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EVALUATING THE EFFECTS OF CHEMOTHERAPY ON COGNITIVE FUNCTION AND QUALITY OF LIFE IN PRE-MENOPAUSAL WOMEN WITH BREAST CANCER

by

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Abstract

A number of studies have documented significant reductions in quality of life (QOL) and cognitive function in women with breast cancer (BrCa) receiving adjuvant chemotherapy. These decrements can be identified in some women even several years following treatment. However, the majority of relevant research has been based on retrospective data in women with BrCa. Moreover, current estimates suggest that 25% of BrCa will be diagnosed in women under age 50, and little data are available regarding younger women's cognitive function and QOL during chemotherapy. This study examined the change in cognitive function and QOL in 20 pre-menopausal women with BrCa receiving chemotherapy. Measures of cognitive functioning and QOL, along with serum hormone values (i.e., estradiol), were analyzed prior to, during, and post-treatment.

Objective measures of cognitive functioning on the High Sensitivity Cognitive Screen (HSCS) did not change over the course of treatment, except for a significant improvement in memory performance. Subjective cognitive difficulties, as assessed with the Breast Cancer Prevention Trial (BCPT) Cognitive Problems subscale and clinical interview, increased significantly over the study period. The HSCS Total score and Memory subscales were not significantly associated with BCPT Cognitive Problems. Chemotherapy-relevant measures of QOL, including menopausal symptoms, fatigue, and depressive symptoms, all significantly worsened over the course of treatment.

Higher levels of blood hemoglobin at baseline, but no QOL measures, predicted an increase in BCPT Cognitive Problems over the course of treatment. Higher baseline hemoglobin, as well as older age and lower hot flashes, predicted an increase in fatigue, and lower baseline hot flashes predicted an increase in depressive symptoms. Lower baseline

levels of serum estradiol and higher depressive symptoms predicted an increase in hot flashes. This in-depth study of pre-menopausal women with BrCa suggests that deficits in cognition, at least in young and highly educated sample such as in the current study, might have been overestimated in previous studies. Continued research with longitudinal study designs and larger samples is necessary to further understand the impact of diagnosis and treatment of young women with BrCa.

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LIST OF ABBREVIATIONS

BCPT:	Breast Cancer Prevention Trial
BDI:	Beck Depression Inventory
CES-D:	Center for Epidemiologic Studies- Depression Scale
CMF:	Cyclophosphamide, Methotrexate, and 5-Fluorouracil
CNS:	Central Nervous System
ER:	Estrogen Receptor
FACT:	Functional Assessment of Cancer Therapy
FEC:	5-Fluorouracil, Epirubicin, Cyclophosphamide
Hb:	Hemoglobin
HSCS:	High Sensitivity Cognitive Screen
IGF-1:	Insulin-Like Growth Factor 1
IGFBP-3:	Insulin-Like Growth Factor Binding Protein 3
MOS-36:	Multiple Outcomes Study Short Form 36 Health Survey
MOS MCS:	Multiple Outcomes Study- Mental Component Summary
MOS PCS:	Multiple Outcomes Study- Physical Component Summary
NAMS:	North American Menopausal Society
NIH:	National Institutes of Health
NIMH:	National Institutes of Mental Health
NGF:	Nerve Growth Factor
POMS:	Profile of Mood States
QOL:	Quality of Life
SD:	Standard Deviation
SF-36:	Short Form-36
TNF-α:	Tumor Necrosis Factor- Alpha

Evaluating the effects of chemotherapy on cognitive function and quality of life in pre-menopausal women with breast cancer

Breast cancer affects more than 200,000 women each year in the United States (American Cancer Society., 2005), and most women diagnosed at an early stage have potentially curable disease. The 5-year survival rate for those diagnosed with localized breast cancer has increased from 80% in the 1950's to 98% in 2000 (American Cancer Society, 2005). Between 1990 and 2000, the mortality rate from breast cancer decreased by 2.3% annually. Decreases were most impressive in women under age 50, for whom annual mortality rates decreased by 3.7%.

Owing to the improved survival associated with administration of adjuvant chemotherapy and/or radiation therapy, the majority of women diagnosed with breast cancer will receive some type of adjuvant treatment (Early Breast Cancer Trialists' Collaborative Group, 2005). Impairment in neurocognitive function can accompany chemotherapy with deficits including memory loss, difficulty with concentration, difficulty learning new material, loss of reading comprehension, distractibility, difficulty in performing multiple tasks (multi-tasking), altered visual/spatial orientation, decreased verbal fluency, and the diminished ability to work with numbers (Ahles & Whedon, 1999). Adult cancer survivors also report persistent changes in cognitive function following chemotherapy (Ahles & Saykin, 2001). The President's Cancer Panel (1999) identified cognitive deficits associated with cancer treatment as having a dramatic

negative impact on quality of life; the Panel cited cognitive deficits and quality of life as problems that should be addressed both clinically and in the research arena.

Research on the impact of chemotherapy on cognitive function can be traced to the early 1980's. This research produced mixed results regarding the impact of therapy on the development of cognitive deficits (Oxman & Silberfarb, 1980; Silberfarb, 1983; Silberfarb, Philber, & Levine, 1980). More recently, studies have revealed relationships among cognitive deficits, treatment with chemotherapy, and diminished quality of life. However, questions remain regarding the neurotoxic impact of chemotherapy: Are the problems acute or chronic? Does the type and duration of therapy make a difference? How does chemotherapy affect the central nervous system? Does undergoing an accelerated menopause and change in the hormonal milieu associated with chemotherapy relate to cognitive change? Do other psychological factors influence the extent of cognitive decline? Does the stage of disease influence the severity or duration of symptoms? The proposed research will attempt to address some of these unanswered questions, specifically focusing on evaluating change in cognitive function and quality of life associated with cancer treatment in a sample of young breast cancer patients receiving a relatively uniform treatment regimen. In the next section, a review is presented to highlight the impact of an accelerated menopause as a result of chemotherapy on cognitive function and quality of life. Next, an evaluation of chemotherapy's impact on fatigue and mood will be presented to establish the role these factors might have on cognitive function and quality of life. This review will establish the foundation for the proposed study.

Cognitive Changes Associated with Chemotherapy in Women With Breast Cancer

A significant reduction in aspects of cognitive function and quality of life are observed in 18-50% of women receiving standard dose adjuvant chemotherapy, both immediately and several years following treatment (Ahles & Saykin, 2001; Brezden et al., 2000; Meyers & Abbruzzese, 1992; Schagen et al., 1999; Van Dam et al., 1998). Although breast cancer has traditionally been considered a disease of older women, current estimates suggest that as many as 25% of those diagnosed with the disease are under age 50 (Bloom, Stewart, Chang, & Banks, 2004), and 7% of breast cancers are diagnosed in women under age 40 (Althuis et al., 2003). The impact of treatment may vary as a function of the recipients' age.

Standard and high-dose chemotherapy, immunotherapy, and hormonal treatment all have been identified as having neurotoxic side effects (Meyers, 2000). The associated deficits in cognitive function are most marked in the areas of verbal fluency, processing speed, concentration and short-term memory (Schagen et al., 2002). Numerous studies have identified cognitive impairments related to cytotoxic drugs that are commonly used in standard dose chemotherapy regimens and have documented effects on the central and peripheral nerves. Specifically, central and peripheral neuropathy, encephalopathy, leukoencephalopthay, ototoxicity, and cerebellar symptoms have been associated with cytotoxic drugs (Tuxen & Werner, 1994).

Previously, it had been thought that most cytotoxic agents did not have the ability to cross the blood-brain barrier. Evidence from more recent studies supports the notion that cytotoxic agents do indeed cross the barrier (Troy, McFarland, & Littman-Powers, 2000; Tuxen & Werner, 1994). The three most common types of central nervous system (CNS) damage that are identified in neurocognitive research as side effects from

cytotoxic drugs are: (1) vascular injury leading to obstruction of small and medium-sized blood vessels, spontaneous thrombosis, ischemia/infarction, and parenchymal necrosis; (2) direct injury to the cerebral parenchyma; and (3) an immunologic effect secondary to an allergic hypersensitivity and an autoimmune vasculitis (Ahles & Saykin, 2001).

Because chemotherapy is typically given in combination, it is difficult to determine which therapy produces a particular cognitive deficit. Most studies evaluating the effects of chemotherapy focus on patients treated with any or some combination of the following drugs: cyclophosphamide, doxorubicin, 5-fluorouracil, methotrexate, cisplatin, vincristine, etoposide, vinblastine, and steroids (Ahles & Saykin, 2001). Therefore, the observed cognitive effects may be from a single agent or from a combination of several agents. Because cancer treatments are not equal, it is likely that they do not produce a uniform effect on cognitive function among patients (Anderson-Hanley, Sherman, Riggs, & Aocha, 2003). As previously described, cognitive function is a multidimensional concept that includes: attention, concentration, learning, memory, problem-solving ability, visuospatial abilities, mental flexibility, psychomotor efficiency, and manual dexterity (Bender, Paraska, Sereika, Ryan, & Berga, 2001). One difficulty in assessing cognitive changes resulting from chemotherapy is the diffuse nature of the deficits that can impact all of these processes (Bender et al., 2001). In addition, many of these changes are also consistent with the natural aging process; determining which factors are due to treatment and which factors are due to aging, or accelerated menopause, is challenging.

Studies have used different methods to determine the impact of chemotherapy. A between-subject design, in which data from healthy controls or normative data are

compared to post-chemotherapy values, has traditionally been used to quantify change in cognitive function and quality of life. More recently, it has been suggested that a prospective, within-subjects design be used to determine change on the individual level (Schagen et al., 2002). A brief review of the literature evaluating cognitive changes and quality of life in women with breast cancer reveals the strengths and limitations of the existing body of work.

In a pivotal study by Wieneke and Dienst (1995), cognitive function in patients with early-stage breast cancer who had completed treatment consisting of 3-18 months of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) was compared to that of healthy controls. The Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Eraugh, 1961) was used to assess depressive symptoms, and a comprehensive battery of neuropsychologic tests was administered to evaluate cognitive function in several domains. Approximately 75% of women who previously had received chemotherapy experienced moderate clinical impairment in one or more measures of cognitive function as compared to published test norms of healthy individuals. Impairment was defined as neuropsychologic test scores that dropped at least one standard deviation from the estimated premorbid functioning. Level of cognitive impairment was positively correlated with duration of treatment, but not correlated with other treatment variables (type of chemotherapy and time since treatment) or depressive symptoms.

In a study by van Dam et al. (1998), cognitive function and quality of life was compared in three groups of women with breast cancer receiving standard-dose chemotherapy, high-dose chemotherapy, or surgery plus radiation only. Standard-dose therapy included 5-fluorouracil, epirubicin, cyclophosphamide (FEC) plus tamoxifen, and

the high-dose regimen was FEC and tamoxifen plus thiotepa and carboplatin. Women were administered a battery of 13 neuropsychological tests approximately two years after receiving their final dose of therapy. Cognitive impairment was defined as having at least three neuropsychologic scores that fell two standard deviations (*SD*) below the mean. A statistically significant difference in cognitive deficit emerged between those who had received high dose chemotherapy versus those not treated with chemotherapy. In the comparison group, only 9% experienced cognitive impairment, compared with 17% in the standard-dose group and 32% in the high-dose group (Van Dam et al., 1998). These data suggest that the cognitive effects of therapy may persist over time and are dose-dependent.

In a subsequent study by the same team of researchers (Schagen et al., 1999), subjects received either standard-dose treatment which included CMF or surgery only. Subjects underwent a battery of 14 neuropsychologic tests between 1.9 years (CMF group) and 2.4 years (surgery group) following therapy. The analysis controlled for anxiety, depression, and time since therapy. Approximately 28% of those treated with CMF experienced cognitive impairment compared with 12% of the comparison group. Patients who received CMF had more problems with concentration and memory compared with those who underwent surgery only. The researchers concluded that women receiving CMF chemotherapy have a significantly higher risk of late cognitive impairment, approximately 2 years following treatment, than breast cancer patients who were not treated with chemotherapy.

