variables. The comparison made for each test of differences is described below:
[a] Non-Hispanic Caucasian compared to all other races and ethnicities combined.
[b]Married or partnered now compared to single, divorced, widowed or other.
[c]Less than or equal to U.S. median income compared to all other incomes.
[d]Less than or equal to 2 in household compared to more than 2 in household.
[e]Employed full- or part-tome compared to retired, unemployed, disabled or other.
[f]High school education or less compared to college education and graduate education.
[g]Interval of treatment every 2 weeks or less compared to every 3 weeks or 4 weeks.
[h]Dichotomized to Yes = 0, No = 1.

Most of the participants were in their early fifties, Caucasian, and married. The women in Sample 2 were more likely to be employed full- or part-time (χ^2 (1, N = 68) =

8.26, $p < .001$) and to live in households with an income above the U. S. median (approximately $53,000 annually) ($\chi^2$ (1, N = 65) = 8.90, $p < .001$) as compared to the women in Sample 1. With respect to clinical characteristics, participants were most likely to have Stage II breast cancer (Sample 1, 42.9% and Sample 2, 59.5%). Although not significantly different, Sample 1 had a greater percentage of Stage III (23.8%) than did Sample 2 (10.8%). In both samples, slightly more than half of the participants had more than two weeks between cycles of chemotherapy (Sample 1, 58.35%, Sample 2, 55.8%) compared to an interval of two weeks or less. Frequently, cyclic chemotherapy is administered sequentially: for example, an anthracycline and cyclophosphamide for several months followed by a taxane for several months. Women in Sample 1 were more likely to have had an anthracycline as the second part of the chemotherapy sequence than women in Sample 2 (χ^2 (1, N = 68) = 4.0331, $p < .05$). In Samples 1 and 2, 38% and 50% of participants received no anthracycline in their regimen, 8% and 9% received no taxane, and 71% and 77% received no trastuzumab, respectively (Table 3).

Table 3

Planned Chemotherapy Regimen by Participant by Sample

Weeks between	Doses	First Drugs in Sequence	Second Drugs in Sequence
		Sample 1	
2	4+ 4	AC	Taxane
3	4	TC	NA
3	8	Gemzar + DT[a]	
3	4	TC	NA
3	6+3	Taxane + carboplatin + Trastuzumab	Trastuzumab
2	4+4	AC	Taxane
2	4+2+1	AC	Taxane & Trastuzumab
2	4+4	AC	Taxane
3	4	TC	NA
1, 2	12 +4+2	Taxane	AC, Trastuzumab
1, 2	12 + 4 +2	Taxane	AC, Trastuzumab
3	6 + 3	Taxane + caroplatin + Trastuzumab	Trastuzumab
2	4 + 4	AC	Taxane
3	6 + 3	Taxane + carboplatin + Trastuzumab	Trastuzumab
3	4	TC	NA
2	4 + 4	AC	Taxane
3	4	TC	Change: Gemzar & Carbo
3	4	AC	NA
4, 2	4 + 4	Taxane	AC
3	6	AC+Taxane	NA
3	6	Taxane+carboplatin +Trastuzumab	Trastuzumab

Weeks between	Doses	First Drugs in Sequence	Second Drugs in Sequence
2	4 + 4	AC	Taxane
1, 2	12 + 4	Taxane	AC
3	6	Cyclophosphamide + fluorouracil + methotrexate	NA
2	4 + 4	AC	Taxane
		Sample 2	
3	4	TC	NA
2	4 + 4	AC	Taxane
3, 1	4 + 4	AC	Taxane
3	1 year	T-DMI[b]	NA
3	1 year	T-DMI[b]	NA
2, 1	4 + 12 +	AC	Taxane + Trastuzumab
2	4 + 4	AC	Taxane
3	4	TC	NA
3, 1	4 + 12	AC	Taxane
3	4	TC	NA
2	4 + 4	AC	Taxane
1	12	Taxane	NA
3	4	TC	NA
2	4 + 4	AC	Taxane
3	4	TC	NA
2	4 + 4	AC	Taxane
3	4	TC	NA
2	4 + 4	AC	Taxane
3	4	TC	NA
2	4 + 4	AC	Taxane

Weeks between	Doses	First Drugs in Sequence	Second Drugs in Sequence
3, 3	4 + 1 year	TC	Trastuzumab
2	6	Taxane + carboplatin + Trastuzumab + pertuzumab	NA
3	4	TC	NA
3	4	TC	NA
3	4	TC	NA
2	4 + 4	AC	Taxane
2	4 + 4	AC	Taxane
2, 1	4 + 12	AC	Taxane
1/3	12/4	Taxane + Trastuzumab + pertuzumab	NA
2	4 + 4	AC	Taxane
3	4	TC	NA
2	4 + 4	Taxane	AC
3	4	TC	NA
2	4 + 4	AC	Taxane
3	4 + 4	Taxane + Trastuzumab + pertuzumab	AC
2	4	AC	NA
3	4	TC	NA
1, 3	12 + 1 year	Taxane	Trastuzumab
2, 1	4 + 12	AC	Taxane
2	4 + 4	AC	Taxane
3	17	T-DMI[b]	NA
2	4 + 4	AC	Taxane
3	4	TC	NA

Notes: NA = Not applicable. AC = Anthracycline+Cyclophosphamide. TC = Taxane+Cyclophosphamide.
[a]Participant withdrew from study
[b]Trastuzumab + emtansine (cytoxic anti-microtubule agent)

The interval of time between First Day of Chemotherapy and Mid-Treatment was similar in Sample 1 (M = 50.4, SD = 15.86 days) and Sample 2 (M = 52.3, SD = 18.9 days). However, the interval between Mid-Treatment and Treatment End (Sample 1, M = *58*.0, SD = 20.2 days and Sample 2, M = 37.5, SD = *20*.8 Days) was significantly different ($t(60) = 3.8291$, $p < .001$), as was the interval between Treatment End and Follow-Up (Sample 1, M = *92*.5, SD = 33.0 days and Sample 2, M = 39.1, SD = 17.8 days) ($t(54) = 7.79$, $p < .0001$). For this reason, we decided not to combine the data sets for the formal analyses.

Reliability of Measurement

Cronbach's alpha was used to assess reliability of measures of attentional function (Attentional Function Index, or AFI), depression (Center for Epidemiologic Studies Depression, or CESD), and fatigue (Schwartz Cancer Fatigue Scale, or SCFS, and Patient-Reported Outcome Measurement Information System, or PROMIS). Cronbach's alphas were greater than .70 for all measures at each time, which indicates adequate reliability of measurement (Nunnally & Bernstein, 1994) (Table 4).

Table 4

Cronbach's Alpha for each Measure across Time by Sample

Measurement Time	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
		Sample 1		
Day of Chemo	.93	.85	.96	.79
Mid-Treatment	.89	.84	.96	.80
Treatment End	.92	.86	.97	.81
Follow-Up	.84	.91	.97	.83
		Sample 2		
Prior to Chemo	.92	.91	.90	.80
Day of Chemo	.94	.90	.92	.83
Mid-Treatment	.96	.93	.97	.87
Treatment End	.94	.95	.97	.91
Follow-Up	.94	.92	.95	.88

Note: N ≥ 24 in all Sample 1 cases; N ≥ 36 in all Sample 2 cases.
[a]Attentional Function Index.
[b]Center for Epidemiological Studies – Depression.
[c]Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue.
[d]Schwartz Cancer Fatigue Scale.

In Sample 1, the initial Cronbach's alphas for AFI and CESD revealed negative scale total correlations in four instances (AFI item 13 at Follow-Up, CESD items 4 and 19 at First Day of Chemotherapy and item 16 at Mid-Treatment). For Sample 1, revised scales without negatively correlated items were created for AFI at Follow-Up and CESD at First Day of Chemotherapy and Mid-Treatment. Cronbach's alphas for revised scales

varied little from full-item scale Cronbach's alphas and, therefore, full-item scales were used in all analyses. Scale scores for AFI (average), CESD (sum), and PROMIS (sum) and SCFS (sum) were generated for each individual at each time.

Samples 1 and 2 Characteristics Related to Attentional Function, Depression, and Fatigue

In both samples, a few strong relationships were found between demographic characteristics and levels of attentional function, depression, and fatigue over time (Tables 5 and 6).

Table 5

Pearson's Product-Moment Correlations between Demographic Characteristics and AFI[a], CESD[b], PROMIS[c], and SCFS[d] by Time, Sample 1

Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
		First Day of Chemotherapy		
Age in years	-.22	.12	.02	-.03
Race and Ethnicities[e]	.09	-.04	.43*	-.00
Marital Status[f]	.04	.35	.57**	.38
Education[g]	.22	-.02	-.23	-.09
Household[h]	.43*	-.21	-.05	-.12
Employment[i]	-.11	.62***	.35	.30
Income[j]	-.22	.16	-.08	.08
		Mid-Treatment		
Age in years	.18	-.36	-.27	-.14
Race and Ethnicities[e]	.06	.04	.33	.27
Marital Status[f]	-.31	.23	.40	.45*
Education[g]	.15	-.29	-.07	-.17
Household[h]	-.09	.46*	.28	.22
Employment[i]	-.17	.17	.38	.31
Income[j]	-.07	-.00	.14	.15

Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
		Treatment End		
Age in years	-.10	-.11	-.04	-.00
Race and Ethnicities[e]	.01	-.13	-.16	-.16
Marital Status[f]	-.06	.21	.20	.29
Education[g]	.26	-23	.14	-.01
Household[h]	.15	.09	-.19	-.12
Employment[i]	-.42*	.32	.41	.38
Income[j]	-.24	.11	.40	.16
		Follow-Up		
Age in years	.18	-.44*	-.43*	-.41*
Race and Ethnicities[e]	.10	.13	-.05	-.01
Marital Status[f]	-.16	.51*	.39	.48*
Education[g]	-.02	-.36*	-.18	-.23
Household[h]	.12	.11	.07	.17
Employment[i]	-.08	.34	.28	.39
Income[j]	-.23	-.16	.11	-.02

Notes: N ≥ 21 in all cases.
[a]Attentional Function Index.
[b]Center for Epidemiological Studies – Depression
[c]Patient-Reported Outcome Measurement Information System – Fatigue
[d]Schwartz Cancer Fatigue Scale.
[e]Non-Hispanic Caucasian compared to all other races and ethnicities combined
[f]Married or partnered now compared to single, divorced, widowed, or other.
[g]High school education or less compared to college education and graduate education
[h]Less than or equal to 2 in household compared to more than 2 in household.
[i]Employed full- or part-time compared to retired, unemployed, disabled, or other
[j]Less than or equal to U.S. median income compared to all other incomes.
*$p < .05$, **$p < .01$, ***$p < .001$.

Table 6

Pearson's Product-Moment Correlations between Demographic Characteristics and AFI[a], CESD[b], PROMIS[c], and SCFS[d] by Time, Sample 2

Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
		Prior to First Day of Chemotherapy		
Age in years	-.04	-.15	.10	.01
Race and Ethnicity[e]	-.19	-.01	-.08	-.06
Marital Status[f]	.02	-.10	-.10	-.13
Education[g]	.12	-.11	-.14	-.19
Household[h]	.18	-.01	.05	.03
Employment[i]	.28	-.24	-.01	-.23
Income[j]	.25	-.33	-.11	-.31*
		First Day of Chemotherapy		
Age in years	.07	-.05	.02	.01
Race and Ethnicity[e]	.07	-.07	-.05	-.11
Marital Status[f]	-.15	-.09	-.14	-.08
Education[g]	.11	-.34*	-.25	-.24
Household[h]	.05	.14	.22	.00
Employment[i]	.06	-.09	-.04	-.02
Income[j]	.07	-.19	.04	-.10

Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
	Mid-Treatment			
Age in years	.12	-.22	-.26	-.28
Race and Ethnicity[e]	.00	-.10	-.05	-.01
Marital Status[f]	-.18	-.06	.07	.15
Education[g]	-.08	-.04	.12	.07
Household[h]	-.02	-.02	.08	-.13
Employment[i]	.19	-.19	-.16	-.15
Income[j]	.10	-.13	-.01	-.14
	Treatment End			
Age in years	.24	-.17	-.19	-.21
Race and Ethnicity[e]	.14	-.10	.01	-.11
Marital Status[f]	-.16	.05	-.04	-.00
Education[g]	-.05	.09	.18	.14
Household[h]	.01	-.16	-.08	-.13
Employment[i]	.09	-.15	.04	.01
Income[j]	.07	-.29	-.15	-.17
	Follow-Up			
Age in years	.07	-.17	-.07	-.12
Race and Ethnicity[e]	.00	-.04	.14	-.03
Marital Status[f]	-.22	.15	.12	.17
Education[g]	.08	-.01	.03	.21
Household[h]	-.03	-.11	.07	-.09
Employment[i]	.06	.03	.22	.30
Income[j]	.26	-.39**	-.18	-.12

Notes: N ≥ 32 in all cases.
[a]Attentional Function Index.
[b]Center for Epidemiological Studies – Depression
[c]Patient-Reported Outcome Measurement Information System – Fatigue
[d]Schwartz Cancer Fatigue Scale.
[e]Nonhispanic Caucasian = 0; All other races and ethnicities = 1
[f]Married or partnered now = 0; Single, divorced, widowed, or other = 1
[g]High school education or less = 0 College education and graduate education = 1
[h]Less than or equal to 2 in household = 0; More than 2 in household = 1.
[i]Employed full- or part-time = 0; Retired, unemployed, disabled, or other = 1.
[j]Less than or equal to U.S. median income = 0; All other incomes = 1
*$p < .05$, **$p < .01$, ***$p < .001$.

Having an education of high school level or less was related to higher levels of depression on the first day of chemotherapy in Sample 2 ($r = -.34$, $p < .05$) and at Follow-Up in Sample 1 ($r = -.36$, $p < .05$). The only other significant relationship in Sample 2 is between income and depression ($r = -.39$, $p < .01$) such that having lower income is related to higher levels of depression at Follow-Up, which is not significant in Sample 1. In Sample 1, relationships between marital status and fatigue (PROMIS on first First Day of Chemotherapy, $r = .57$, $p < .05$; SCFS at Follow-Up, $r = .48$, $p < .05$) indicated that being married or partnered is related to lower levels of fatigue. Also in Sample 1, age is related to depression and fatigue (CESD, $r = -.44$, $p = .05$; PROMIS, $r = -.43$, $p < .05$; SCFS, r -.41, $p = <.05$) such that being older is related to lower levels of depression and fatigue.

Correlations between clinical characteristics and attentional function, depression, and fatigue are presented in Tables 7 and 8.

Table 7

Pearson's Product-Moment Correlations between Clinical Characteristics and AFI[a], CESD[b], PROMIS[c], SCFS[d] by Time, Sample 1

Clinical Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
		First Day of Chemotherapy		
Age	-.22	.12	.02	-.03
Stage	.13	-.09	.09	.04
Days since last study visit	--	--	--	--
Days since chemotherapy	--	--	--	--
Weeks between chemo[e]	-.25	.08	-.03	.05
First drug in sequence				
Anthracycline[f]	-.34	.04	-.22	.09
Taxane[f]	-.01	.00	.13	-.15
Trastuzumab[f]	.01	.43*	.10	.15
Second drug in sequence				
Taxane[f]	-.26	-.00	-.31	-.00
Trastuzumab[f]	-.04	.47*	.10	.05
Anthracycline[f]	-.02	.19	.23	.13
Surgery[f]	.00	.18	.37	.24
Radiation[f]	-.32	.22	-.09	.18
		Mid-Treatment		
Age	.18	-.32	-.27	-.14

Clinical Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
Stage	.11	.23	-.08	-.03
Days since last study visit	-.17	.20	.21	.24
Days since chemotherapy	-.18	.28	.53**	.29
Weeks between chemo[e]	-.42	-.07	-.03	.05
First drug in sequence				
Anthracycline[f]	-.21	.21	-.18	.01
Taxane[f]	.16	-.35	-.03	-.18
Trastuzumab[f]	.17	-.10	-.18	-.11
Second drug in sequence				
Taxane[f]	-.32	.20	-.14	.01
Trastuzumab[f]	.31	-.36	-.06	-.11
Anthracycline[f]	.09	-.09	.07	-.11
Surgery[f]	.27	-.27	-.12	-.04
Radiation[f]	.03	-.17	-.14	-.19
		End of Treatment		
Age	-.10	-.11	.04	-.00
Stage	.08	.12	-.12	.14
Days since last study visit	-.18	.01	-.01	.14
Days since chemotherapy	-.18	.18	.40*	.30
Weeks between chemo[e]	-.35	.11	.33	.17
First drug in sequence				
Anthracycline[f]	-.33	.31	.32	.29

Clinical Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
Taxane[f]	.23	-.33	-.41*	-.45*
Trastuzumab[f]	.25	-.14	-.16	-.17
Second drug in sequence				
Taxane[f]	-.38	.27	.33	.25
Trastuzumab[f]	.21	-.17	-.09	-.09
Anthracycline[f]	.18	-.07	-.11	-.13
Surgery[f]	.17	-.09	-.24	-.10
Radiation[f]	-.13	.23	.37	.45*
		Follow-Up		
Age	.19	-.44*	-.43*	-.41*
Stage	.05	.36	.25	.29
Days since last study visit	.40	-.39	-.43*	-.44*
Days since chemotherapy	.53**	-.11	-.45*	-.52**
Weeks between chemo[e]	-.28	-.19	-.03	-.14
First drug in sequence				
Anthracycline[f]	-.20	-.11	-.14	-.12
Taxane[f]	.13	.01	-.05	-.08
Trastuzumab[f]	.28	.02	-.32	-.15
Second drug in sequence				
Taxane[f]	-.15	-.15	-.14	-.17
Trastuzumab[f]	.21	-.06	-.24	-.11
Anthracycline[f]	-.15	-.07	.06	.15
Surgery[f]	-.17	-.05	-.11	-.02

Clinical Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
Radiation[f]	.02	.12	.00	.09

Note: N ≥ 20 at all measurement times. Monoclonal antibodies (other than trastuzumab) in treatment regimen were either not used or not recorded in Sample 1.
[a]Attentional Function Index.
[b]Center for Epidemiological Studies – Depression.
[c]Patient-Reported Outcome Measurement Information Survey, Fatigue
[d]Schwartz Cancer Fatigue Scale.
[e]Two weeks or less compared with more than two weeks between chemotherapy administrations.
[f]Dichotomized into Yes = 0 and No = 1.
*$p < .05$, **$p < .01$, ***$p < .001$

Table 8

Pearson's Product-Moment Correlations between Clinical Characteristics and AFI[a], CESD[b], PROMIS[c], SCFS[d] by Time, Sample 2

Clinical Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
		Prior to Chemotherapy		
Age	-.04	-.15	.10	.01
Stage	-.18	.19	-.04	.15
Menopausal Status	-.16	.07	.27	.23
Days since last study visit	--	--	--	--
Weeks between chemo[e]	-.03	-.07	.05	.06
First drug in sequence				
Anthracycline[f]	-.01	.09	.19	.15
Taxane[f]	.12	-.17	-.12	-.15
Trastuzumab[f]	-.09	-.04	-.14	-.07
Pertuzumab/T-DM1 Antibody[f,g]	-.08	-.07	-.13	-.10
Second drug in sequence				
Taxane[f]	-.06	.18	.20	.17
Trastuzumab[f]	.01	-.05	.04	.08
Anthracycline[f]	.04	-.23	-.27	-.18
Adjunct Medication				
Dexamethasone[f]	.08	.14	.24	.12
Diphenhydramine[f]	-.04	.17	.22	.20
Benzodiazepine[f]	-.09	-.03	.03	.09

Clinical Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
		First Day of Chemotherapy		
Age	.07	-.05	.02	.01
Stage	-.04	.08	.08	-.08
Menopausal Status	-.05	.13	.10	.17
Days since last study visit	.02	-.15	.03	-.11
Weeks between chemo[e]	.01	.02	-.03	.12
First drug in sequence				
Anthracycline[f]	-.08	.04	.05	.10
Taxane[f]	.10	-.15	-.12	-.14
Trastuzumab[f]	.17	.23	.25	.32*
Pertuzumab/T-DM1 Antibody[f,g]	.07	.24	.33*	.38*
Second drug in sequence				
Taxane[f]	-.07	.08	.06	.11
Trastuzumab[f]	.16	.09	-.05	.14
Anthracycline[f]	.05	-.31*	-.22	-.04
Adjunct Medication				
Dexamethasone[f]	.09	.20	.20	.17
Diphenhydramine[f]	-.06	.23	.30*	.30*
Benzodiazepine[f]	-.01	-.13	-.08	-.01
		Mid-Treatment		
Age	.12	-.22	-.26	-.28

Clinical Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
Stage	-.30	.43**	.26	.11
Menopausal Status	.00	-.02	.00	-.02
Days since last visit	-.16	-.03	-.04	.03
Weeks between chemo[e]	.14	-.19	-.24	-.03
First drug in sequence				
Anthracycline[f]	.07	-.10	-.16	.02
Taxane[f]	.08	.01	.08	-.10
Trastuzumab[f]	-.09	-.07	.04	.00
Pertuzumab/T-DM1 Antibody[f,g]	-.05	-.13	-.02	-.04
Second drug in sequence				
Taxane[f]	.08	-.08	-.15	-.01
Trastuzumab[f]	.05	-.14	-.18	-.34*
Anthracycline[f]	.03	-.19	-.21	-.12
Adjunct Medication				
Dexamethasone[f]	.12	-.05	.08	.06
Diphenhydramine[f]	-.04	.01	.01	.02
Benzodiazepine[f]	.02	-.06	-.25	-.20
		End of Treatment		
Age	.24	-.17	-.1	-.20
Stage	-.27	.19	.10	.06
Menopausal Status	.12	.05	.11	.03
Days since last study visit	-.01	-.16	.04	-.01