To address the limitations of their previous research, these authors conducted a longitudinal study using subjects recruited from their original study. Three groups of

breast cancer patients and a control population of healthy women underwent an evaluation of cognitive performance and assessment of treatment-related symptoms (Schagen, Muller, Mellenberg, & Van Dam, 2006). Subjects received high-dose chemotherapy, standard-dose chemotherapy, or were early-stage breast cancer patients and received radiation only. All subjects underwent neuropsychological testing pre-treatment and 6-months following treatment. Noticeable differences in baseline characteristics among the group identified: subjects receiving radiation only were older and did not achieve menopause at the same rate as the other treatment groups. There were no noticeable differences between the four groups at the initial assessment but more of the subjects receiving high-dose chemotherapy experienced deterioration in cognitive performance over time compared to controls. There were no noticeable differences in cognitive performance at the subsequent time point in women receiving standard-dose treatment or radiation therapy only.

Cognitive function and mood state were compared between women who were currently undergoing treatment, women who had completed adjuvant chemotherapy at least one year previously, and healthy controls (Brezden et al., 2000). The High Sensitivity Cognitive Screen (HSCS) (Fogel, 1991) and the Profile of Mood States (POMS) (McNair & Kahn, 1984) were administered. The HSCS assesses six cognitive domains: memory, language, visual-motor, spatial, attention and concentration, and self-regulation and planning. The POMS is a self-administered assessment of six moods: tension-anxiety, anger-hostility, fatigue-inertia, depression-dejection, vigor-activity, and confusion-bewilderment. HSCS scores were significantly worse in those currently receiving adjuvant treatments versus the control group. In subjects at least one year

since treatment, a non-significant difference was observed, but suggested that cognitive deficits might be maintained over time. There were no significant differences in mood between those receiving treatment and the controls, suggesting that cognitive function was unlikely to be associated with mood disturbances.

To determine if patients experience long-term neuropsychologic impact from standard-dose chemotherapy, Ahles and colleagues (2002) evaluated survivors of breast cancer or lymphoma approximately 10 years after receiving their diagnosis. This study compared those who had received standard-dose chemotherapy versus those who received surgery and/or radiation therapy only. Survivors who had been treated with systemic chemotherapy had significantly worse scores on the battery of neuropsychologic tests compared to those treated with surgery and/or radiation alone. Specific domains that were affected by systemic treatment were verbal memory and psychomotor functioning. In addition, individuals who had received chemotherapy also self-reported greater problems with working memory. This study provided the longest follow-up to date on the impact of chemotherapy on neuropsychologic function, but the researchers found that only a subset of individuals had significant long-term deficits (Ahles et al., 2002).

These previous studies have observed that women receiving adjuvant treatment for breast cancer do experience cognitive impairment relative to a comparison group (Phillips & Bernhard, 2003). But these studies focused on treatment versus control comparisons to infer change in cognitive function rather than examining change over the course of chemotherapy. Therefore, these studies need to be interpreted cautiously because of a variety of inherent methodological problems (Bender et al., 2006). Recent

studies have used a within-subject design comparing pre- and post-treatment values to assess the impact of chemotherapy in women with breast cancer (Schagen et al., 2002; Tannock, Ahles, Ganz, & Van Dam, 2004). A longitudinal study (Wefel et al., 2004) of 18 women who underwent a neuropsychological battery before treatment and at 3 weeks post-chemotherapy and 1-year post-chemotherapy revealed that 33% of women exhibited cognitive impairment prior to the initiation of chemotherapy and that 61% of this cohort had a decline in one or more cognitive domains following treatment. Impairment was defined by meeting one of two criteria based on published normative data from a healthy population: either one or more tests with a 1.5 *SD* below the mean score or one test with a 2.0 *SD* below the mean. Specific performance domains that declined were attention, learning, and speed of processing. This was the first research to demonstrate the impact on cognitive function in a prospective study of women with non-metastatic breast cancer treated with standard chemotherapy. Although this study is limited by the small sample size, it provides a framework for future studies. To further explore the incidence of baseline cognitive deficits, research by Cimprich and colleagues (2005) evaluated pre-treatment factors related to cognitive function in women with a newly diagnosed breast cancer. One-hundred eighty-four women aged 27-86 years old were evaluated with standard measures prior to surgery for breast cancer. Scores on objective measures of attention and short-term memory fell within the normal range of health adults. Objective measures were not correlated with self-report measures of effectiveness (Cimprich, So, Ronis, & Trask, 2005). However, age was significantly correlated with objective performance and subjective report with the older, post-menopausal group having the poorer performance. More years of education was significantly related to better

performance on objective measures, but education was not associated with subjective report of cognitive functioning. The final predictor of poor performance on objective measures was the presence of other chronic health conditions; however, co-morbid health conditions were not predictive of subjective report. Unfortunately, this study did not evaluate subsequent time points and only presented pre-treatment level of functioning.

A recent meta-analysis (Anderson-Hanley et al., 2003) examined 30 studies which have evaluated the neuropsychological effects of chemotherapeutic treatments for adults with various cancers. The authors also commented on the use of between-subjects and within-subjects designs. Because the between-subjects, cross-sectional design uses comparison groups that do not undergo treatment, an artificially inflated between-groups difference may appear, owing to the possibility that the issues and concerns of cancer patients might not be representative of the general population (Anderson-Hanley et al., 2003). Specifically, treatment and control groups might differ in a number of factors including physical health, psychological state, level of independence, and social relationships. These differences might underlie apparent group differences in cognitive function. In addition, assessing cognitive function only following treatment may actually be picking up pre-existing cognitive deficits, not those resulting from treatment. Anderson-Hanely et al. (2003) emphasized the benefits in using longitudinal designs in which variables such as education and prior experiences are held constant, and change over time in the dependent variable can be assessed. A within-subject design also may be useful in assessing subtle cognitive changes that are not identified in a cross-sectional analysis. However, one limitation commonly noted when psychometric tests are repeated in the within-subjects design is that of a practice effect, typically resulting in

improvement in the re-test score. The authors pointed out that in a sample of cancer patients, a small negative change in cognitive function from pre- to post-test might be observed, and although not statistically significant, may actually hold clinical significance (Anderson-Hanley et al., 2003).

One clear theme appears in the literature on cognitive change and treatment for breast cancer: some individuals do experience short- and long-term deficits in cognitive domains. Specifically, attention, verbal memory, visuospatial function, and executive functions appear to be influenced by chemotherapy. Limitations in the above-reviewed studies include both the small sample sizes and a preponderance of cross-sectional, between-group study designs (Ahles et al., 2002). Also, the heterogeneity of the study samples, which included pre- and post-menopausal women, women with a variety of stages of disease, and assorted treatment regimens makes comparing the results among studies difficult. In order to assess individual change, a within-subjects design is considered superior (Schagen et al., 2002; Tannock et al., 2004), but the practice effect must be accounted for in the study design. The current study attempted to address these previously reported limitations of assessing change in cognitive function. This study utilized a within-subjects design in a sample that is relatively uniform in age, menopausal status, and treatment regimen. To assess cognitive performance the High Sensitivity Cognitive Screen (HSCS) (Fogel, 1991), the Cognitive Difficulties Scale (McNair & Kahn, 1984) and the Breast Cancer Prevention Trials Cognition subscale (Stanton, Bernaards, & Ganz, 2005) were administered (Table 1) prior to, during, and immediately following treatment. Self-report of perceived change in cognitive performance was also collected by clinical interview. To examine subtle and global changes in cognition, we

examined change in HSCS subtest scores and change in total scores. We addressed criticisms noted in the review by Anderson-Hanley et al. (2003) by attempting to capture subtle changes in cognitive function within a homogenous sample of young women with breast cancer.

Accelerated Menopause, Cognitive Function, and Quality of Life

There is mounting evidence that estrogen may play an important role in brain function, and estrogen deprivation might lead to cognitive decline (Sherwin, 1998, 2003). The brain is a target organ for hormones, yet the impact of their effect on the brain still is not fully understood (Greene & Dixon, 2002). Women who have experienced surgical menopause by undergoing a bilateral salpingo-oophorectomy have demonstrated pre- to post-surgical declines in verbal memory that was enhanced by estrogen replacement therapy (Sherwin, 2005). Chemotherapy can also induce menopause. Previous research has suggested that women who experience chemotherapy-induced menopause might have similar deficits in cognitive function to that observed by those undergoing surgical menopause, but no studies to date have addressed this question directly (Ahles et al., 2002).

The current trend to treat early-stage breast cancer with chemotherapy continues to increase (Mansour et al., 1998), but the short- and long- term impact of therapy is not completely understood. It has been suggested that particular cognitive domains are influenced by estrogen deprivation, specifically verbal memory, processing speed, and reasoning (Sherwin, 1998, 2003). Estrogenic effects appear to occur in a variety of ways, including the accumulation or the production and secretion of the neurotransmitter acetylcholine, increased cerebral blood flow, increased enlargement and maturation of

the dendritic spines of the nerve cells located in the hypothalamus and hippocampus, and an increase in nerve growth factor and receptor activation (Rice, Graves, McCurry, & Larsen, 1997; Toran-Allerand et al., 1992). Estrogen receptors (ER) are also found in abundance in several area of the brain: the cerebral cortex, hypothalamus, pituitary gland, and the limbic system (Ciocca & Roig, 1995). More specifically, ER-α receptors are mainly found in the hypothalamus while ER-β receptors are found throughout the brain and are associated with superior cerebral functions and memory (Angelopoulos, Barbounis, Liviadas, Kaltsas, & Tolis, 2004). It has been proposed that estrogen affects memory-linked processes in postmenopausal women by altering brain activation patterns in the hippocampus and hypothalamus (Angelopoulos et al., 2004). Estrogen depletion causes a decrease in high-affinity choline uptake and choline acetyltransferase activity in the hippocampus and frontal cortex. Estrogen replacement reverses this effect (Simpkins et al., 1997).

Adjuvant chemotherapy with alkylating agents dramatically decreases ovarian function and systemic hormone levels, which may, in turn, be responsible for cognitive changes (Valagussa, Moliterni, Zambetti, & Bonadonna, 1993). Preliminary results from a large, national trial found that 50% of women under age 40 and 80% of women over age 40 who receive adjuvant chemotherapy will remain postmenopausal following treatment (Swain et al., 2005), and approximately 80% of all women in the study reported amenorrhea at 6 months from the onset of treatment. Ahles and Saykin (2002) have suggested further exploration of the association between estrogen deprivation and chemotherapy, both of which are known to influence verbal memory. In a review of the impact of hormones on cognition by Greene and Dixon (2002) other hormones also have

been identified as playing a role in maintaining cognition. Testosterone provides benefits to the brain, whereas progesterone may have a negative impact on cognition (Greene & Dixon, 2002). To date, little research has evaluated the impact of chemotherapy on serum hormone levels and the role that hormonal variation may play on cognitive function and quality of life.

Symptoms of accelerated menopause may also exacerbate cognitive decline and compromise quality of life. Common side effects of accelerated menopause include night sweats, hot flashes, mood instability, and sexual dysfunction (Ganz et al., 2000). It has been suggested that between 40-60% of breast cancer survivors experience hot flashes, but few other post-menopausal symptoms have been thoroughly evaluated (Crandall, Peterson, Ganz, & Greendale, 2004). Research has not yet evaluated the contribution of reproductive hormones and chemotherapy in women with breast cancer compared to like-women who have not undergone chemotherapy. A pilot study, currently underway, explores changes in ovarian function and associated menopausal symptoms in premenopausal women with breast cancer receiving chemotherapy (Loprinzi et al., 2005). Loprinzi et al. are attempting to recruit 20 subjects who will have repeated androgen levels evaluated, and associations with fatigue, weight, psychological symptoms, vasomotor symptoms, and libido will be examined. A blood draw and questionnaires will be administered prior to initiation of treatment, mid-treatment, and post-treatment (approximately 6 months following completion of treatment). However, this study is not evaluating cognitive function. Also, results of this study may be confounded by the fact that many patients receive additional treatment such as adjuvant anti-hormonal therapy or radiation therapy, which might affect post-treatment values. In the present study, we

collected serum hormone values along with the battery of psychometric tests pre-treatment, mid-treatment, and post-treatment, but prior to the administration of any anti-hormonal or radiation therapy. We assessed the relation of hormone levels to changes in cognitive function and quality of life variables. Through this analysis, we explored whether reproductive hormones are influenced by chemotherapy in young women being treated for breast cancer and whether deficits in reproductive hormones are associated with changes in cognitive function and other unwanted side-effects.