Clinical Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
Weeks between chemo[e]	.11	.06	-.01	.18
First drug in sequence				
Anthracycline[f]	.04	.20	.15	.16
Taxane[f]	.14	-.30*	-.20	-.22
Trastuzumab[f]	.05	-.19	-.07	.10
Pertuzumab/T-DM1 Antibody[f,g]	-.05	-.17	-.10	-.11
Second drug in sequence				
Taxane[f]	.03	.24	.18	.19
Trastuzumab[f]	.23	-.22	-.14	-.21
Anthracycline[f]	.10	-.26	-.38*	-.32*
Adjunct Medication				
Dexamethasone[f]	.14	.02	.21	.12
Diphenhydramine[f]	.22	.07	.04	.15
Benzodiazepine[f]	.05	-.13	-.18	-.25
		Follow-Up		
Age	.07	-.17	-.07	-.12
Stage	-.27	-.06	-.22	-.35*
Menopausal Status	-.09	.11	.20	.04
Days since last study visit	-.30	.03	-.00	-.05
Weeks between chemo[e]	-.30	.07	-.22	.06
First drug in sequence				
Anthracycline[f]	.00	.25	.15	.24

Clinical Characteristics	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
Taxane[f]	.09	-.31*	-.14	-.25
Trastuzumab[f]	-.08	.15	.16	.00
Pertuzumab/T-DM1 Antibody[f,g]	-.08	.10	.05	.10
Second drug in sequence				
Taxane[f]	.03	.30	.20	.26
Trastuzumab[f]	-.02	.03	.14	-.14
Anthracycline[f]	.03	.05	-.06	.14
Adjunct Medication				
Dexamethasone[f]	-.05	.10	.17	-.01
Diphenhydramine[f]	-.05	.24	.25	.07
Benzodiazepine[f]	.09	-.10	-.16	-.02

Note: N ≥ 31 at all measurement times.
[a]Attentional Function Index.
[b]Center for Epidemiological Studies – Depression.
[c]Patient-Reported Outcome Measurement Information Survey, Fatigue
[d]Schwartz Cancer Fatigue Scale.
[e]Two weeks or less compared with more than two weeks between chemotherapy administrations.
[f]Dichotomized such that Yes = 0 and No = 1 for analysis.
*$p < .05$, **$p < .01$, ***$p < .001$

The strongest correlations to emerge were between the number of days that had elapsed between the most recent dose of chemotherapy and (a) fatigue at Mid-Treatment (PROMIS, $r = .53$, $p < .01$) and (b) attentional function at Follow-Up ($r = .53$, $p < .01$) in Sample 1. These results indicate that a greater number of days since chemotherapy is related to higher (worse) fatigue and higher (better) attentional function. Information about the number of days that had elapsed between chemotherapy administration and study visit was not available for Sample 2. Stage of cancer and depression are strongly

related (r = .43, p < .01) in Sample 2 such that higher stage of cancer is related to higher (worse) depression. Age is related to depression (r = -.44, p < .05) and fatigue (SCFS , r = -.41, p < .05;PROMIS, r = -.43, p < .05) at Follow-Up such that as age increases, depression and fatigue decrease (improve). In Sample 1, having trastuzumab in either the first part of the sequence or the second part of the sequence of chemotherapy drugs is related to depression (first part r = .43, p < .05; second part r = .47, p < .05) on First Day of Chemotherapy such that having trastuzumab is related to having lower levels of depression.

Characteristics of Attentional Function, Depression, and Fatigue

Strong significant relationships amongst attentional function, depression, and fatigue are confirmed at all measurement times with the exception of attentional function (AFI) on the First Day of Chemotherapy administration in Sample 1 where relationships with depression and fatigue are not significant. Relationships are such that higher levels (worse) of depression and fatigue are related to lower levels (worse) of attentional function. Scores for AFI were highly correlated with scores for CESD, PROMIS and SCFS on the First Day of Chemotherapy in Sample 2 while these relationships are not significant in Sample 1 (Tables 9 and 10).

Table 9

Pearson's Product-Moment Correlations between AFI[a], CESD[b], PROMIS[c], and SCFS[d] at all Measurement Times by Time, Sample 1

Main Variables	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
		First Day of Chemotherapy		
AFI	--			
CESD	-.27	--		
PROMIS	-.24	.54**	--	
SCFS	-.23	.70***	.79***	--
		Mid-Treatment		
AFI	--			
CESD	-.59**	--		
PROMIS	-.62**	.54**	--	
SCFS	-.69***	.67***	.83***	--
		Treatment End		
AFI	--			
CESD	-.67***	--		
PROMIS	-.69***	.71***	--	
SCFS	-.60**	.82***	.87***	--
		Follow-Up		
AFI	--			

Main Variables	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
CESD	-.32	--		
PROMIS	-.66***	.76***	--	
SCFS	-.54**	.82***	.87***	--

[a]Attentional Function Index.
[b]Center for Epidemiology Studies – Depression.
[c]Patient-Reported Outcome Measurement Instrument Systems – Fatigue.
[d]Schwart Cancer Fatigue Scale.
*p<.05, **p<.01, ***p<.001.

Table 10

Pearson's Product-Moment Correlations between AFI[a], CESD[b], PROMIS[c], and SCFS[d] by Time, Sample 2

Main Variables	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
		Prior to First Day of Chemotherapy		
AFI	--			
CESD	-.58***	--		
PROMIS	-.40**	.67***	--	
SCFS	-.54***	.83***	.78***	--
		First Day of Chemotherapy		
AFI	--			
CESD	-.35*	--		
PROMIS	-.39*	.63***	--	
SCFS	-.48**	.78***	.77**	--
		Mid-Treatment		
AFI	--			
CESD	-.73***	--		
PROMIS	-.73***	.69**	--	
SCFS	-.72***	.73***	.83***	--

Main Variables	AFI[a]	CESD[b]	PROMIS[c]	SCFS[d]
		Treatment End		
AFI	--			
CESD	-.73***	--		
PROMIS	-.58***	.70***	--	
SCFS	-.70***	.85***	.89***	--
		Follow-Up		
AFI	--			
CESD	-.62***	--		
PROMIS	-.53***	.62***	--	
SCFS	-.45**	.69***	.71***	--

[a]Attentional Function Index.
[b]Center for Epidemiology Studies – Depression.
[c]Patient-Reported Outcome Measurement Instrument Systems – Fatigue.
[d]Schwartz Cancer Fatigue Scale.
*p<.05, **p<.01, ***p<.001.

In preparation for responding to specific aims 1 and 2, means and standard deviations for scale scores at all measurement times were calculated for the AFI (Table 11), CESD (Table 12), PROMIS (Table 13) and SCFS (Table 14).

Table 11

Mean and Standard Deviation (SD) for AFI[a] *by Time, Samples 1 and 2*

Main Variables	N	Mean[b]	*SD*	Min	Max
		Sample 1			
Day of Chemo	25	60.07	22.82	0	100
Mid-Treatment	24	56.81	18.26	23.38	100
Treatment End	24	52.62	20.94	19.94	100
Follow-Up	24	61.51	16.92	34.62	98.46
		Sample 2			
Prior to Chemo	43	67.77	18.43	13	96
Day of Chemo	41	68.05	19.32	30	98
Mid-Treatment	42	66.95	20.01	20	99
Treatment End	41	63.17	19.68	9	99
Follow-Up	38	72.29	18.33	18	99

[a]Attentional Function Index. 13-item visual scale where 0 = *Not at all* and 100 = *Extremely well* or *A great deal*. Items 9-13 are reverse coded.
[b]Participants' mean scores from 13-items was used to calculate overall means.

Table 12

Mean and Standard Deviation (SD) for CESD[a], by Time, Samples 1 and 2

Main Variables	N	Mean[b]	*SD*	Min	Max
		Sample 1			
Day of Chemo	25	14.92	9.20	4	38
Mid-Treatment	25	19.08	9.88	0	41
Treatment End	25	18.36	9.87	0	35
Follow-Up	25	11.32	9.43	0	33
		Sample 2			
Prior to Chemo	44	10.00	9.15	0	51
Day of Chemo	44	9.02	8.78	0	46
Mid-Treatment	44	13.00	11.82	0	55
Treatment End	44	10.50	12.14	0	56
Follow-Up	44	7.73	9.68	0	50

[a]Center for Epidemiology Studies – Depression. 20-item scale with items scored from 0 – 3 where 0 = *Rarely or none of the time* and 3 = *Most or all of the time*, items 4, 8, 12, and 16 reverse coded.
[b]Participants' raw score totals for 20-item scale was used to calculate scale means.

Table 13

Mean and Standard Deviation (SD) for PROMIS[a] by Time, Samples 1 and 2

Main Variables	N	Mean[b]	*SD*	Min	Max
		Sample 1			
Day of Chemo	25	19.08	8.20	8	36
Mid-Treatment	25	24.20	8.65	0	38
Treatment End	25	25.60	9.66	0	40
Follow-Up	25	16.76	7.00	0	32
		Sample 2			
Prior to Chemo	44	15.66	6.11	0	36
Day of Chemo	44	13.70	6.43	0	30
Mid-Treatment	44	21.02	9.41	0	39
Treatment End	44	20.34	10.08	0	40
Follow-Up	44	17.27	10.03	0	22

[a]Patient-Reported Outcome Measurement Instrument Systems – Fatigue. 7-item scale. Each item with 5 response options ranging from 1 to 5 where 1 = *Not at all*, or *Never* and 5 = *Very much* or *Always*. Raw score totals possible from 8 – 40.
[b]Participants' raw score totals for 7-item scale was used to calculate scale means.

Table 14

Mean and Standard Deviation (SD) for SCFS[a] by Time, Samples 1 and 2

Main Variables	N	Mean[b]	SD	Min	Max
		Sample 1			
Day of Chemo	25	12.00	3.84	6	20
Mid-Treatment	25	14.28	5.10	0	23
Treatment End	25	15.32	5.80	0	24
Follow-Up	25	11.20	4.69	0	22
		Sample 2			
Prior to Chemo	44	9.16	3.43	0	25
Day of Chemo	44	8.75	3.66	0	24
Mid-Treatment	44	11.61	5.09	0	24
Treatment End	44	10.75	5.76	0	27
Follow-Up	34	9.27	5.72	0	22

[a]Schwartz Cancer Fatigue Scale. 6-item scale. Each item response ranging from 1 = *not at all* to 5 = *extremely* for a possible total raw score from 6 to 30.
[b]Participants' raw score totals for 6-item scale used to calculate means.