We were interested in the relations of reproductive hormones, cognitive function, and indicators of quality of life. Quality of life is a broad construct that typically involves self-reported status in physical, functional, and social domains (Fitzpatrick, 2004). To our knowledge, no study has evaluated the association between hormonal changes, cognitive function, and quality of life variables in premenopausal women undergoing chemotherapy. On standard measures of depression and quality of life, younger breast cancer patients demonstrate greater changes in mood and poorer emotional functioning than older patients (Ganz, Greendale, Peterson, Kahn, & Bower, 2003). Younger women may also incur a greater disruption to their daily functioning at home and at the work place. Further, chemotherapy-induced menopause may place an additional burden on young women. In order for women to make informed decisions regarding their treatment options and to implement potentially useful lifestyle modification, women need to be educated by their clinicians regarding the differential impact of treatments as a function of age and stage of life (Janz et al., 2004). The current study was intended as a step toward that goal.

Evaluation of the Impact of Fatigue and Mood on Cognitive Function

Fatigue is a nonspecific construct that involves subjective feelings of tiredness, weakness, and/or lack of energy (Bower et al., 2000) and is reported by approximately 50% to 85% of women taking adjuvant chemotherapy. It can adversely affect neurocognitive function (Meyers, 2000; Schagen et al., 1999). Fatigue may last well beyond the treatment period for months or years in breast cancer patients who received adjuvant chemotherapy (Andrykowski, Curran, & Lighner, 1998). Fatigue does appear to plateau after 2-3 years and then remains relatively constant, but does not return to the pre-treatment level (Flechterner & Bottomley, 2003).

During adjuvant therapy, there are multiple possible causes of fatigue including anemia resulting from chemotherapy and/or radiation, depression, stress, hormonal changes, pain, and other concomitantly administered medications including steroids and antidepressants (Berman et al., 1997; Friedman, Lehane, Weinberg, Mirabi, & Cooper, 1993; Gouchie & Kimura, 1991; Mendoza et al., 1999; Meyers & Abbruzzese, 1992; Newton, Slota, Yuzpe, & Tummon, 1996; Sherwin, 1996). It has been suggested that one cause of fatigue in breast cancer patients is the disease itself, and it may worsen as a result of treatment (Glaus, 1998). In a large case-control study of breast cancer patients, fatigue was considered to be the most distressing side effect of treatment (Bower et al., 2000). These researchers also found cognitive deficits in some patients, but the relationship to fatigue was not clear. In a study in which fatigue was measured with questionnaires that target domains affected by fatigue women treated for breast cancer were compared to a matched comparison group of normal women who did not have breast cancer and were not receiving chemotherapy (Mar Fan et al., 2002; Tchen,

Downie, & Theriault, 2001; Tchen et al., 2004). Women treated for breast cancer experienced significant fatigue and menopausal symptoms compared to the controls.

Similarities exist between the symptoms experienced in fatigue and anxiety, and those consistent with menopause (Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998). Fatigue has also been associated with depressed mood and anxiety in breast cancer survivors (Hann et al., 1998). In a large sample of over 2000 breast cancer survivors (Bower et al., 2000), variables associated with fatigue were compared in women who recently completed treatment for breast cancer, those who had previously completed treatment, and healthy controls. Fatigue was not identified as an independent side effect of the treatment but was found to be linked to depressive symptoms, pain and sleep problems (Bower et al., 2000). Bower et al. (2000) also found that those recently treated for breast cancer experienced more side effects than those who had already completed treatment. Those who experienced side effects noted that symptoms lessened over time. In addition, women treated for breast cancer experienced greater fatigue than did healthy controls. Difficulty sleeping is common for breast cancer survivors and is also associated with higher levels of fatigue (Andrykowski et al., 1998; Broeckel et al., 1998). In summary, fatigue can occur as a result of breast cancer, as a result of breast cancer treatments, or as a symptom of menopause.

It is difficult to distinguish fatigue from the other chemotherapy-induced side effects. The causes of fatigue and the causes of cognitive deficits are likely to be multidimensional and examination of additional variables can be useful in determining the source of the side effects. The current study used fatigue-specific assessments including the FACT (Cella, 1997), along with serum hemoglobin levels, to assess

baseline fatigue and symptoms prior to, during, and post- treatment. A decrease in hemoglobin for women receiving chemotherapy below 12g/dL has been associated with fatigue and a decreased quality of life. To assess depressive mood, the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Center for Epidemiologic Studies Depression Scale (CES-D) were used. Using measures designed to assess fatigue and associated symptoms, we attempted to describe which side effects may be related to treatment and how they may be associated with cognitive function and global quality of life.

Summary

The results of this study help to facilitate our understanding of the impact of chemotherapy on a growing population of young breast cancer patients. Potential deficits in cognitive functioning and quality of life are important aspects to consider when making decisions regarding breast cancer treatments. Data from this study may provide a foundation for continued research on the impact of chemotherapy in a population of women that remains poorly understood.

Study Aims

1. Evaluate whether or not premenopausal women with breast cancer who are receiving chemotherapy experience changes in cognitive function, as well as changes in physical symptoms and quality of life variables.
2. Explore the relationship among cognitive function and other variables associated with receiving chemotherapy for breast cancer including: change in serum hormone levels (estradiol, progesterone, testosterone, IGF1/IGFBP3), self-reported symptoms collected on the Breast Cancer Prevention Trial Symptom Scales (Stanton et al., 2005), depressive symptoms, and fatigue.

Hypotheses

We predicted that young women with breast cancer receiving chemotherapy would experience decrements in cognitive function and quality of life, and increases in menopausal symptoms and fatigue over the course of treatment. We also predicted that deficits in cognitive function, and an increase in treatment-related symptoms and fatigue, would be associated with accelerated menopause (i.e., decline in estradiol). Relationships among other relevant quality of life variables were explored.

Method

Participants

Twenty-eight pre- or peri-menopausal (at least one period within the past 6 months) women between the ages of 25 and 55 with breast cancer were invited to participate in this research conducted at the University of Kansas Medical Center and its affiliates, and 20 patients agreed to participate. Participants were diagnosed with breast cancer for the first time, had no current evidence of distant disease, and their planned course of treatment included receiving either adjuvant (following definitive surgery for breast cancer) or neo-adjuvant chemotherapy (treatment prior to definitive surgery for breast cancer) every two or three weeks. Women with a long-term history of depression or mental illness, or with a history of any primary hematologic disorder or malignancy were excluded from study participation.

Procedure

Potential subjects were identified by the treating clinician and the study coordinator as meeting the eligibility criteria. Prospective subjects received a complete explanation of the study requirements. Patient identifiers were kept confidential, and study participants signed an institutional review board-approved consent form. Participation lasted the duration of their recommended chemotherapy treatment (on average four to six cycles). Subjects completed treatment in approximately 8 to 12 weeks from treatment initiation.

Study participants received the current standard of care treatment as practiced by clinicians at the University of Kansas Cancer Center for women with breast cancer. Subjects received four to six cycles of adriamycin or epirubicin plus cyclophosphamide

(AC or EC), or an alternative therapy including Herceptin or Carboplatnimum (Carbo) plus Taxotere every two to three weeks. Assessments were administered and serum hormone levels drawn prior to initiation of chemotherapy, mid-treatment (prior to the third cycle of chemotherapy), and two or three weeks following the final cycle of chemotherapy. The final assessment (post-treatment) was completed prior to the initiation of any additional treatment, such as radiation therapy or anti-hormonal treatment. All subjects completed a menstruation log which was used to document menopausal symptoms throughout the study.

Measures

Demographic variables were collected through patient interview and from chart review. Variables including age, race, level of education, current employment, medical history, current medications, and stage of disease were also collected. At each assessment point, hemoglobin level, concomitant medications, menopausal and chemotherapy related symptoms, a battery of psychological questionnaires, and subjective measures of cognitive function were administered (Table 1). Objective assessment of cognitive function was administered pre- and post-treatment.

Cognitive functioning was measured based on recommendations of the National Institutes of Mental Health (NIMH) workshop on neuropsychological assessment (Butters et al., 1990) and other researchers (Sherwin, 1998). Several tests were used to assess objective and subjective memory and attention/concentration (i.e., ability to sustain attention, ability to hold stimuli in memory, verbal memory, multi-tasking) (Picket, Therberger, Brown, Schweitzer, & Nissensen, 1999; Van Dam et al., 1998). The High Sensitive Cognitive Screen (HSCS) (Faust & Fogel, 1989) is a clinician-

administered psychometric test that consists of a selection of moderately difficult items testing six major domains of neuropsychological performance: memory, language, attention/concentration, visual/motor, spatial, and self-regulation and planning. The HSCS is sensitive in detecting subtle cognitive impairment and has been validated for subjects in the age range of 16 to 65 years. The HSCS predicts a normal versus abnormal result of comprehensive neuropsychologic assessment with 93% accuracy, and it predicts global versus restricted deficits with 87% accuracy. It has high inter-rater and test-retest reliability (Brezden et al., 2000). Most of the items are adapted from standard neuropsychologic tests. Test items are presented orally or in written format. Responses include verbal answers, writing and drawing samples and arm and hand movement in response to commands. Scores are classified by level of performance nd the degree of abnormality is also described (i.e., mild, moderate, or severe). Because we attempted to define subtle changes in cognitive function, the authors of the HSCS recommend that a direct item analysis (i.e., number of trials to achieve accurate sentence recall) of performance is generally more appropriate than using a categorical interpretation. We developed a tool that allowed us to score and identify change per item, category, and overall classification (Table 2). We measured overall cognitive functioning across the six cognitive domains (total HSCS score) and measured specific performance items to describe subtle changes in cognition. Higher scores represented worse cognitive function. Subjective cognitive functioning was assessed with the Cognitive Difficulties Scale (CDS) (McNair & Kahn, 1984), which consist of 26 self-report items on a psychometrically adequate scale. A factor analysis of the CDS identified meaningful factors which corresponded to memory deficits associated with neurological dysfunction.

Health-related quality of life was assessed with the MOS-SF-36 (Ware & Sherbourne, 1992), which was used to compare our study sample to other cancer patients and healthy populations. The MOS-SF-36 contains eight individual subscales (Hays, Stewart, Sherbourne, & GN., 1993; Ware & Sherbourne, 1992). Each subscale is scored from 0 to 100, with 100 being the most favorable score. The subscales are physical functioning, role function-physical, bodily pain, social functioning, emotional well being, role function-emotional, energy/fatigue, and general health perceptions (Ware & Sherbourne, 1992). Adequate psychometric properties, general population norms, and norms in relevant groups (e.g., breast cancer patients) for the MOS-SF-36 are documented. The primary scales used for analysis was the Physical and Mental Component Summary Scores, which are additive functions of the subscales.

The Breast Cancer Prevention Trial (BCPT) Symptom Checklist (Ganz, Day, Ware, Redmond, & Fisher, 1995), a 43-item list of common physical and psychological symptoms including symptoms that may be related to menopause or chemotherapy toxicity (e.g., hot flashes, headache), was administered. Participants indicated whether they have experienced each symptom in the past four weeks (yes/no) and symptom severity (0 = not at all; 4 = extremely). Eight factors have been identified that correspond to physical symptoms associated with cancer treatment, chemoprevention, menopause, and normal aging: hot flashes, nausea, bladder control, vaginal problems, musculoskeletal pain, cognitive problems, weight problems, and arm problems (Stanton et al., 2005).

Depressive symptoms were measured with the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Center for Epidemiologic Studies Depression Scale (CES-D) (Hann et al., 1998). The BDI is a consolidated collection of depressed patient's

descriptions of their experiences into 21 symptoms and attitudes, which are rated on a 4-point scale ranging from 0 (not experiencing the symptom) to 3 (significantly experiencing the symptom). The BDI demonstrates high internal consistency, with alpha coefficients of .86 and .81 for psychiatric and non-psychiatric populations, respectively (Beck, Steer, & Garbin, 1988). The CES-D is a short, self-report scale of depression intended for the general population (Radloff, 1977). Studies among cancer patients demonstrated internal consistency with Cronbach alpha coefficients of 0.87 for a healthy comparison group and 0.89 for a cancer patient sample. The test-retest reliability is 0.51 ($p < 0.001$) for a healthy comparison group and 0.57 ($p < 0.001$) for a cancer patient sample (Hann et al., 1998).

Fatigue was assessed with a symptom-specific questionnaire, the Functional Assessment of Cancer Therapy (FACT) (Cella, 1997), consisting of the FACT-Fatigue (F) (Yellen, Cella, Webster, Blendowske, & Kaplan, 1997), the FACT-An, and 7 related items that are used to assess symptoms of anemia and fatigue. The 41-item FACT-F and the 48 item FACT-An scores were found to be stable (test-retest $r = 0.87$ for both) and internally consistent (coefficient alpha range = 0.95-0.96). The 13-item Fatigue subscale covers specific fatigue symptoms. Patients answered questions on a five-point scale for how true the statements have been for them in the past 7 days. The symptom-specific subscales also showed good stability (test-retest r range = 0.84-0.90), and the Fatigue subscale showed strong internal consistency (coefficient alpha range = 0.93-0.95) (Cella, 1997). Internal consistency of the miscellaneous nonfatigue items was lower but acceptable (alpha range = 0.59-0.70), particularly in light of their strong relationship to patient-rated performance status and hemoglobin level. Assessment of convergent and

discriminant validity for the FACT-F revealed a significant positive relationship with other known measures of fatigue, a significant negative relationship with vigor, and a predicted lack of relationship with social desirability. The total scores of both scales differentiated patients by hemoglobin level ($p < 0.05$) and patient-rated performance status ($p < 0.0001$). The FACT-An also differentiated patients by hemoglobin level ($p < 0.05$) and patient-rated performance status ($p <$ or $= 0.001$).

Blood was collected pre-treatment, mid-treatment, and post-treatment and stored for later analysis after subjects had completed all three time points and their serum could run simultaneously. Serum assays required approximately 20mL of blood which were collected in three 9mL red/grey gel clot tubes, allowed to clot for 30 minutes, spun at 3500 rpm for 15 minutes, and the serum was pipetted into 3 polypropylene storage tubes (approximately 5mL each). Serum hormone levels, including estradiol, progesterone, and testosterone were analyzed at the Ligand Assay and Analysis Laboratory within the Center for Research in Reproduction at the University of Virginia Health Sciences (Haisenleder, 2007). Serum was batched and analyzed at the completion of the study. In addition, serum hormones levels for IGF-1 and IGFBP-3 were analyzed at the University of Kansas Breast Cancer Prevention Center Laboratory (under the direction of Brain Petroff, DVM, Ph.D.) Additional serum was banked in a –80 ^{o}C freezer for later analysis of exploratory biomarkers, nerve growth factor (NGF) and tumor necrosis factor-alpha (TNF-ά).

Hemoglobin levels were assayed weekly, as per standard practice for patients receiving chemotherapy. Hemoglobin levels were recorded in the medical chart for each patient and were extracted from the chart with patients' informed medical consent.

Hemoglobin levels that most closely corresponded to baseline, mid- and post- treatment assessments were used for the analysis.

Sample Size

The sample size estimates were based on the primary hypothesis: Young women with breast cancer receiving chemotherapy would experience a decline in cognitive function over the course of their treatment. From a review of the limited data evaluating women pre- and post-chemotherapy, we estimated that the mean cognitive decline on the HSCS would be 10% on an individual subscale, with a standard deviation of 5%. To achieve 75% power to detect a 10% difference between pre- and post-treatment values, with an alpha of 0.05 using a using a two-sided test, we estimated that 20 subjects would be required (Length, 2001).

Analysis Plan

We used repeated measures analyses of variance, with Time as a three-level factor, to examine pre-mid-post changes in cognitive function using the Cognitive Difficulties Scale and the BCPT Cognition subscale; in addition we used the pre- and post-treatment values on the HSCS subscales. Repeated measures analysis was also used to assess changes in serum estradiol levels, serum hemoglobin levels, fatigue, menopausal symptoms, depressive symptoms, and quality of life measures. Follow-up paired t-tests were conducted to determine the locus of significant effects (i.e., Time 1 to Time 2, Time 2 to Time 3, Time 1 to Time 3).

We also evaluated the relationship between any significant change in cognitive function and the following individual variables: serum estradiol levels, symptoms of fatigue, serum hemoglobin level, depressive symptoms, menopausal symptoms, and

measures of quality of life. We examined predictors of change in cognitive function and other variables likely to be affected by chemotherapy (i.e., estradiol, hemoglobin, FACT-F subscale, FACT-Social & Family Wellbeing, FACT- Functional Wellbeing, SF-36 Physical Function, BCPT Weight Problems scale, BCPT Hot Flashes scale, BCPT Nausea scale, and the BDI) by computing partial correlations between predictors and Time 3 dependent variables partialing out the Time 1 values on dependent variables.

Results

Sample Characteristics and Study Recruitment

As depicted in Table 3, participants were 20 pre-menopausal women with a recent diagnosis of breast cancer who were chemotherapy naive. Subjects had undergone a biopsy and/or definitive surgery and their planned treatment included chemotherapy (Adrimycin or Epirubicin plus Cyclophosphamide, Herceptin or Carboplatinum plus Taxotere). Women were treated by three breast oncologists at the University of Kansas Cancer Center. Twenty-eight women were invited to participate and were provided with a written overview of the study. Twenty women agreed to participate, provided written informed consent, completed the study, and their results are presented in this analysis. Eight women decided not to participate in the study; six women felt the study was too burdensome prior to starting treatment and two women lived out of the area and did not want to make the additional time commitment. The median age of the 20 women was 43 (range 28-51) years old, the majority of the subjects were white (85%), 75% of the subjects were married, 80% of the subjects had at least a college education, and 85% were working full or part-time. Most women had early-stage disease and had received a lumpectomy.

Effects on Cognitive Functioning

As displayed in Table 4, repeated measures analyses of variance revealed no significant effect of treatment on objective cognitive functioning measured by the HSCS with the exception of the HSCS memory subscale, which demonstrated a significant improvement in memory between baseline and post-treatment assessments. HSCS comparison values from women undergoing adjuvant chemotherapy for breast cancer (Brezden et al., 2000), women one year post-treatment for breast cancer, and healthy female controls are displayed in Table 5. Our study sample exhibited levels of cognitive functioning at post-treatment similar to or better than women who had completed treatment one year earlier or healthy controls, and better than recent treatment completers in Brezden et al. (2000).

Subjective measures of cognitive functioning revealed mixed results. The CDS did not demonstrate a significant decline in cognitive functioning over the course of treatment. Subjective report on the CDS indicated that subjects "seldom" experienced cognitive difficulties. When comparing baseline values to a group of women at high-risk for breast cancer, subjects scored worse (higher) (Stanton, Vodermaier, McDowd, Kimler, & Fabian, 2007). However, subjective changes in cognitive functioning emerged on the BCPT Cognitive Problems scale. Using a paired sample t-test (i.e., Time 1 to Time 2, Time 2 to Time 3, Time 1 to Time 3), with Bonferroni correction for multiple comparisons (p-value set at .05/3 = .016), significant differences were found from Time 2 to Time 3, (t (19) = -3.70, p= <.001), and Time 1 to Time 3, (t (19) = -2.91, p= <.009), but not between Time 1 to Time 2 (t (19) = -.45, p = .66). BCPT cognitive function at baseline was similar to comparisons who recently underwent treatment for breast cancer

and was much higher (worse) than those seen in women at increased risk for developing breast cancer (Table 5). BCPT cognitive function post-treatment was worse compared to other women who recently underwent treatment for breast cancer.

Clinical interview post-treatment assessed the subject's perception of cognitive deterioration. A majority of subjects (19/20) reported difficulty with word finding, memory, and speed of processing.

Change in Serum Hormone Levels and Menopause Status

Only three subjects reported having a single menstrual period following the initiation of their chemotherapy regimen. All others stopped menstruating. As shown in Table 6, repeated measures analyses of variance revealed changes in serum hormones and hemoglobin levels over the course of treatment. A significant decrease in estradiol occurred from mean premenopausal levels (range 53 to 406 pg/ml) at baseline to mean postmenopausal levels (range non-detectable to 45 pg/ml) at subsequent time points (Haisenleder, 2007). Paired sample t-tests indicated that estradiol decreased from Time 1 to Time 2 (t (19) = 4.49, p = <.001), Time 2 to Time 3 (t (19) = 3.74, p= <.001), and Time 1 to Time 3 (t (19) = 5.34, p= <.001).

Similarly, a significant decrease in mean hemoglobin levels from normal (Hb $\geq$12 g/dL) at baseline to mildly anemic (Hb< 12g/dL) at subsequent time points (Rizzo et al., 2002) was observed. Hemoglobin levels decreased significantly from Time 1 to Time 3 (t (19) = 6.84, p <.001), whereas change from Time 1 to Time 2 (t (19) = 1.50, p=.149), and Time 2 to Time 3 (t (19) = 1.56, p=.135, were not significant. Non-significant increases were noted in testosterone and progesterone levels, and IGF1/IGFBP-3 ratios remained unchanged.

Quality of Life Variables

Depressive symptoms. Repeated measures analyses of variance detected a significant increase in depressive symptoms (Table 7) on the BDI over the course of treatment. Using a paired sample t-test (i.e., Time 1 to Time 2, Time 1 to Time 3, and Time 2 to Time 3), significant increases in depressive symptoms were observed from Time 1 to Time 3 (t (19) = -3.77, p <.001), and Time 2 to Time 3 (t (19) = -3.89, p <.001), but not from Time 1 to Time 2 (t (19) = -1.27, p=.218). Mean group BDI scores at baseline and mid-treatment were not elevated to the cutoff of 10 (Beck et al., 1961), which is suggestive of mild clinical depression, but the post-treatment mean was over the threshold. The BDI Cognitive-Affective subscale and the Somatic-Performance subscale (Ritterband & Spielberger, 2001) both evidenced a significant increase in symptoms (Table 7) over the course of treatment. Twenty percent of subjects at baseline, 35% of subjects mid-treatment, and 55% of subjects post-treatment had a BDI score of at least 10, indicating that a number of subjects had symptoms suggestive of at least mild clinical depression (Table 8).

In contrast, a non-significant increase in depressive symptoms (Tables 7 and 8) was observed on the CES-D. Mean CES-D levels were not elevated over the course of treatment, but 30% of subjects at baseline, 20% of subjects mid-treatment, and 50% of subjects post-treatment had a CES-D score of at least 16 (Radloff, 1977), the cutoff suggestive of clinical depression.

Health- related quality of life. The SF-36 and the FACT were used to assess psychological and physical functioning. Lower scores on the SF-36 and FACT reflect poorer quality of life. Table 9 provides normative data on the SF-36 subscales broken

down by age (Jenkinson, Coulter, & Wright, 1993) and a comparison sample of recently diagnosed breast cancer patients who had undergone a lumpectomy only (Ganz et al., 2004). As shown in Table 10, repeated measures analysis of variance on the MOS Mental Component Summary Scale did not yield a significant change over the course of treatment. Similar results were found on the SF-36 subscales assessing Emotional Function, Mental Health, and Social Functioning. The mean baseline Mental Health subscale (Table 9) was similar to those seen in other studies of women with early-stage breast cancer and compared to a normative data set (Ware, 1994; Ware, Snow, Kosinski, & Gandek, 1993). However the Mental Component Summary Score and the Role Function- Emotion, were considerably lower (worse) than the comparison populations.