Visual analysis of the means reveals trends of lower (worse) attentional function (AFI) and higher (worse) depression (CESD) and fatigue (PROMIS and SCFS) at Mid-Treatment for Sample 1 and Sample 2. Follow-Up fatigue in Sample 2 measured with PROMIS does not return to First Day of Chemotherapy level and this is the single instance in which attentional function, depression, and fatigue does not return to baseline levels or better by Follow-Up.

Figures 3–6 show "spaghetti" plots of individual trajectories of attentional function, depression, and fatigue. These figures reveal substantial heterogeneity in the shape of individual trajectories across time.

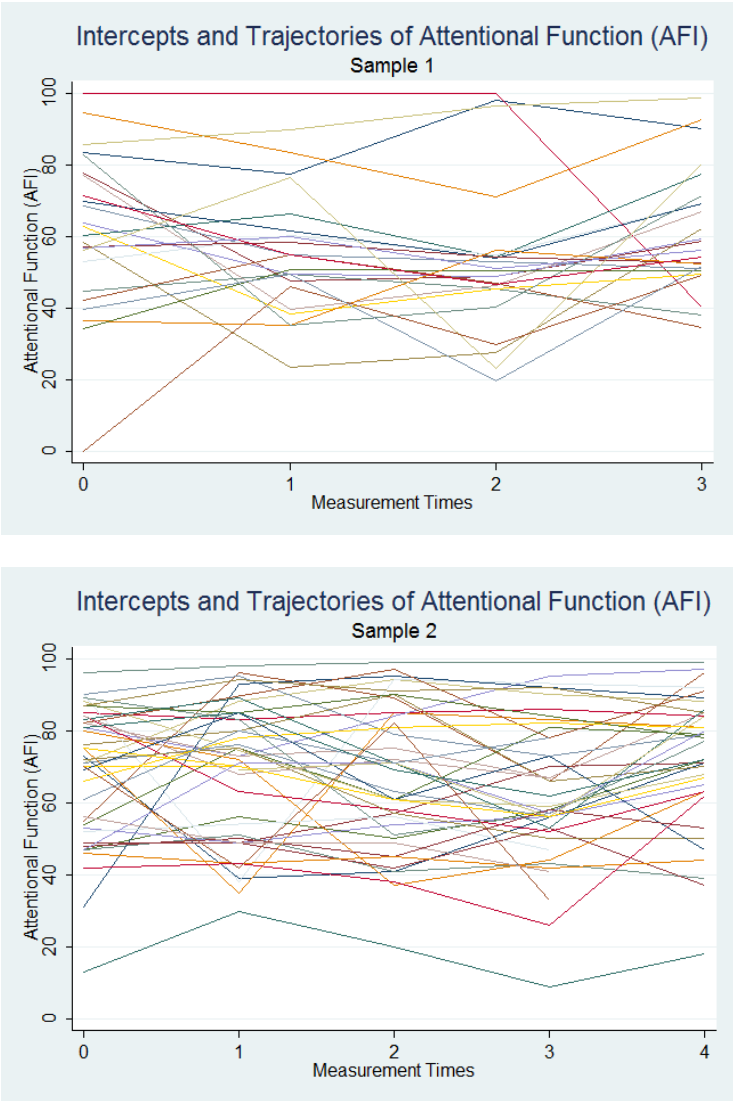
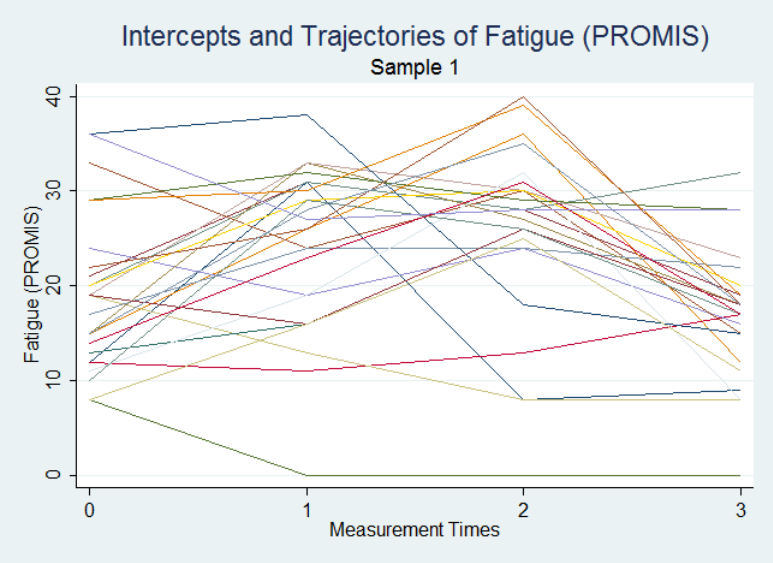


Figure 3. Intercepts and Trajectories of Attentional Function (AFI)**.**

Note: Graphs fit with raw scale scores.

[a]Attentional Function Index**.**



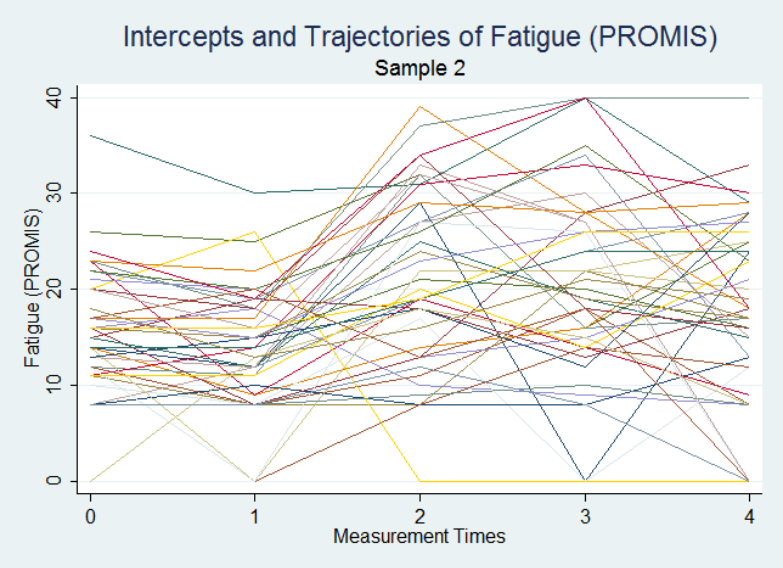
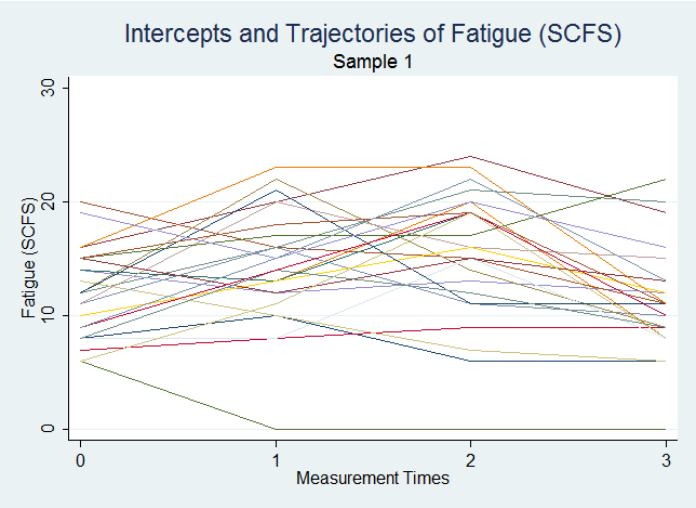


Figure 4. Intercepts and trajectories of fatigue (PROMIS).

Note: Graphs fit with raw scale scores.

[a]Patient-Reported Outcomes Measurement Information System**.**



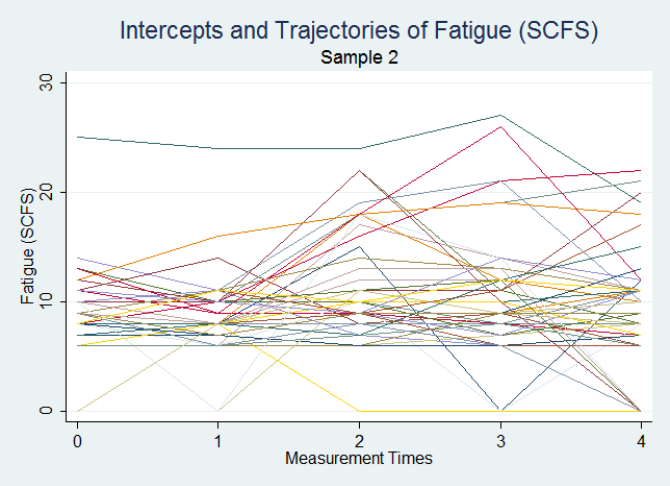
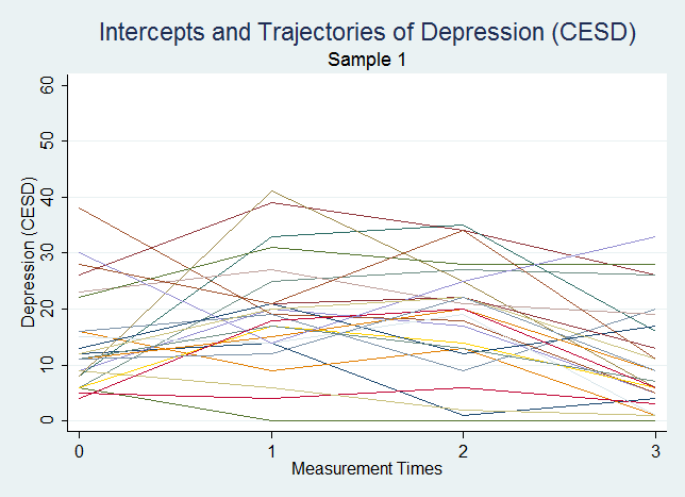


Figure 5. Individual Intercepts and Trajectories of Fatigue (SCFS[a]), Samples 1 and 2.

Note: Graphs fit with raw scale scores.

[a]Schwartz Cancer Fatigue Scale**.**



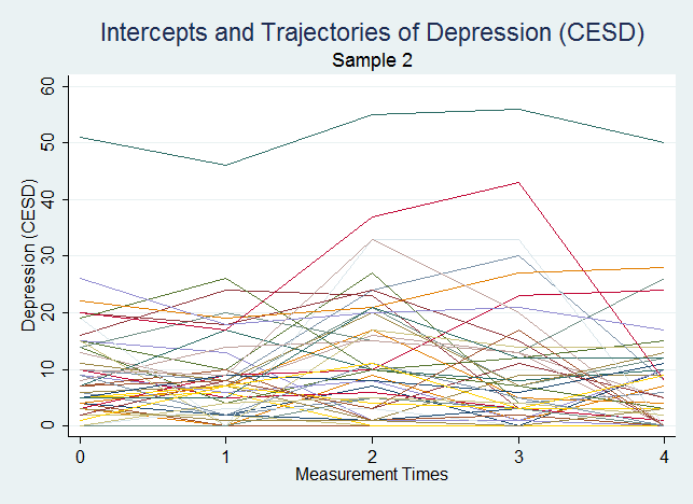


Figure 6. Individual Intercepts and Trajectories of Depression (CESDa), Samples 1 and 2.

Note: Graphs fit with raw scale scores.

[a]Center for Epidemiological Studies – Depression

Aim 1

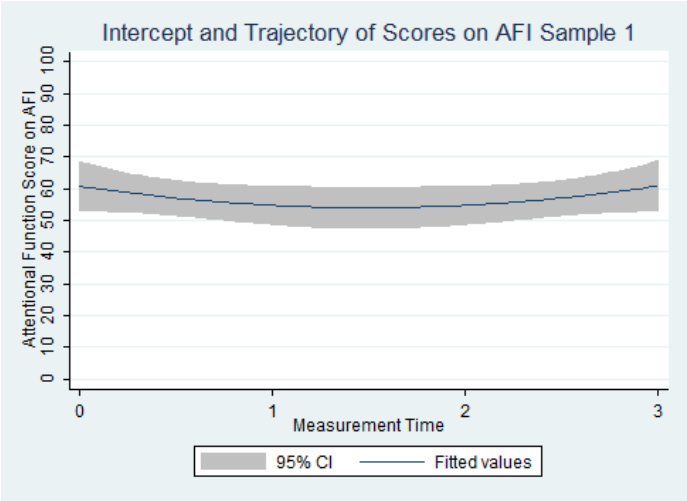
Hypothesis 1

> *Women with breast cancer receiving chemotherapy experience a decrease or worsening in levels of attentional function from the time before start of chemotherapy to the end of treatment with chemotherapy, and then attentional function increases or improves during the six months following the end of chemotherapy treatment.*

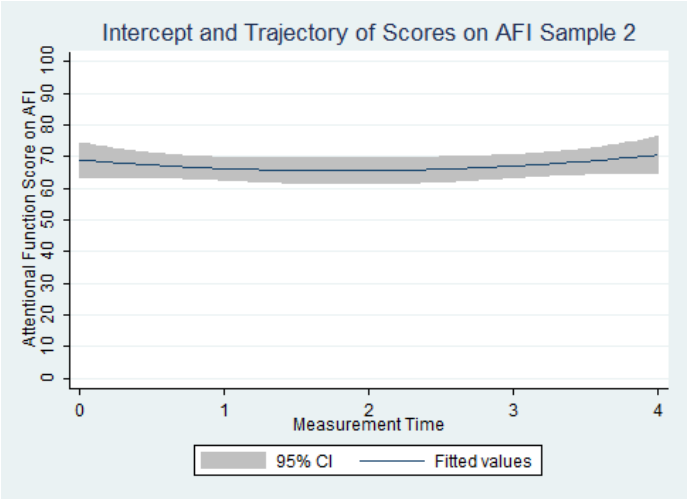
For attentional function in Sample 1, a quadratic trajectory fits the data better than a linear trajectory (χ^2 (1) = 5.14, p = .0233). The addition of a random slope to the quadratic trajectory model results in a non-conformability error. Model parameter estimates and a graph of the trajectory of mean AFI scale scores indicated a quadratic trajectory with a decrease (worsening) of attentional function during treatment and an increase (improvement) in attentional function that starts to occur between Mid-Treatment and Treatment End (Figure 7).

For attentional function in Sample 2, a quadratic trajectory fit the data better than a linear trajectory (χ^2 (1) = 3.13, p = .0768) and the addition of a random slope did not improve the model fit (χ^2 (1) = 2.06, p = .3474). Model parameter estimates and a graph of the data confirmed a quadratic trajectory with attentional function decreasing (worsening) during treatment and increasing (improving) during the interval of time between Mid-Treatment and Treatment End (Figure 7).

In Samples 1 and 2, AFI mean scale scores indicate that levels of attentional function returned to, or improved from, First Day of Chemotherapy levels by Follow-Up.



Intercept	60.87***
Linear Effect	-9.87*
Quadratic Effect	3.22*



Intercept	68.89**
Linear Effect	-3.39*
Quadratic Effect	.91*

Figure 7. Attentional Function (AFIa) Line Graph with 95% Confidence Intervals, Samples 1 and 2.

Note: Graphs fit with raw scale scores.

[a]Attentional Function Index.

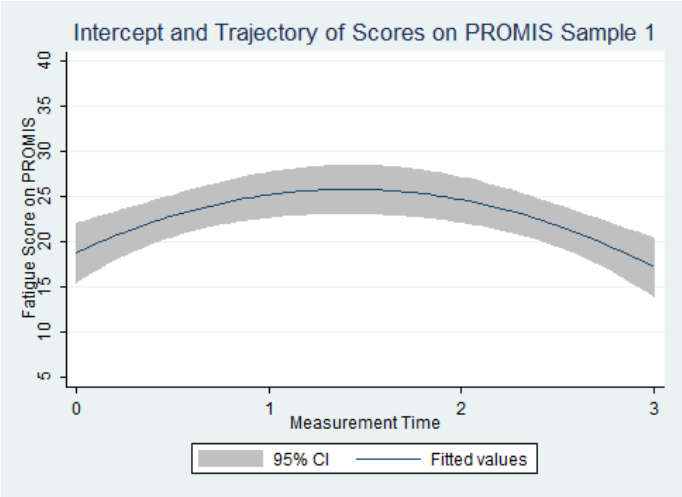
*$p < .05$, **$p < .01$, ***$p < .001$

Hypothesis 2

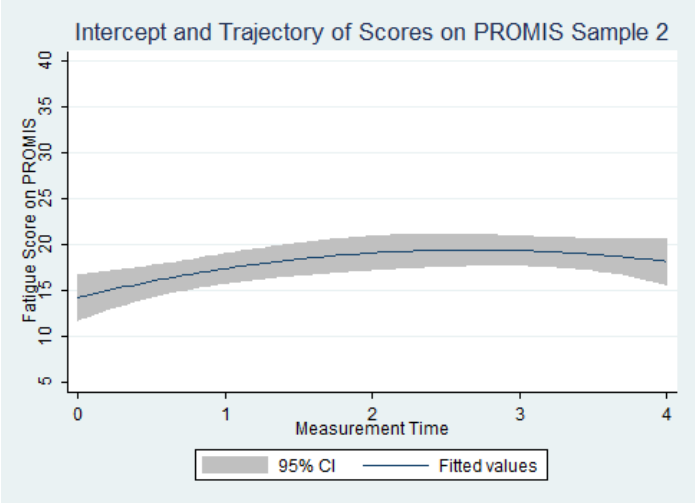
> *Women with breast cancer receiving chemotherapy experience an increase or worsening in levels of fatigue from the time before start of chemotherapy to the end of treatment with chemotherapy, and then fatigue decreases or improves during the six months following the end of chemotherapy treatment.*

For fatigue assessed with the PROMIS scale in Sample 1, a quadratic trajectory fits the data better than a linear trajectory (χ^2 (1) 27.32, p = .0000) and the addition of a random slope does not improves the model fit (χ^2 (1) = .00, p = .9994). For fatigue assessed with the SCFS scale in Sample 1, a quadratic trajectory fits the data better than a linear trajectory (χ^2 (1) = 20.99, p = .0000) and the addition of a random slope does not improved the model fit (χ^2 (1) = 2.04, p = .2608).

For Sample 1, model parameter estimates and graphs of the raw PROMIS and SCFS scale scores confirm a quadratic trajectory with an increase (worsening) of fatigue after start of chemotherapy and a decrease (improvement) in fatigue that begins between Mid-Treatment and Treatment End. Review of PROMIS and SCFS mean scale scores confirms that in Sample 1 fatigue levels at Follow-Up are similar to or indicate improvement in fatigue from levels on First Day of Chemotherapy (Figures 8 and 9).



Intercept	18.76***
Linear Effect	9.91***
Quadratic Effect	-3.49***



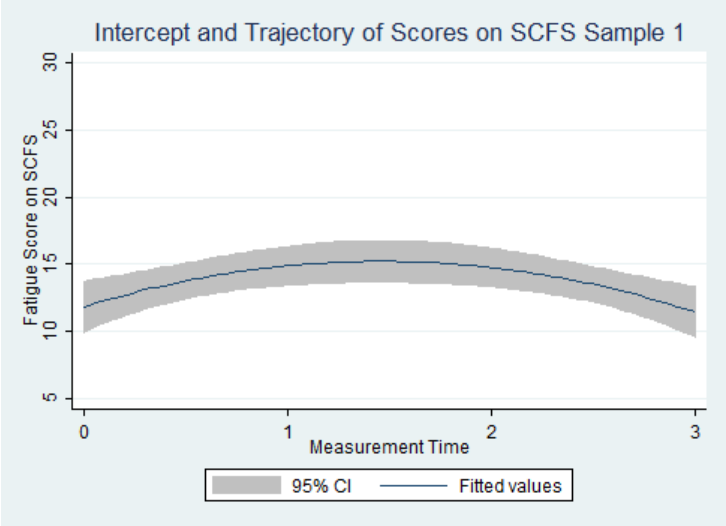
Intercept	14.17**
Linear Effect	3.91*
Quadratic Effect	-.73**

Figure 8. Fatigue (PROMISa) Line Graph with 95% Confidence Intervals, Samples 1 and 2.

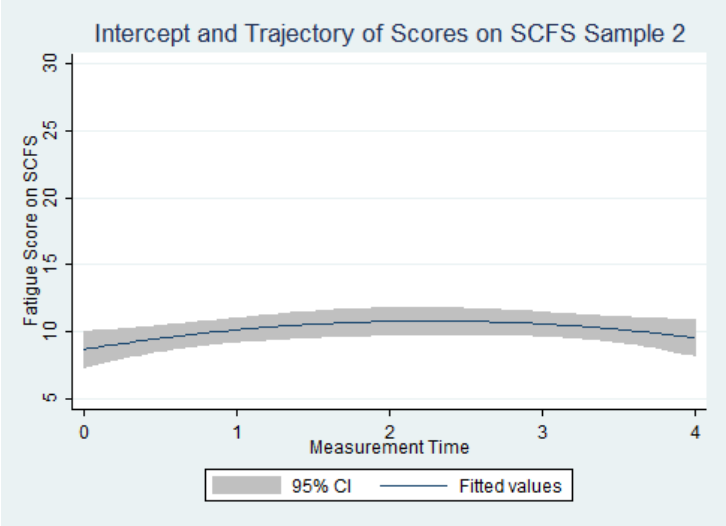
Note: Graphs fit with raw scale scores.

[a]Patient-Reported Outcomes Measurement Information System.

*$p < .05$, **$p < .01$, ***$p < .001$.