Change in physical functioning was assessed with a repeated measures analysis of variance on the MOS Physical Component Summary Scale, which did not reveal a significant change in scores over the course of treatment (Table 10). As shown in Figure 1, mean baseline MOS PCS and MOS MCS scores were lower than the comparison sample of breast cancer patients. Repeated measures analysis of variance revealed a significant negative impact on Physical Health sub-scale. Other SF-36 subscales reflecting physical health (i.e., General Health, Bodily Pain, Role Physical Functioning, Vitality), did not demonstrate significant changes over the course of treatment (Table 10).

The FACT-General (range 0-108) full scale yielded a marginally significant change over the course of treatment. Repeated measures analyses of variance revealed a significant increase in fatigue symptoms commonly associated with cancer treatment (Table 11), as well as two other quality of life domains. The FACT-Fatigue subscale (range 0-52), the FACT-Anemia subscale (range 0-80), the FACT-Functional Wellbeing

subscale (range 0-28), and the Social/Family Wellbeing subscale (range 0-28), all evidenced a significant decrease in quality of life from baseline (Table 11). The FACT-Emotional Wellbeing subscale (range 0-24) and the FACT- Physical Wellbeing subscale (range 0-28) did not change significantly over the course of treatment.

FACT baseline and post-treatment values were similar to those found in a sample of women receiving adjuvant chemotherapy for breast cancer, who had a median baseline FACT-G of 77 and a median baseline FACT-F subscale of 31. These values were significantly lower than that of healthy, matched controls, who had a median baseline FACT-G of 94 and a median FACT-F subscale of 46 (Mar Fan et al., 2005). In a prospective study of women with breast cancer who underwent a baseline and 6-month follow-up assessment of fatigue, similar FACT-F subscale scores were observed (baseline = 40.27 (*SD*=9.12) and 6-month = 36.43 (*SD*=11.99) (Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005).

Breast cancer-related symptoms. Repeated measures analyses of variance revealed an increase in symptoms related to breast cancer treatment measured by the BCPT Symptom Scales (Table 12). Higher scores indicate a worse symptom profile. The BCPT Total score increased significantly over the course of treatment. Pair-wise comparisons revealed no significant change from Time 1 to Time 2 (t (19)= -1.69, p = .108), but significant changes from Time 1 to Time 3 (t (19) = -4.86, p = <.001), and Time 2 to Time 3 (t (19) = -4.83, p = <.001). Repeated measures of analysis of variance revealed an increase in subjective reports of hot flashes. Pair-wise comparisons revealed no significant change from Time 1 to Time 2 (t (19)= -1.96, p = .065), but significant changes from Time 1 to Time 3 (t (19) = -5.79, p = <.001), and Time 2 to Time 3 (t (19)

= -4.45, p = <.001). Repeated measures of analysis of variance also indicated an increase in symptoms related to weight problems and nausea. Pair-wise comparisons of symptoms related to weight problems revealed no significant change from Time 1 to Time 2 (t (19) = -.75, p = .46) or Time 2 to Time 3(t (19) = -1.93, p = .069), but a significant change from Time 1 to Time 3 (t (19) = -2.14, p = .046). Pair-wise comparisons of symptoms related to nausea exhibited significant change from Time 1 to Time 2 (t (19) = -3.71, p = <.001) and Time 1 to Time 3 (t (19) = -3.33, p = .004), but not a significant change from Time 2 to Time 3 (t (19) = 1.71, p = .104). The BCPT Vaginal Problems, Bladder Control, and Musculoskeletal Pain subscales did not reveal significant changes over the course of treatment. As displayed in Table 12, scores at post-treatment were higher than those reported in a sample of women at high-risk for breast cancer and similar to women with breast cancer recently treated with adjuvant chemotherapy (Stanton et al., 2005), except that nausea was higher post-treatment in the current sample.

Predictors of Change in BCPT Cognitive Problems

Because the BCPT Cognitive Problems scale was the only cognitive indicator to evidence significant change, partial correlations were computed on the post-treatment BCPT cognitive problems scale as the dependent variable, partialing out BCPT pre-treatment cognitive problems, with the other variables that evidenced significant change at Time 3 as predictors (i.e., estradiol, hemoglobin, FACT-F subscale, FACT-Social & Family Wellbeing, FACT- Functional Wellbeing, SF-36 Physical Function, BCPT Weight Problems scale, BCPT Hot Flashes scale, BCPT Nausea scale, and the BDI) as well as demographic variables including age and education. In addition, analyses of

covariance, with each post-treatment dependent variable as a dependent variable, the corresponding baseline dependent variable as the covariate, and the cancer-related variables of cancer stage (Stage I versus Stages 2-4), time of chemotherapy (adjuvant versus neoadjuvant), and chemotherapy dose (standard versus dose-dense) as separate independent variables. In no case was the cancer-related variable a significant predictor of outcomes, and they are not discussed further.

Both the baseline and post-treatment predictor variables were examined as related to change in BCPT Cognitive Problems. As displayed in Table 13, higher baseline hemoglobin levels were associated with an increase in cognitive problems (pr (17) = .50, p = .03). In addition, higher baseline BDI depressive symptoms predicted a tendency towards an increase in post-treatment cognitive problems (pr (17) = .44, p = .059). As displayed in Table 14, partial correlations indicated that the post-treatment FACT-Functional Wellbeing subscale was the only variable that had a significant negative correlation with the BCPT Cognitive Problems scale (pr (17) = -.48, p = .04). A decrease in perceived cognitive function was related to lower functional well-being. No other correlations were significant.

Predictors of Change in FACT-Fatigue

Predictors of change in other important dependent variables were explored. Dependent variables were chosen based on a significant change over the course of treatment identified within the present study and on the basis of the empirical literature revealing the variables as important side effects of chemotherapy. The selected outcome variables were: the FACT-F subscale, the BDI, and the BCPT Hot Flash scale.

Partial correlations were computed on the post-treatment FACT-F subscale score as the dependent variable, partialing out the pre-treatment FACT-F subscale score, with the same predictors at baseline and post-treatment as specified for the BCPT Cognitive Problems. As shown in Table 15, older age, higher baseline hemoglobin, and lower BCPT Hot Flash score at baseline predicted an increase in fatigue. When age was also controlled in the partial correlation only lower scores on the BCPT Hot Flash scale predicted an increase in fatigue (*pr* = .47, *p* = .05).

When post-treatment correlates were examined (Table 16), an increase in reported symptoms of fatigue was significantly associated with lower post-treatment FACT-Functional Wellbeing (*pr* (17) = .68, *p* = <.001) and with worse post-treatment SF-36 Physical Function scores (*pr* (17) = .62, *p* = <.001), as well as higher depressive symptoms (*pr* (17) = -.55, *p* = .016) and higher (worse) BCPT Nausea (*pr* (17) = -.49, *p*= .035).

Predictors of Change in BDI Depressive Symptoms

Partial correlations were computed using post-treatment depressive symptoms (BDI) as the dependent variable, partialing out pre-treatment BDI depressive symptoms, and the baseline predictors (Table 17). Lower baseline BCPT Hot Flash scores were significantly associated with worsening BDI scores (*pr* (17) = -.61, *p* =.006). When post-treatment scores on the predictor variables were examined (Table 18), significant associations were obtained between increasing depressive symptoms and higher post-treatment FACT- Fatigue (*pr* (17) = -.60, *p* = .007) and FACT-Functional Wellbeing (*pr* (17) = -.73, *p* = <.001).

Predictors of Change in BCPT Hot Flashes

An increase in BCPT Hot Flash scores was predicted by lower pre-treatment estradiol levels (*pr* (17) = -.49, *p* = .033) and higher pre-treatment BDI symptoms (*pr* (17) = .51, *p* = .027). No significant relationships were identified between predictor variables post-treatment and change in BCPT Hot Flashes (Table 20).

Discussion

Research suggests that between 18-50% (Ahles et al., 2002; Brezden et al., 2000; Van Dam et al., 1998; Wieneke & Dienst, 1995) of women with breast cancer experience cognitive decline after receiving adjuvant chemotherapy. The cause of these deficits remains unknown; however, it has been speculated that chemotherapy, fatigue, accelerated menopause, or quality of life factors (Cassano, Puca, Scapicchio, Trabucchi, & Patients., 2002) may all have an impact on functioning. The current preliminary study represents an attempt to evaluate the association of these factors with cognitive functioning in a group of pre-menopausal women with a recent diagnosis of breast cancer. To address this issue, the current study examined the physical and emotional correlates of chemotherapy at three time points: pre-treatment, mid-treatment, and post-treatment.

Cognitive Performance

Unlike previous studies, which found significant deficits in memory, our study revealed an improvement over the course of treatment. This improvement is likely due to a practice effect. It is possible that because women were presented with a single task at two assessment points, success was high. In contrast, subjects' self-report via interview indicated that they perceived significant deficits in memory and word finding and their increasing BCPT Cognitive Problems scores suggested problems with forgetfulness and

concentration. A possible explanation is that the subjects were young, highly educated, and pre-menopausal; therefore, cognitive problems due to the natural course of aging were not present. Self-report also revealed that women were accustomed to "multi-tasking" and perceived a change in this high level of functioning as a significant decline in performance. This perceived decline in function is supported by a partial correlation demonstrating a significant relationship between an increase in the BCPT Cognitive Problems score and lower post-treatment FACT-Functional Wellbeing. Because the neuropsychological tests used within the present study do not reflect the complexities of daily life, they might not be sensitive to subtle losses in cognitive functioning. If these young, highly educated subjects were presented with a task requiring high-level processing in multiple cognitive domains simultaneously, perhaps the outcome would be different.

Results from this study differ from those of other researchers who report a significant proportion of subjects with some level of pre-treatment cognitive deficits. In a prospective, longitudinal study of women with breast cancer treated with adjuvant chemotherapy, researchers reported that 33% of subjects had pre-morbid cognitive deficits (Wefel et al., 2004). Subjects in the Wefel study had a mean of 14 years of education (SD = 2.6) or equivalent to some college, compared to the present study in which 80% of subjects had a college degree and a mean of 16 years of education. In the current study, none of the subjects fell within an impaired range. Subjects in both studies were similar in age; therefore, a more plausible explanation might be based on years of education or different methods of assessment. Similar to our findings, recent research on pre-treatment cognitive performance yielded baseline scores on objective tests of

attention and short-term memory that fell within the normal range for healthy adults (Cimprich et al., 2005).

A likely explanation for the high proportion of previous studies reporting pre-treatment cognitive dysfunction was highlighted in a meta-analysis by Falleti and colleagues (2005), who found that the more tests administered to assess performance, the greater the probability that an individual will meet criteria of impairment. Because previous studies have administered multiple tests of cognition, the likelihood of finding a decline in cognitive performance is increased and therefore a correction for multiplicity should be performed. To support this approach, research has been undertaken to explore the marked variation in an individual's cognitive test performance. To date, little is known about the normal range of intra-individual variation (Schretlen, Munro, Anthony, & Pearlson, 2003), but those authors found that in a battery of neuropsychological tests the maximum discrepancy values ranged from 1.6 *SD* to 6.1 *SD*, between the subjects' highest and lowest performance value. Sixty-six percent of those undergoing assessment produced a maximum discrepancy of greater than 3 *SD*.

Another caution in interpreting the level of cognitive dysfunction in previous studies is the definition of dysfunction. According to the neuropsychological testing literature, 2 *SD* below the mean defines some level of impairment. However, when multiple tests are administered and extreme levels of intra-individual variability are seen, it would be premature to label a subject with cognitive decline based on one test falling within the impaired range. This high level of intra-individual variability and inconsistency in defining cognitive impairment should be considered when interpreting a battery of neuropsychological tests.

Most similar to results of the present study, Brezden (2000) reported scores on the High Sensitivity Cognitive Screen that differed between women treated for breast cancer and controls. A non-significant difference was found in women one year post-treatment and controls. Comparing scores in women with breast cancer undergoing chemotherapy, women at least one year post-treatment, and healthy female controls, our results were most similar to those women who were at least one year post treatment or the healthy controls (Brezden et al., 2000). Taking age into consideration, our subjects were most similar to the healthy controls (M = 49); however, all three groups in the Brezden study had a mean age older than that of the present study. It has been reported that age is a significant predictor of pre-morbid functioning (Cimprich et al., 2005), and likely explains why our sample is more closely related to that of the younger controls. In contrast, Mar Fan and colleagues (2002) reported that 50% of the subjects with breast cancer compared with 41% of the controls had some level of cognitive deficits identified by the High Sensitivity Cognitive Screen at baseline. Such high levels of cognitive dysfunction are difficult to comprehend, but older age may be a factor.

Self-reported Cognitive Function

As highlighted by Castellon, Silverman, and Ganz (2005), the research evaluating cognitive function in women with breast cancer has used a variety of assessment tools, has revealed inconsistent findings, and has reported deficits in cognitive performance across multiple domains. Those authors emphasized that only a subset of patients who receive chemotherapy demonstrate cognitive compromise. Because there are many factors that influence cognitive performance, the present study attempted to specify factors, such as change in menopausal status, fatigue, and depression that could

potentially manifest as cognitive deficits. As outlined by the National Institutes of Health State of the Science Conference Statement (2004), depression and fatigue are among the most common side effects of cancer and the treatment of cancer. The inter-relationship between depression, fatigue, and cognitive performance is not fully understood. Self-reported cognitive compromise is not associated with actual performance on neuropsychological measures (Castellon, Silverman, & Ganz, 2005). This finding is consistent with results from the present study in that the only significant indicator of a decline in cognitive performance was demonstrated on the BCPT Cognitive Problems subscale. Corroborating the results on the BCPT Cognitive Problems scale, subject report in clinical interviews also revealed a perceived decline in cognitive performance. It also should be noted that all but one HSCS subscale in the present study evidenced a slight improvement from baseline to post-treatment, however, the visual motor scale exhibited an extremely small and non-significant decline in performance ($n^2 = .01$).

Predictors of Increased Cognitive Problems

Hemoglobin. In an exploratory analysis by Tchen and colleagues (2003) hemoglobin level was not significantly associated with cognitive function. However, these authors reported that too few subjects were identified as having cognitive dysfunction, therefore, they were unable make a definitive conclusion (Tchen et al., 2003). The present study demonstrates that higher levels of baseline hemoglobin levels predicted a post-treatment increase (worsening) in BCPT Cognitive Problems. A possible explanation could be that 11/20 subjects in the present study had a baseline hemoglobin level of 13-14g/dL and were found to drop by >2g/dL over the course of treatment. The other 9/20 subjects had a baseline hemoglobin level of 11-12g/dL and

experienced a 1g/dL decline over the course of treatment. It is possible that the higher the baseline hemoglobin level and/or the larger the drop due to treatment, results in a greater the impact on cognitive performance. Future studies are necessary to explore this question.

Fatigue. Researchers have reported that in cancer patients receiving chemotherapy, effect sizes for declines in memory were similar to those observed in healthy adults at the end of a normal work day who were experiencing fatigue (awake for 12 hours) (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005). Fatigue is a well-established factor that can negatively impact cognitive functioning. Small fatigue-related losses in attention and memory may contribute to the subjective experience of distress because keeping up with the demands of daily life become more difficult (Cimprich et al., 2005). Subtle losses have been defined as "attentional fatigue" (Kaplan, 1995) , and might be amenable to interventions to enhance attention. In the present study, symptoms of fatigue measured by the FACT-F and the FACT-An subscales significantly increased between baseline and post-treatment. High fatigue may have an association with perceived decline in cognitive performance. Although not statistically significant in this small sample, the magnitude of the partial correlation between post-treatment fatigue (FACT-F) and change in BCPT Cognitive Problems (*pr* (17) = -.40) supports this link.

Depression. Memory and executive function are known to be negatively impacted in individuals suffering from depression (Anticainen et al., 2001). People suffering from major depression may have trouble initiating tasks, making decisions, planning future actions, or organizing thoughts. There appears to be a loss of coordination between working, short-term, and long-term memory. Few studies have

independently evaluated depression as a factor influencing cognitive function. Subjective reports collected within other measures of quality of life and depressed mood (e.g. POMS) have not been linked to cognitive function. Wieneke and Dienst (1995) administered the Beck Depression Inventory (BDI) and found that 23/28 (82%) of subjects scored close to the range of normal mood. No significant relationship was identified between the BDI and any of the neuropsychological tests. As this study was cross-sectional, it was not able to capture pre-morbid depressive symptoms and because subjects had completed treatment 0.5-12 months prior to testing, it is possible that depressive symptoms may have improved as an effect of time. More recently, Bender and colleagues (2006) evaluated the impact of depressive symptoms in a group of breast cancer patients using the Beck Depression Inventory II (BDI-II). They reported that most of the subjects in each of the 3 study arms (Group 1 received chemotherapy only; Group 2 received chemotherapy plus tamoxifen; Group 3 had a diagnosis of DCIS and underwent surgery but did not receive chemotherapy or tamoxifen) were not depressed, mean depression scores at all three time points was 10 or less, and scores decreased (improved) with each subsequent time point. Women scoring higher on the BDI-II, indicating greater depressive symptoms, perceived more cognitive problems. In the present study, 80% of the baseline scores on the BDI were within the normal range; however, scores increased (worsened) over the course of treatment and by Time 3, only 45% of subjects remained in the normal range. The decrease in reported cognitive performance paralleled the increase in reported symptoms of depression. Further, although not statistically significant, baseline and post-treatment depressive symptoms were related to an increase in cognitive problems (pr = .30). This trend was similar to

that reported by Wefel and colleagues (2004), who reported in a group of pre- and post-menopausal women with breast cancer, an increase in reported symptoms of depression was significantly associated with an increase in cognitive problems.

Menopausal Status

Previous studies have not taken change in estrogen levels into account as a predictor of cognitive function during chemotherapy. Wefel and colleagues (2004) evaluated cognitive performance in women with breast cancer taking menopausal status, but not estradiol level, into account and reported a non-significant difference between the two groups, such that post-menopausal women were somewhat more likely to experience problems with cognitive function than pre-menopausal women. Women in our study had significant decreases in estradiol, from pre-menopausal levels at baseline to post-menopausal levels at post-treatment. All subjects discontinued menses by the mid-treatment point. As a result of the drop in estradiol and discontinuation of menstrual periods, an increase in menopausal symptoms would be expected. The present study did identify significant increases in symptoms of menopause identified by the BCPT Hot Flash scale (change from Time 1 to Time 3). However, neither hot flashes nor estradiol levels had significant associations with change in cognitive problems. Of note, subjects perceived the interruption of menses as an indicator that their treatment was "working."

The Selection of Neuropsychological Battery as an Influence on Findings

There remains a lack of consensus regarding the methods used to assess cognitive functioning. It is imperative to develop tools that minimize the practice effect, tap into target cognitive domains, and are appropriate for individuals with higher levels of education. The present study attempted to assess specific cognitive domains within a

limited period of time using an objective measure consistent with previous studies, the HSCS. Unlike previous studies which have required administration times of 1-4 hours (Mar Fan et al., 2005; Schagen et al., 2002; Wefel et al., 2004; Wieneke & Dienst, 1995), the present study attempted to decrease the overall administration time and number of tests performed. Decreased administration time might have played a role in high subject compliance. However, it has been reported that the longer the administration time and the more assessments given, the greater likelihood that subjects experience an increase in fatigue and display intra-individual variability (Schretlen et al., 2003). By limiting the number of assessments given and shortening the administration time to 30 minutes, the present study attempted to address some of these prior study design limitations. If more assessments were administered to subjects, the likelihood of identifying cognitive dysfunction would likely increase. The young age and high education level of the sample also would require an extremely sensitive cognitive assessment in order to demonstrate any subtle changes in performance.

Statistical Analysis as an Influence on Findings

In an investigation of methodology used to evaluate cognitive impairment resulting from chemotherapy, Shilling and colleagues (2006) dramatically demonstrated the variability of cognitive deficits within a given data set. Using a population of 92 breast cancer patients undergoing treatment, the authors used seven different analytic approaches similar to those reported in other studies of cognitive function. The astonishing result demonstrated that depending on the type of analysis used, there was a sizable discrepancy of cognitive decline ranging from 12-68.5% (Shilling, Jenkins, & Trapala, 2006). The authors suggested that a standard method for analysis be employed

to promote comparability among studies. Other researchers have voiced this similar concern (Castellon et al., 2005) and have found it difficult to compare results of similar studies due to lack of consistent reporting of important data, reference points, and results useful for comparison (e.g. effect size). In the present study, comparisons were made with other published data, but were limited to those for which subscale values and detailed data were presented.

Compliance as an Influence on Findings

Women who agreed to participate in the study all completed the study. This lack of attrition differs from that found by Bender et al. (2001), who had a 22-34% dropout rate by the second assessment point. One reason for the high level of compliance demonstrated by subjects in this study was the convenient scheduling of assessments at the same times of other treatment related visits, thus preventing additional trips to the Cancer Center. Also, interim phone contacts were made to subjects to remind subjects of their upcoming appointments. Finally, the battery of assessments was brief. The present finding cannot be due to attrition.

Predictors of Change in Additional Dependent Variables of Interest: Hot Flashes, Fatigue, and Depression

Predictors of an Increase in BCPT Hot Flashes

Previous research has reported mixed results regarding the relationships between menopausal symptoms and quality of life and cognitive problems in women with breast cancer. Tchen and colleagues (2003) reported that menopausal symptoms were significantly inter-related to fatigue ($p = <.0001$) and in an exploratory analysis, hot flashes were strongly correlated with fatigue and global quality of life ($p = <.0001$).

However, cognitive dysfunction classified by the HSCS was not correlated with menopausal symptoms (Tchen et al., 2003).

In the present study, low baseline estradiol levels (which then fell further) were a significant predictor of an increase in BCPT Hot Flash scores. Higher baseline depressive symptoms also predicted an increase in BCPT Hot Flashes. Women with a previous history of depression are likely to have worsening symptoms during the menopause and it is possible that other menopausal symptoms (Schmidt & Rubinow, 2006) are exacerbated as well. Further exploration of mood and menopausal side effects during treatment for breast cancer is warranted.

Predictors of FACT-Fatigue

Decreasing hemoglobin levels have been associated with fatigue in numerous studies (Bower et al., 2000; Cella, 1997; Chang & Couture, 2003; Flechterner & Bottomley, 2003; Glaus, 1998). The present study identified several predictors of an increase in post-treatment fatigue including higher baseline hemoglobin levels and age. The drop in hemoglobin over the course of treatment and increase in cancer-related fatigue is a likely relationship based on empirical support and the present findings.

Lower baseline levels of BCPT Hot Flashes were also predictive of an increase in fatigue. Mixed findings are reported in the literature indicating that fatigue is more severe in women who complain of menopausal symptoms (Goldstein et al., 2006), while others have shown no association (Bower et al., 2000; Broeckel et al., 1998). Little research has evaluated subjects based on menopausal status; this may explain the lack of consensus regarding the relationship between menopausal symptoms and fatigue.

Subjects in the present study were younger and healthier that in previous reports, and therefore, were more likely to experience a negative impact as a result of cancer and its treatment. Higher baseline performance and younger age might be a likely predictor of a decline in perceived physical and emotional functioning. Post-treatment predictors of fatigue revealed a significant relationship between increased symptoms of fatigue and lower FACT-Functional Wellbeing and MOS-36 Physical Function. This may explain why the MOS-PCS and the MOS-MCS were worse than those reported by comparison studies. A recent study in older survivors with breast cancer demonstrated that cancer specific well-being and general emotional health do not change substantially after a breast cancer diagnosis (Clough-Gorr, Ganz, & Silliman, 2007). Older patients are more likely to have co-morbidities, experience worse baseline health performance, and are likely to be post-menopausal.

Predictors of an increase in BDI depressive symptoms

Women who reported lower levels of baseline BCPT Hot Flashes were more likely to have increased depressive symptoms. Perhaps women transitioning into menopause as a result of their treatment would report an increase in depressive symptoms.