Intercept	11.80***
Linear Effect	4.66***
Quadratic Effect	-1.6***



Intercept	8.63***
Linear Effect	1.90**
Quadratic Effect	-.42**

Figure 9. Fatigue (SCFSa) Line Graph with 95% Confidence Intervals, Sample 1 and Sample 2.

Note: Graphs fit with raw scale scores.

[a]Schwartz Cancer Fatigue Scale.

*$p < .05$, **$p < .01$, ***$p < .001$.

For fatigue assessed with the PROMIS scale in Sample 2, a quadratic trajectory fit the data better than a linear trajectory (χ^2 (1, N = 205) = 6.22, p = .0127) and the addition of a random slope improved the model fit (χ^2 (1, N = 205) = 6.27, p = .0435). For fatigue assessed with the SCFS scale in Sample 2, a quadratic trajectory fit the data better than a linear trajectory (χ^2 (1, N = 205) = 7.28, p = .0070) and the addition of a random slope improved the model fit (χ^2 (1, N = 205) = 11.70, p = .0029).

Random effects are the variance components of the equation and include difference in the intercept at the level of the subject, difference across subjects in the slopes, and covariance between subject slopes and intercepts across all subjects. The random slope aspect of the SCFS model indicates that the heterogeneity in the individual slopes is greater than what we would expect by chance.

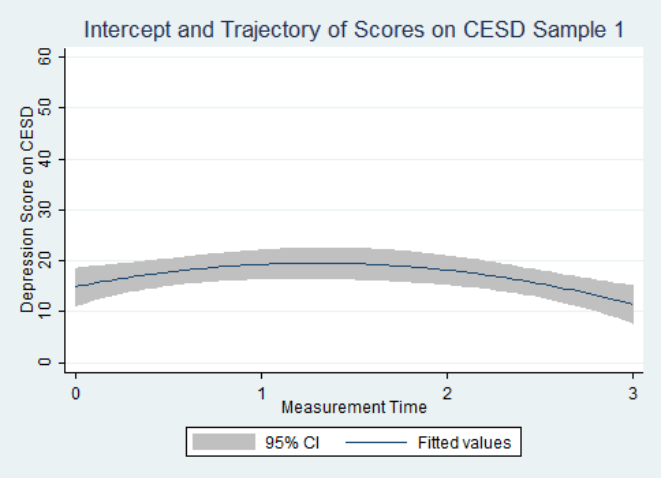
For Sample 2, model parameter estimates and graphs fit to raw scale scores indicate that fatigue increases (worsens) after start of treatment with chemotherapy and begins to decrease (improve) between Mid-Treatment and Treatment End (Figures 8 and 9). The graph of Sample 2 PROMIS data and Sample 2 mean PROMIS scale scores indicate fatigue has not yet returned to First Day of Chemotherapy by Follow-Up. Fatigue as measured with SCFS in Sample 2 appears to return to First Day of Chemotherapy levels by Follow-Up.

Hypothesis 3

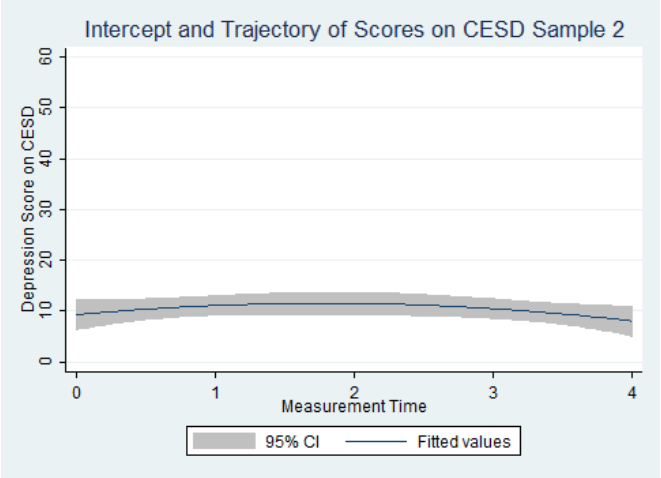
> *Women with breast cancer receiving chemotherapy experience an increase or worsening in levels of depression from the time before start of chemotherapy to the end of treatment with chemotherapy, and then depression decreases or improves during the six months following the end of chemotherapy treatment.*

For depression in Sample 1, a quadratic trajectory fits the data better than a linear trajectory (χ^2 (1) = 15.45, p = .0001). And the addition of a random slope to the equation does not improves the model fit (χ^2 (1) = .90, p = .6389). For depression in Sample 2, a quadratic trajectory fits the data better than a linear trajectory (χ^2 (1) = 7.84, p = .0051). And the addition of a random slope to the equation is a better fit when evaluated information criteria.

Model parameter estimates and graphs of CESD raw scale scores indicate that depression increases (worsens) after First Day of Chemotherapy treatment and then decreases (improves) between Mid-Treatment and Treatment End (Figure 10). Mean scale scores indicate that levels of depression at Follow-Up are improved from First Day of Chemotherapy levels.



Intercept	14.85***
Linear Effect	7.25**
Quadratic Effect	-2.8***



Intercept	9.23***
Linear Effect	2.57*
Quadratic Effect	-.72**

Figure 10. Depression (CESDa) Line Graph with 95% Confidence Intervals, Sample 1 and Sample 2.

Note: Graphs fit with raw scale scores.

[a]Center for Epidemiological Studies—Depression.

*$p < .05$, **$p < .01$, ***$p < .001$

Aim 2

Hypotheses 4 and 5 are addressed by considering results of correlations of fatigue and attentional function at First Day of Chemotherapy. Hypotheses 6 and 7 are addressed by adding time varying and time invariant covariates to a fixed quadratic model for attentional function. The variable *age* is added to the models a priori to control for effects of age. In Sample 1 correlational analyses in this study indicate a significant relationship between age and depression (r = -.44, p < .05) and age and fatigue (PROMIS, r = -.43, p < .05; SCFS, r = -.41, p < .05) at Follow-Up such that as age increases depression and fatigue decrease (improve). Correlations between age and attentional function did not reach significance in this study and no significant relationships between age and depression or fatigue were found in Sample 2.

Hypothesis 4

> *At baseline, higher levels of fatigue predict lower levels or worse attentional function in women with breast cancer before initiation of treatment with chemotherapy.*

Fatigue is not significantly related to attentional function on First Day of Chemotherapy in Sample 1 (PROMIS, r = -.24, *NS;* SCFS, r = -.23, *NS*) but is significant related to attentional function in Sample 2 (PROMIS, r = -.39, p < .05; SCFS, r = -.48, p < .01) such that as fatigue increases (worsens) attentional function decreases (worsens).

Hypothesis 5

At baseline, higher levels of depression predict lower levels or worse attentional function in women with breast cancer before initiation of treatment with chemotherapy.

Depression is not statistically significantly related to attentional function on First Day of Chemotherapy in Sample 1 (r = -.27, *NS*) but is statistically significant related to attentional function in Sample 2 (r = -.35, $p < .05$) such that as fatigue increases (worsens) attentional function decreases (worsens).

Hypothesis 6

Trajectories of fatigue predict trajectories of attentional function in women with breast cancer during treatment with chemotherapy and up to six months following the end of treatment with chemotherapy, such that as levels of fatigue increase or worsen, levels of attention decrease or worsen; and as levels of fatigue decrease or improve, levels of attentional function increase or improve.

Fixed quadratic models of attentional function were fit with fatigue data (SCFS and PROMIS), controlling for age, for both samples. The coefficient for fatigue was

statistically significant in all models (Sample 1, PROMIS, β = -1.06, *SE* = .22; *z* = -4.83, *p* < .001; SCFS, β = -1.91, *SE* = .41; *z* = -4.70, *p* < .001; and Sample 2, PROMIS, β = -.95, *SE* = .15; *z* = -6.21, *p* < .001; SCFS, β = -1.77, *SE* = .23; *z* = -6.60, *p* < .001) such that for every unit increase (worsening) in fatigue there is a decrease (worsening) of attentional function (Table 15).

Table 15

Parameter Estimations for Attentional Function (AFI[a] Fixed Quadratic Model) with Fatigue (PROMIS[b] and SCFS[c]) controlling for Age, Samples 1 and 2

	---- PROMIS[b] ----		---- SCFS[c] ----	
Parameters	Sample 1	Sample 2	Sample 1	Sample 2
		Fixed Effects		
Intercept	81.03*** (13.01)	77.19*** (11.37)	84.61*** (13.42)	106.52*** (34.06)
Linear Time	1.83 (4.67)	-.47 (2.16)	.20 (4.54)	-.49 (2.20)
Quadratic Time	-.81 (1.53)	.54 (.52)	-.15 (1.47)	.33 (.53)
PROMIS[b]	-1.06*** (.22)	-.95*** (.15)	--	--
SCFS[c]	--	--	-1.91*** (.41)	-1.77*** (.27)
Age	-.01 (.22)	.13 (.21)	-.03 (.22)	.06 (.19)
		Random Effects		
Intercept	137.81 (57.54)	134.46 (38.21)	141.63 (57.72)	106.52 (34.06)
Residual	157.68 (27.26)	132.34 (15.81)	158.46 (27.22)	138.09 (16.77)

Notes: Covariance (unstructured) (SE)
[a]Attentional Function Index
[b]Patient-Reported Outcomes Measurement Instrument Survey – Fatigue
[c]Schwartz Cancer Fatigue Scale
*$p < .05$, **$p < .01$, ***$p < .001$

Hypothesis 7

Trajectories of depression predict trajectories of attentional function in women with breast cancer during treatment with chemotherapy and up to six months following the end of treatment with chemotherapy.

A fixed quadratic model of attentional function was fit with depression data, controlling for age, for both samples (Table 16).

Table 16

Parameter Estimations for Attentional Function (AFI[a] Fixed Quadratic Model) with Depression (CESD[b]) controlling for Age, Samples 1 and 2

Parameters	Sample 1	Sample 2
	Fixed Effects	
Intercept	76.37*** (13.31)	78.40*** (10.00)
Linear Time	-3.75 (4.44)	-1.61 (2.19)
Quadratic Time	.92 (1.45)	.43 (.54)
CESD[b]	-.76*** (.19)	-.91*** (.13)
Age	-.08 (.22)	.00 (.18)
	Random Effects	
Intercept	145.08 (58.74)	91.40 (29.18)
Residual	170.46 (29.10)	141.41 (16.96)

Notes: Covariance (unstructured) (SE)
[a]Attentional Function Index
[b]Center for Epidemiological Studies – Depression
*$p < .05$, **$p < .01$, ***$p < .001$

The coefficient for depression was statistically significant in both models (Sample 1, β = -.76, *SE* = .19; *z* = -3.87, $p < .001$; and Sample 2, β = -.91, *SE* = .13; *z* = -6.96, $p < .001$) such that for every unit increase (worsening) in depression there is a decrease (worsening) of attentional function of .76 (Sample 1) and .91 (Sample 2) on the AFI scale.