An increase in BDI depressive symptoms was significantly correlated with worsening post-treatment FACT-Fatigue and FACT-Functional Wellbeing. Similar research found that increased symptoms of fatigue were reported concurrently with psychological distress (depression) in 1/3 of women with breast cancer approximately 10 months post-treatment (Goldstein et al., 2006). These authors emphasized the difficulty of defining fatigue versus depression due to the complex co-morbidity between the two;

one does not precede the other but shares a common symptom profile. Similar findings were reported by Ahn and colleagues (2007) who found that depression and fatigue emerged as the strongest predictors of negative health-related quality of life in a multivariate analysis.

Limitations of the Research

Women participating in the present study received different types of chemotherapy, and the small sample precluded exploring the impact due to the specific chemotherapy administered. A majority of subjects received a cyclophosphamide and anthracyclin-based regimen, but some subjects received treatment based on updated practice guidelines including Herceptin and Taxotere. Larger studies will be required to explore the impact of the specific treatment on cognitive function and quality of life; however, due to changing treatment regimens, this factor might be difficult to control.

The small sample size restricts the types of analyses conducted and interpretations of the data. As demonstrated by previous research, accruing and completing a study with extensive data collections at multiple time points can be challenging. In the present study, the available pool of pre-menopausal patients, time requirements, and the need for external funding to complete the project were all barriers. Due to these unforeseen barriers, modifications from the original randomized study design were made, the sample size was decreased, and a limited number of cognitive and quality of life assessments were performed. Future analyses of markers of cognitive change (e.g. TNF-α and NGF) will be performed when additional funding is secured.

There has been considerable variability in defining cognitive deficits. Previous studies have made comparisons to normative data, healthy controls, and other cancer

patients not receiving chemotherapy (Castellon et al., 2005). In the current study comparisons were made using the patient as her own control, to normative data, high-risk controls, and other breast cancer patients, depending on available data. A majority of the studies to date have been cross-sectional, and it is difficult to conclude that a deficit exists when the pre-morbid level of functioning is not known. Although there was not a control group in the present study, significant within-subjects differences were observed in memory (improvement) and in self-reported cognitive dysfunction, as well as an increase in menopausal symptoms, fatigue, and depressive symptoms. Wefel et al. (2004) is an example of a longitudinal study that assessed cognitive performance prior to initiating chemotherapy and 6-month after completing treatment (12-month total time interval), but that used different measures of cognitive performance. Due to the small sample size (n=18) and the finding that 33% of subjects had pre-morbid cognitive dysfunction in Welfel et al. (2004), it is difficult to compare their results to the current findings. The present study did not reveal any pre-morbid cognitive deficits, but the only objective measure used was the HSCS and the sample is highly educated. At present, there remains a question as to the true incidence of pre-morbid cognitive deficits in the population of young women with breast cancer.

Implications and Future Directions

Future directions should include the use of neuroimaging, such as functional MRI (fMRI), in which diagnostic tools may help illuminate possible neurological substrates associated with a decline in cognitive performance (Castellon et al., 2005). The use of fMRI is expensive, but in conjunction with a targeted neuropsychological battery of tests, promises to yield an interpretable neurocognitive profile. Future neuropsychological

batteries should incorporate multiple domains within a complex testing situation. Experts working in the field need to tackle this challenge in order to develop a standardized assessment battery. Next steps should include the performance of larger studies in multiple institutions, increasing the diversity of subjects. As studies become increasingly expensive to run, collaborations among experts within the oncology community are a likely solution.

This preliminary study provides the first examination of a homogenous sample of pre-menopausal women who participated in a longitudinal study of cognitive performance and quality of life before, during, and after receiving chemotherapy. Biological and neuropsychologic markers of change were assessed at each time point. Although improved memory, subjective report of decreased cognitive performance, a decrease in estradiol levels and increased symptoms related to menopause, fatigue, and depression were demonstrated, the small sample size rendered it difficult to detect robust predictors of these changes. Results from this study may provide future researchers with information that other factors besides chemotherapy may negatively impact cognitive function and quality of life in pre-menopausal women with breast cancer undergoing chemotherapy. Specifically, initially high hemoglobin (and perhaps the subsequent drop) might be important precursors or perceived cognitive problems and fatigue, and initially low estradiol (and the subsequent continued decline) might promote hot flashes. A more complete examination of the impact of chemotherapy and associated physiological changes on cognitive function, fatigue, depression, and menopausal symptoms, is required within a larger, multi-center study. At present, the prevalence of baseline and post-treatment cognitive dysfunction related to chemotherapy, menopause, depression, or

fatigue remains unclear. However, that pre-treatment levels of cognitive performance were within normal limits and that perceived cognitive function declined but actual performance did not suggest that changes were too subtle to be detected with the assessment administered. Others have identified much higher levels of pre- and post-treatment cognitive dysfunction and their findings should not be generalized to a relatively young, highly educated group of women undergoing chemotherapy.

Although no causal conclusions can be drawn, findings of this study suggest that subjective cognitive function, depressive symptoms, fatigue, and hot flashes are significant problems in young women during chemotherapy. Use of supportive medication (epoetin alfa) to increase hemoglobin levels (Andrykowski et al., 1998; Bower et al., 2000; Chang & Couture, 2003) and the use of moderate exercise (McNeely et al., 2006; Wagner & Cella, 2004) have both been demonstrated to improve the symptoms of fatigue. Vasomotor symptoms and mood instability secondary to menopause and treatment have been effectively minimized with the use of selective serotonin reuptake inhibitors (Hickey, Saunders, & Stuckey, 2005) and diet modification (North American Menopausal Society, 2004). Symptoms of depression have been effectively treated with the use of cognitive behavioral therapy and/or selective serotonin reuptake inhibitors (National Institutes of Health, 2004). Cognitive performance may be enhanced by behavior modification including physical and mental exercise, developing routines and lists, and identifying specific targets that can be modified to enhance performance (Mayo Clinic, 2006).

This study attempted to provide a comprehensive assessment of pre- and post-treatment cognitive function in a homogenous population of newly diagnosed women

with breast cancer. There was a perceived decline in cognitive function and overall performance, but objective testing did not identify these subtle changes. Changes in fatigue, depressive symptoms, and menopausal symptoms were also notable. This study highlights the importance of informing patients of the potential side-effects of breast cancer and its treatment with the goal of prevention or early intervention.

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APPENDIX A

TABLES

Table 1

Self and Staff-Administered Assessments of Cognitive Function and Quality of Life

Reference	Assessment Tool	Domains Assessed	Method of Administration
Faust & Fogel, 1989.	**High Sensitivity Cognitive Screen (HSCS)** ***Only measured at Baseline & Off-study time points***	**Memory, language, attention, concentration, visual/motor, spatial, self regulation & planning**	**Staff**
McNair, 1984.	**Cognitive Difficulties Scale**	**Attention, memory,multi-tasking**	**Self**
Ware, 1993 & 1994.	**RAND 36-Item Health Survey (SF-36)**	**Physical & role function, bodily pain, social functioning, emotional well being, energy/fatigue, general health**	**Self**
Ganz, 2000. **Stanton, 2005.**	**Breast Cancer Prevention Trial Symptom Checklist (BCPT)**	**Physical & psychological symptoms related to menopause & chemo toxicity**	**Self**
Cella, 1997.	**Functional Assessment of Cancer Therapy- Anemia (FACT-An)** ***Reported at Baseline & Off-study time points***	**Symptoms of anemia & fatigue**	**Self**
1. Beck, 1961 & 1988. **2. Radloff, 1977.**	**1. Beck Depression Inventory (BDI)** **2. Center for Epidemiologic Studies Depression Scale (CES-D)**	**Depressive symptoms**	**Self**

Table 2

High Sensitivity Cognitive Screen Scoring Sheet

High Sensitivity Cognitive Screen Modified Scoring Sheet			
	Patient score	**Interpretation**	**Subtest Severity**
Memory 1A (sentences)			
trial 1	/13		
trial 2	/13		
*trial 3**	/13		
Summary	**(39 - total) [T]**		
Memory 1B (word pairs)			
trial 1	/6		
trial 2	/6		
*trial 3**	/6		
Summary	**(18-total) [T]**		
Memory 1C (sentence recall)	**(13 - total)**		
*Difference from 1A**			
Memory 1D (word pair recall)	**(6- total)**		
*Difference from 1B**			
MEMORY SUBTEST	**(sum)**		
Language A (repetition)*	**# of errors**		
Language B (fluency)			
S	/8		
T	/8		
*Summary**	**(16 - total)**		
Language C (naming)*	**(30 - total)**		
Language D (reading)*	**# of errors**		
Language E (writing)*	**# of errors**		
LANGUAGE SUBTEST	**(sum)**		
Visual Motor (page A)*	# of errors		
Spacial (page A)*	# of errors		
Attention and Concentration A (alternating numbers)	# of errors		
Attention and Concentration B (signaling to numbers)	# of errors		
ATTENTION AND CONCENTRATION SUBTEST	**(sum)**		
Self-Regulation and Planning A (conflicting stimuli)	# of errors		
Self-Regulation and Planning B (sentence construction)	# of errors		
SELF-REGULATION AND PLANNING SUBTEST	**(sum)**		
Memory Subtest Sum			
Language Subtest Sum			
Attention and Concentration Subtest Sum			
Self-regulation Subtest Sum			
TOTAL SUM	**(SUM)**		

Table 3

Study Sample Characteristics

Characteristic		**Subjects N=20 (SD)**
Median Age (years)		43 (5.82)
Race:	White	17
	Black	1
	Hispanic	2
Education:	High school	4
	College	14
	Post-graduate	2
Employment:	Not working	3
	Part-time	2
	Full-time	15
Marital Status:	Married/Coupled	15
	Single/Divorced/Widowed	5
Tumor Stage:	not reported	1
	I	11
	II	6
	III	1
	IV	1
Lymph Node Status:	Positive	5
	Negative	15
ER/PR Status:	ER+/PR+	15
	ER-/PR-	5
Type of Therapy:	Adjuvant	9
	Neoadjuvant	11
Dosing of Therapy:	Standard	7
	Dose-dense	13
Tx Regimen:	AC or EC	14
	Taxotere + Carbo	4
	Taxotere + Herceptin	2
Type of Surgery:	Lumpectomy	14
	Mastectomy	6

Table 4

Cognitive Function at Baseline, Mid- and Post-treatment Repeated Measures Analyses of Variance

Measure	Baseline	Mid-Treatment	Post-treatment	F		
	M (SD)	*M (SD)*	*M (SD)*	(*df=1,19)*	*p*	η^2
Cognitive Difficulties Scale	25.85 (13.98)	23.80 (14.58)	28.15 (13.66)	1.07	.313	.05
BCPT Cognitive Problems Scale	0.75 (0.67)	0.82 (0.70)	1.32 (0.89)	8.44	.009	.31
HSCS Memory Scale	16.00 (10.55)	N/A	12.75 (7.56)	4.76	.042	.31
HSCS Language Scale	2.45 (2.56)	N/A	1.80 (2.50)	1.17	.292	.20
HSCS Attention	0.75 (1.12)	N/A	0.65 (1.04)	0.16	.694	.06
HSCS Self Regulation & Planning	3.00 (2.00)	N/A	1.90 (1.62)	4.04	.059	.18
HSCS Visual/Motor	.20 (0.41)	N/A	.25 (0.55)	0.137	.716	.01
HSCS Spatial	.65 (0.67)	N/A	.55 (0.76)	0.487	.494	.03

BCPT = Breast Cancer Prevention Trial

HSCS = High Sensitivity Cognitive Screen

Table 5

Comparison Values for Measures of Cognitive Function

Measure	High Risk Comparisons[1] M	Recently treated BrCa Patients[1] M	Recently treated BrCa Patients[2] M	Chemoprevention Trial Participants[3]	BrCa Patients Treated >1 yr[2] M	Healthy Female controls[2] M
Cognitive Difficulities Scale	N/A	N/A	N/A	22.0	N/A	N/A
BCPT Cognitive Problems Scale	0.42	0.73	N/A	N/A	N/A	N/A
HSCS Memory Scale	N/A	N/A	24.0	N/A	15.0	15.0
HSCS Language Scale	N/A	N/A	8	N/A	8.0	4.0
HSCS Attention	N/A	N/A	1.0	N/A	1.0	1.0
HSCS Self Regulation & Planning	N/A	N/A	3.0	N/A	4.0	3.0
HSCS Visual/Motor	N/A	N/A	1.0	N/A	1.0	1.0
HSCS Spatial	N/A	N/A	2.0	N/A	1.5	1.0

[1](Stanton et al., 2005); [2](Brezden et al., 2000), [3](Stanton, et al., 2007).