Exploratory Analysis of Attentional Function, Depression, and Fatigue

Study results raise the question: If we include both fatigue and depression in the model simultaneously which one will have the strongest impact on attentional function? To answer this question, a fixed quadratic model of attentional function was fit with depression (CESD) and fatigue (PROMIS), controlling for age, for each sample (Table 17).

Table 17

Parameter Estimations for Attentional Function (AFI[a], Fixed Quadratic Model) with Covariates, controlling for Age, Samples 1 and 2

Parameters	Sample 1	Sample 2
	Fixed Effects	
Intercept	84.48*** (12.71)	82.954*** (9.79)
Linear Time	2.29 (4.65)	-.32 (2.17)
Quadratic Time	-1.06 (1.52)	.36 (.52)
CESD[b]	-.37 (.23)	-.61*** (.16)
PROMIS[c]	-.84** (.26)	-.61** (.18)
Age	-.05 (.21)	.03 (.18)
	Random Effects	
Intercept	123.73 (54.08)	86.83 (27.95)
Residual	156.62 (27.26)	133.12 (16.00)

Notes: Covariance (unstructured) (SE)
[a]Attentional Function Index
[b]Center for Epidemiological Studies – Depression
[c]Patient-Reported Outcomes Measurement Instrument Survey -- Fatigue
*$p < .05$, **$p < .01$, ***$p < .001$

While only models fit with PROMIS data are presented in the exploratory analysis results, model results were similar when fit with fatigue data from the PROMIS or SCFS. In models with both depression and fatigue as predictors, fatigue remained

significant (Sample 1, β = -.83, *SE* = .23; *z* = -3.18, *p* <.01; Sample 2, β = -.61, *SE* = .18; *z* = -3.33, *p* <.01). In Sample 1, the addition of fatigue to a model with depression results in depression being statistically insignificant (β = -.37, *SE* = .23; *z* = -1.62, *p* = .104) while in Sample 2 depression remains highly significant (β = -.61, *SE* = .16; *z* = -3.88, *p* <.001).

CHAPTER 5

DISCUSSION

Summary of Results

Our results provide evidence that attentional function, depression, and fatigue are related to each other and share a pattern of change over time. The significant quadratic effects in our longitudinal multilevel models indicate that these symptoms worsen between the beginning of treatment with chemotherapy and the middle of treatment then begin to improve by the end of treatment. Attentional function, depression, and fatigue measured by the SCFS continue to improve to baseline or better at three to six months following the end of treatment. The exception to this pattern is fatigue measured by the PROMIS, which did not reach baseline levels at Follow-Up. The finding that, controlling for age, the trajectory of fatigue predicts the trajectory of attentional function and the trajectory of depression also predicts attentional function in both Samples 1 and 2 supports the conclusion that the trajectories of change of these variables are related.

Strengths and Limitations

Introduction

In order to interpret these results, strengths and limitations of this study will be considered. This section reviews relevant aspects of the research design, methods, and analyses and discuss selected conceptual and clinical issues specific to research with women receiving chemotherapy for breast cancer.

Research Design

The prospective longitudinal design with points of measurement defined by clinical landmarks and the timing of data collection prior to a chemotherapy treatment is a strength of the study. This design avoids the shortcomings of cross-sectional designs in evaluating change over time; longitudinal designs are better able to capture the dynamic aspects of participants' symptom profiles (Xiao, Bruner, Jennings, & Hanlon, 2014). The inclusion of measures taken prior to and following treatment as well as two measures taken during treatment allows for examination of patterns at clinically relevant time points. The design standardizes measurement points across treatment regimens that vary in duration of a cycle (two weeks to four weeks) and in the number of cycles of treatment required. The timing of data collection minimizes confounding effects of treatment-related supportive care medications, such as anti-emetics and steroids, given early in the cycle because data collection was done at the very end of a chemotherapy cycle.

The complex relationships among symptoms, treatment, and time also present challenges in study design and to the interpretation of results. The chemotherapy regimens in use today often include sequenced chemotherapy agents. This means that the chemotherapy agents administered during the initial period of treatment end and different agents are given in a second or even a third period of the regimen. These planned changes in treatment mean that the trajectory of side effects may change from period to period and make it difficult to determine the level and pattern of side effects for each period as there is no washout period between them. Symptoms such as fatigue also show a pattern of change within a treatment cycle such that there is a pattern of rapid increase in both worst and average fatigue in the days following receipt of chemotherapy followed by a decline

(Schwartz, 2000). In the case of breast cancer chemotherapy, most of the detailed information on levels and patterns of symptoms reflects experience with chemotherapy regimens that did not include any sequencing of agents.

In the present study, the timing of data collection would be expected to yield the lowest fatigue scores during the cycle. It is not known if attentional function and depression exhibit predictable patterns of worsening and improvement over the course of a single cycle of chemotherapy because there are few studies that include enough time points to capture such a pattern. Our results show that there was variation in fatigue over time even though our data probably do not reflect the highest levels of fatigue experienced during the treatment cycle.

The results of our prospective longitudinal study with assessment times at significant clinical landmarks provide important evidence of the level, direction, magnitude, and shape of change of attentional function, depression, and fatigue in women with breast cancer receiving chemotherapy as well as relationships amongst these symptoms, but our results are limited in their ability to provide evidence of temporal sequencing of symptoms.

Measures

We used established measures and included two fatigue instruments to address both the feelings-of-fatigue and the impact-on-quality-of-life approaches to conceptualizing fatigue. Using established measures is a strength of the study, and our results suggest that there may be differences in the relationship of attentional function to fatigue depending upon the conceptualization represented by the instrument.

Demographic Characteristics of Samples

The samples were homogeneous for key demographic variables as most participants were non-Hispanic Caucasians in their early 50s and married or partnered. Sample 1 and 2 differed significantly in employment, income and education. Sample 1, from the NW U.S. generally was less well educated, made less money, was employed full- or part-time at a lower percentage than Sample 2 (from the NE U.S). Participants in Sample 1 rated attentional function, depression, and fatigue at lower levels than Sample 2 at all measurement times. Clinical differences between samples led to a decision to not combine the samples for analysis, and sample size limits our ability to include these interesting demographic variables in multilevel analyses. Homogeneity in race and ethnicity limits generalizability of sample results.

Age

Small sample sizes in both samples in the study preclude controlling for many covariates in multivariate models, but age was selected to include in the models because of an inconsistent pattern of correlations with age in previous studies. Recent studies indicate that younger women report lower levels (worse) attentional function than older women (Cimprich et al., 2005; Merriman et al., 2014; Merriman et al., 2010; Von Ah, Russell, et al., 2009). We found an inverse relationship of age to depression and fatigue but no relationship of age to attentional function in Sample 1 three to six months after the end of treatment with chemotherapy. No associations between age and attentional function, depression, and fatigue were found in Sample 2.

Symptom Management Interventions

This study does not include data on behavioral approaches and pharmacologic approaches used for symptom management, so it is not possible to control for the use of specific interventions by individual subjects.

Chemotherapy Regimen

In Sample 1, participants were on one of six chemotherapy regimens for invasive breast cancer. Five of the regimens were listed in NCCN guidelines and the 6th is an adapted version of a listed regimen that reverses the order of the cytotoxic agents. The inclusion of trastuzumab in the regimen depends upon the receptor status of the tumor. In both samples chemotherapy regimens usually started with an anthracycline/ cyclophosphamide combination followed by a taxane or started with a taxane/ cyclophosphamide combination followed by no other chemotherapy. Three participants in Sample 2 were on a study protocol with T-DMI, a monoclonal antibody conjugate with trastuzumab and a cytotoxic agent (DMI). Anthracycline is frequently cited as a potential agent underlying problems with cognition but little is known of the effect of taxanes, transtuzumab, or cyclophosphamide on cognition. Dose-response studies are being conducted to further elucidate the relationship between chemotherapy and problems of cognition (Collins, MacKenzie, Tasca, Scherline, & Smith, 2013). In this study we do not have a sufficient sample size to be able to explore relationships between specific chemotherapy regimen type or duration and symptoms.

Multilevel Modeling

Our use of longitudinal multilevel modeling is a strength of our study. MLM is a statistical method for analyzing the trajectory of change over time that can account for the baseline status of an individual or group on the dependent variable of interest as well as the impact of clinical characteristics that vary across individuals (Collins et al., 2009). Benefits of MLM include its ability to reliably model varying numbers and spacing of assessments across respondents (Raudenbush, 2001; Raudenbush & Bryk, 2002), its ability to model individual linear or nonlinear change, and its relative freedom from restrictive assumptions regarding issues such as sphericity and heteroscedasticity (Collins et al., 2009; Kwok et al., 2008). MLM can make use of all available data in the estimation of model parameters due to its flexible treatment of the time predictor (Muthen & Curran, 1997). The treatment of time as a continuous instead of discrete variable in MLM can increase the statistical power for detecting effects (Muthen & Curran, 1997). Our data for attentional function were best fit to a fixed quadratic model in Samples 1 and 2, indicating that we did not have sufficient inter-individual variability to use the random aspect of the model. MLM allows time-varying variables to be modeled along with a time-varying dependent variable. In addition, time invariant covariates can be added to the model to account for additional variance. Each participant provides data from each measurement point, acting as their own control in the study, increasing the power of the model. MLM is a powerful analytic technique that allows us to answer questions about the relationship between trajectories of one variable and the trajectory of another variable.

Attentional Function

This study is limited to the assessment of one aspect of cognition, self-report of attentional function. Attentional function is important to other cognitive abilities, such as acquiring important information, planning activities, making decisions, completing tasks and accomplishing goals (Cimprich et al., 2005; Lezak et al., 2004). However, it is one of many aspects of cognitive functioning. A battery of tests to assess the full range of neuropsychological functioning requires a trained individual to perform the test and two to three hours of time with the participant to complete it. The ecological validity of use of neuropsychological batteries in neurologically intact populations has been questioned (Spooner & Pachana, 2006). Of critical importance is the impact of long and extensive neuropsychological testing on patients. In a recent study, 8 of 68 cancer patients and 4 of 64 health controls quit a study designed to assess cognitive effects of chemotherapy in breast cancer patients because they found the assessments too stressful (Collins et al., 2013). While assessment of attentional function does not provide a comprehensive objective assessment of cognitive functioning, as would a battery of objective neuropsychological tests, the quick, focused, self-assessment AFI provides important information that can be measured repeatedly during the study period.

Clinical Significance

The research conducted for this study indicates that there are predicable patterns of change in attentional function, depression, and fatigue during treatment with chemotherapy. Such patterns have implications for patient education, informal and formal support networks, and informed consent. Education and reassurance are among the most important approaches clinicians can take with patients and families regarding problems

with cognition that may happen during chemotherapy (Gordon, 2014). These results may provide some validation of some patients' experiences, increase anxiety for others anticipating treatment, or relieve those who can anticipate more reversible declines than they might imagine (Anderson-Hanley, Sherman, Riggs, Agacha, & Compas, 2003). Interventions might be designed to assist patients in managing any anticipated cognitive changes (Ferguson, Ahles, et al., 2007). Attentional function demands are high during cancer and treatment as patients and families are incorporating large amounts of information. During and following chemotherapy treatment nurses can assess levels of attentional function and prepare and deliver educational material based at a level and in a manner consistent with their assessment findings.

Summary and Implications

This secondary analysis using data from two studies of women with breast cancer receiving treatment with chemotherapy provides results that contribute to the science of symptom management. The convergence of results from two samples confers validity. Those instances where results do not agree offer opportunities for further exploration.

Future Research

Capturing daily fluctuations in symptoms provides precise information on fluctuations that can be modeled to better understand the sequencing of symptoms in a cluster. There is a dramatic day-to-day fluctuation in fatigue (Schwartz, 2000; Schwartz et al., 2000) and a pattern of a rapid increase in both worst and average fatigue in the days following receipt of chemotherapy (Schwartz, 2000); however, a similar pattern for depression has not been not found (Jim et al., 2011). Reports of fatigue and depression

are higher in earlier chemotherapy infusions than later ones (Jim et al., 2011). Results from a study of lagged symptom changes using a Latent Change Score model approach indicate that nighttime awakening is associated with earlier subsequent peaks in fatigue, and increased fatigue is associated with greater subsequent depressed mood; these results are noteworthy because they suggest that there is a temporal sequence of symptom onset during platinum-based chemotherapy for gynecological cancer (Jim et al., 2013).

Exploration of subgroups of symptom reports is an important area of symptom management science. In patients with breast cancer who received surgery, a 3-class solution for attentional function resulted from a growth mixture model: high class (41.6%); moderate attention class (25.4%); and low-moderate class (33.0%) and each class had a different trajectory following surgery (Merriman et al., 2014). Interested in the neuropsychologic symptom, Kim et al. (2012) conducted a cluster analysis using data from women with breast cancer being treated with chemotherapy or radiation, concluding that patients were classified into four distinct subgroups: all low symptom, high fatigue and low pain, high pain, and all high symptom. Patient classification patterns were consistent across the treatment trajectory. These types of findings are useful to determine who needs more intensive symptom management during treatment (H. J. Kim, Barsevick, Beck, et al., 2012).

There are many possible causes of symptoms such as disease, a specific treatment modality, a comorbid condition, another symptom, and an interaction with another symptom (Barsevick et al., 2006). Future studies of attentional function should include assessment of anxiety, sleep disruption, and pain along with attentional function,

depression, and fatigue. In conjunction with a lagged symptom change design and daily measures of symptoms, results from a study incorporating attentional function, depression, fatigue, anxiety, sleep disruption, and pain might further illuminate important relationships among variables. The resulting symptom model would prove helpful for exploring potential mechanisms underlying symptoms and for those interested in developing targeted interventions to address symptoms.

Conclusions

The purpose of this study was to describe how levels of attentional function, fatigue, and depression change over time and whether levels and trajectories of fatigue and depression predict levels and trajectories of attentional function in women with breast cancer being treated with chemotherapy. Participants were assessed at clinically significant measurement times, including a baseline measurement prior to the start of chemotherapy using brief, valid, and reliable measure. Our use of multilevel modeling allows the inclusion of time-varying co-variables along with our time-varying main variable, attentional function. Our results suggest that the trajectories of attentional function, depression, and fatigue each exhibit a quadratic curve such that after start of chemotherapy each symptom worsens until approximately mid-treatment and then starts to improve before the end of treatment, returning to pretreatment levels by three to six months after the end of treatment. The exception to this pattern is fatigue measured by the PROMIS, which did not reach baseline levels at Follow-Up. The trajectories of fatigue and depression each predict the trajectory of attentional function such that a worsening of fatigue or depression predicts a worsening of attentional function.

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Appendix A

PROMIS Fatigue Short Form 8a and Schwartz Cancer Fatigue Scale

PROMIS Item Bank v1.0 – Fatigue – Short Form 8a

Fatigue – Short Form 8a

Please respond to each question or statement by marking one box per row.

	During **the past 7 days…**	Not at all	A little bit	Somewhat	Quite a bit	Very much
1	I feel fatigued	☐	☐	☐	☐	☐
2	I have trouble <u>starting</u> things because I am tired.....	☐	☐	☐	☐	☐
	In the past 7 days…					
3	How run-down did you feel on average? ...	☐	☐	☐	☐	☐
4	How fatigued were you on average?	☐	☐	☐	☐	☐
5	How much were you bothered by your fatigue on average?.....	☐	☐	☐	☐	☐
6	To what degree did your fatigue interfere with your physical functioning?	☐	☐	☐	☐	☐
	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
7	How often did you have to push yourself to get things done because of your fatigue?	☐	☐	☐	☐	☐
8	How often did you have trouble finishing things because of your fatigue?	☐	☐	☐	☐	☐

ID: _____

SCHWARTZ CANCER FATIGUE SCALE

Today's Date: _____

The words and phrases below describe different feelings people associate with fatigue. Please read each item and place an **X** in the box that indicated how much fatigue has made you feel in the past **2 to 3 days**.

	Not at all	**A little**	**Moderately**	**Quite a bit**	**Extremely**
1. Tired	☐	☐	☐	☐	☐
2. Difficulty thinking	☐	☐	☐	☐	☐
3. Overcome	☐	☐	☐	☐	☐
4. Listless	☐	☐	☐	☐	☐
5. Worn out	☐	☐	☐	☐	☐
6. Hopeless	☐	☐	☐	☐	☐

Appendix B

The Attentional Function Index

The Attentional Function Index

I. At this time, how well do you feel you are functioning in each of the areas below?
Place a mark through the line at whatever point best describes how you are doing in each area at present.

1. Getting started on activities (tasks, jobs) you intend to do.
   Not at all _____ Extremely well
2. Following through on your plans.
   Not at all _____ Extremely well
3. Doing things that take time and effort.
   Not at all _____ Extremely well
4. Making your mind up about things.
   Not at all _____ Extremely well
5. Keeping your mind on what you are doing.
   Not at all _____ Extremely well
6. Remembering to do all the things you started out to do.
   Not at all _____ Extremely well
7. Keeping your mind on what others are saying.
   Not at all _____ Extremely well
8. Keeping yourself from saying or doing things you did not want to say or do.
   Not at all _____ Extremely well
9. Being patient with others.
   Not at all _____ Extremely well

II. **At this time, how would you rate yourself on:**

10. How hard you find it to concentrate on details.
    Not at all _____ A great deal
11. How often you make mistakes on what you are doing.
    Not at all _____ A great deal
12. Forgetting to do important things.
    Not at all _____ A great deal
13. Getting easily annoyed or irritated.
    Not at all _____ A great deal

Note: Lines are not printed to 100 mm scale.

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Appendix C

CESD

Listed below are some statements. We would like you to tell me how often you felt or behaved this way — **DURING THE PAST WEEK.**

1 = Rarely or none of the time (less than 1 day)
2 = Some or a little of the time (1–2 days)
3 = Occasionally or a moderate amount of time (3–4 days)
4 = Most or all of the time (5–7 days)

During the PAST WEEK, on how many days did you feel or behave this way?	**Rarely or None less than1 day**	**Some or A Little 1–2 days**	**Occasionally or Moderate 3–4 days**	**Most or All 5–7 days**
1. I was bothered by things that usually don't bother me.	1	2	3	4
2. I did not feel like eating; my appetite was poor.	1	2	3	4
3. I felt that I could not shake off the blues even with help from my family or friends.	1	2	3	4
4. I felt that I was just as good as other people.	1	2	3	4
5. I had trouble keeping my mind on what I was doing.	1	2	3	4
6. I felt depressed.	1	2	3	4
7. I felt that everything I did was an effort.	1	2	3	4
8. I felt hopeful about the future.	1	2	3	4
9. I thought my life had been a failure.	1	2	3	4
10. I felt fearful.	1	2	3	4
11. My sleep was restless.	1	2	3	4
12. I was happy.	1	2	3	4
13. I talked less than usual.	1	2	3	4
14. I felt lonely.	1	2	3	4
15. People were unfriendly.	1	2	3	4
16. I enjoyed life.	1	2	3	4
17. I had crying spells.	1	2	3	4
18. I felt sad.	1	2	3	4
19. I felt that people disliked me.	1	2	3	4
20. I could not get "going."	1	2	3	4

Appendix D

Demographic and Health History Questionnaires

Demographics/Health History

Instructions: Please complete this form upon beginning the research study. The information you provide will be used only for this project and will not be seen by anyone else.

1. Date of Birth (mm/dd/yyyy): ☐☐ Month ☐☐ day ☐☐☐☐ year

2. Gender
   - ☐ Male
   - ☐ Female

3. Ethnicity
   - ☐ Hispanic
   - ☐ Non Hispanic

4. Race
   - ☐ Caucasian or White
   - ☐ African American or Black
   - ☐ Native Hawaiian or other Pacific Islander
   - ☐ Native American / Alaskan
   - ☐ Other _____

5. Highest education completed
   - ☐ Less than high school
   - ☐ High school graduate / GED
   - ☐ Associate / technical degree
   - ☐ Bachelor's degree
   - ☐ Advanced degree
   - ☐ Other _____

6. Marital status (Check one box)
   - ☐ Married / Partnered
   - ☐ Divorced / Separated
   - ☐ Widowed
   - ☐ Single

7. Employment (Check one box)

☐ Retired ☐ Homemaker
☐ Full time ☐ Unemployed
☐ Part time ☐ Disabled

8. To whom do you provide direct, daily care? (Check all that apply)

☐ Child / children ☐ None
☐ Elderly parent ☐ Other _____

9. How many people, including yourself, live in your household? _____

10. Your household income level (Check one)

☐ Under $25,000 ☐ $100,000-149,999
☐ $25,000-49,999 ☐ $150,000-199,999
☐ $50,000-74,999 ☐ $200,000+
☐ $75,000-99,999

11. Your Occupation

☐ Business, financial ☐ Education, training, library
☐ Office and Administrative ☐ Arts, entertainment, media
☐ Sales ☐ Retail
☐ Architecture, engineering ☐ Food prep or food service
☐ Life, physical, social science ☐ Protective service (fire, law enforcement)
☐ Legal ☐ Farming, fishing, forestry
☐ Construction, maintenance ☐ Production, transportation
☐ Other _____

12. When was your breast cancer diagnosed? ☐☐ ☐☐☐☐

Month Year

13. What stage of breast cancer are you diagnosed with?

0 ☐ I ☐ II ☐ III ☐ IV ☐

Current Medications:

List drug, dose, how often taken, and the reason that the drug was prescribed.

Drug name	Dose	How many times per day?	Prescribed for what purpose?

Continue to other side if more space is needed