BrCa = breast cancer

BCPT = Breast Cancer Prevention Trial; HSCS = High Sensitivity Cognitive Screen

Table 6

Within-Subjects Change in Serum Hormone Levels Over the Course of Treatment

Serum Measure	Baseline *M (SD)*	Mid-Tx *M (SD)*	Post-Tx *M (SD)*	*F* (*df*=1,19)	*p*	η^2
Estradiol (pg/mL)	64.79 (28.84)	41.12 (16.08)	28.68 (10.93)	28.52	<.001	.60
Testosterone (ng/mL)	118.53 (68.32)	121.15 (48.21)	121.28 (46.75)	0.54	.470	.03
Progesterone (ng/mL)	14.29 (10.78)	14.58 (5.70)	14.55 (5.61)	1.22	.284	.06
IGF1/IGFBP3 ratio (ng/mL)	0.187 (0.03)	0.180 (0.04)	0.190 (0.05)	0.06	.805	.003
Hemoglobin (Citron et al.) (mg/dL)	12.66 (1.30)	11.90 (2.20)	11.17 (0.78)	46.82	<.001	.71

Table 7

Baseline, Mid-treatment, and Post-Treatment Repeated Measures Analyses of Depressive Symptoms

Measure	Baseline M (*SD*)	Mid-Treatment *M (SD)*	Post-treatment *M (SD)*	F (*df* = 1,19)	*P*	η^2
BDI	7.70 (5.00)	8.95 (6.60)	11.65 (7.10)	14.20	<.001	0.43
BDI Cognitive-Affective subscale	4.35 (2.72)	5.25 (3.82)	6.95 (3.63)	13.32	.002	0.41
BDI Somatic-Performance subscale	3.35 (3.10)	3.70 (3.48)	4.70 (3.98)	5.75	.027	0.23
CES-D	13.85 (10.98)	12.60 (11.16)	15.15 (9.50)	0.531	.477	0.03

BDI = Beck Depression Inventory

CES-D = Center for Epidemiologic Studies- Depression Scale

Table 8

Self-Reported Symptoms Meeting Criteria Suggestive of Clinical Depression

Depression Scale	**Baseline % (N)**	**Mid-Treatment % (N)**	**Post-Treatment % (N)**
Normal (Range 0-9)	80% (16/20)	65% (13/20)	45% (9/20)
Beck Depression Inventory $\geq$ 10	20% (4/20)	35% (7/20)	55% (11/20)
Severity of BDI Depressive Symptoms			
Mild (Range 10-18)	75% (3/4)	71% (5/7)	64% (7/11)
Moderate (Range 19-29)	25% (1/4)	29% (2/7)	36% (4/11)
Severe (Range 30-63)	0	0	0
CES-D $\geq$ 16	30% (6/20)	20% (4/20)	50% (10/20)

BDI = Beck Depression Inventory

CES-D = Center for Epidemiologic Studies- Depression Scale

Table 9

Mean (SD) Scores for the SF-36 Subscales and Physical and Mental Component Summary Scores: Normative Data by Age (Jenkinson et al., 1993) and for Newly Diagnosed Breast Cancer Patients Who Underwent a Lumpectomy (Ganz et al., 2004)

Normative Data Age (years)				**Lumpectomy Only**
Variable	**25-34**	**35-44**	**45-55**	***M (range)***
MOS PCS	n/a	n/a	n/a	47.1 (45.4-48.7)
MOS MCS	n/a	n/a	n/a	48.8 (47.2-50.5)
Mental Health	71.6 (15.2)	71.6 (17.8)	73.2 (18.2)	67.7 (64.8-70.5)
Physical Health	92.9 (13.3)	89.4 (16.1)	84.8 (18.3)	78.7 (75.0-82.3)
Role function- Physical	92.9 (13.3)	89.4 (16.1)	84.8 (18.3)	59.3 (52.4-66.2)
Role function- Emotional	80.6 (34.0)	80.3 (33.6)	80.8 (33.6)	68.2 (61.7-74.7)
General Health	77.3 (18.5)	74.1 (20.3)	73.1 (19.9)	73.0 (69.9-76.1)
Bodily Pain	82.1 (21.1)	79.4 (22.0)	77.4 (22.3)	73.3 (69.6-76.9)
Social Function	87.1 (18.9)	86.7 (20.5)	87.0 (20.8)	82.7 (78.9-86.6)
Vitality	58.3 (19.5)	58.2 (19.9)	59.4 (20.3)	53.4 (49.6-57.1)

MOS PCS = Medical Outcomes Study of Physical Component Summary Scale;

MOS MCS = Medical Outcomes Study of Mental Component Summary Scale

Table 10

SF-36 Summary Component Scales and Subscales

Measure	Baseline *M* (*SD*)	Mid-Treatment *M (SD)*	Post-treatment *M (SD)*	F (*df* = 1,19)	*p*	η^2
MOS PCS	37.23 (11.27)	41.46 (10.99)	40.65 (10.87)	1.00	.330	.05
MOS MCS	41.52 (8.33)	42.35 (6.78)	41.29 (8.22)	.01	.909	.001
Mental Health	69.60 (19.00)	73.80 (18.00)	70.80 (18.50)	.09	.774	.004
Physical Health	76.50 (24.77)	68.00 (24.73)	62.25 (25.21)	4.91	.039	.21
Role function- Physical	33.75 (40.78)	28.75 (35.61)	25.00 (33.44)	2.08	.165	.02
Role function- Emotion	43.33 (30.78)	51.67 (31.49)	40.01 (38.39)	.14	.716	.01
General Health	69.55 (22.21)	67.65 (20.17)	64.40 (20.73)	2.21	.154	.10
Bodily Pain	65.30 (26.77)	66.40 (24.29)	70.35 (23.26)	.48	.496	.03
Social Functioning	29.38 (29.32)	30.00 (28.79)	41.25 (26.62)	4.04	.059	.18
Vitality	55.20 (22.21)	52.00 (21.79)	46.25 (21.45)	.47	.500	.10

MOS PCS = Medical Outcomes Study of Physical Component Summary Scale;

MOS MCS = Medical Outcomes Study of Mental Component Summary Scale

Table 11

Measure of Quality of Life: FACT-General and Subscales

Measure	Baseline M (*SD*)	Post-treatment *M (SD)*	F (*df* = 1,19)	*p*	η^2
FACT-General	84.76 (13.79)	79.76 (14.91)	4.20	.055	.18
FACT-Fatigue Subscale	35.73 (10.54)	29.64 (12.90)	7.59	.013	.29
FACT-Anemia Subscale	58.55 (12.85)	49.14 (15.30)	5.77	.027	.23
FACT-Physical Wellbeing	22.65 (4.61)	20.10 (6.33)	3.82	.066	.17
FACT-Emotional Wellbeing	16.6 (5.14)	17.59 (2.97)	1.31	.267	.06
FACT-Functional Wellbeing	19.14 (5.36)	15.78 (4.85)	8.30	.010	.30
FACT-Social/Family	24.61 (2.96)	23.51 (3.78)	5.14	.035	.21

FACT= Functional Assessment of Cancer Treatment

Table 12

Breast Cancer Prevention Trial Checklist: Baseline, Mid-treatment, and Post-treatment Repeated Measures Analyses of Quality of Life Symptoms ([1]Stanton, Bernaards, & Ganz, 2005)

Measure	Baseline M (*SD*)	Mid-Treatment *M (SD)*	Post-treatment *M (SD)*	F (*df* = 1,19)	*p*	η^2	[1]High Risk Comparison	[1]Recently Treated Comparison
BCPT Total	0.45 (0.40)	0.59 (0.37)	0.90 (0.41)	23.64	<.001	.55	0.48	0.73
BCPT Hot Flashes	0.35 (0.52)	0.75 (0.72)	1.73 (0.92)	33.51	<.001	.59	0.50	1.22
BCPT Weight Problems	0.50 (0.65)	0.63 (0.69)	0.98 (0.83)	4.58	.046	.19	0.71	0.98
BCPT Nausea	0.15 (0.46)	0.73 (0.75)	0.63 (0.60)	11.08	.004	.37	0.14	0.17
BCPT Muscloskeletal Pain	0.79 (1.07)	0.85 (0.78)	0.92 (0.88)	0.392	.539	.02	0.77	1.06
BCPT Vaginal Problems	0.25 (0.62)	0.08 (0.18)	0.38 (0.76)	0.459	.506	.02	0.29	0.49
BCPT Bladder Control	0.15 (0.33)	0.10 (0.26)	0.23 (0.50)	1.31	.267	.06	0.40	0.32

BCPT=Breast Cancer Prevention Trial Checklist

Table 13

Partial Correlations of Post-Treatment BCPT Cognitive Problems with Baseline Predictor Variables Partialing Out Baseline BCPT Cognitive Problems

Scale	BCPT Cognitive Problems Subscale T3
BCPT Hot Flash T1	-.20
BCPT Weight Problems T1	-.16
BCPT Nausea T1	-.21
FACT-F Subscale T1	-.33
FACT-Social & Family T1	.21
FACT-Functional T1	-.40
BDI T1	.44
MOS-36 Physical Function T1	-.23
Estradiol T1	.05
Hemoglobin T1	.50*
Age	.07
Education	-.29

*p < .05 level, two-tailed. **p < .01, two-tailed; T3 = Post-treatment; BCPT = Breast Cancer Prevention Trial; MOS = Medical Outcomes Study; FACT= Functional Assessment of Cancer Treatment; BDI = Beck Depression Inventory

Table 14

Partial Correlations of Post-Treatment BCPT Cognitive Problems with Post-Treatment Predictor Variables Partialing Out Baseline BCPT Cognitive Problems

Scale	BCPT Cognitive Problems Scale T3
BCPT Hot Flashes T3	.05
BCPT Weight Problems T3	.07
BCPT Nausea T3	.31
FACT-F Subscale T3	-.40
FACT-Social & Family T3	.15
FACT-Functional T3	-.48*
BDI T3	.33
MOS-36 Physical Function T3	-.01
Estradiol T3	-.17
Hemoglobin T3	.34

*p < .05 level, two-tailed. **p < .01, two-tailed; T3 = Post-treatment; BCPT = Breast Cancer Prevention Trial; MOS = Medical Outcomes Study; FACT= Functional Assessment of Cancer Treatment; BDI = Beck Depression Inventory

Table 15

Partial Correlations of Post-Treatment FACT-F Subscale with Baseline Predictor Variables Partialing Out Baseline FACT-F Subscale

Scale	FACT- F Subscale T3
BCPT Cognitive Problems T1	-.08
BCPT Hot Flash T1	.65 **
BCPT Weight Problems T1	-.14
BCPT Nausea T1	.11
FACT-Social & Family T1	.21
FACT-Functional T1	.36
BDI T1	-.23
MOS-36 Physical Function T1	-.09
Estradiol T1	-.16
Hemoglobin T1	-.47*
Age	-.59**
Education	-.07

*p < .05 level, two-tailed. **p < .01, two-tailed; T3 = Post-treatment; BCPT = Breast Cancer Prevention Trial; MOS PCS = Medical Outcomes Study; FACT= Functional Assessment of Cancer Treatment; BDI = Beck Depression Inventory

Table 16

Partial Correlations of Post-Treatment FACT-F Subscale with Post-Treatment Predictor Variables Partialing Out Baseline FACT-F Subscale

Scale	FACT-F Subscale Scores T3
BCPT Cognitive Problems	-.30
BCPT Hot Flashes T3	-.07
BCPT Weight Problems T3	-.10
BCPT Nausea T3	-.49*
FACT-Functional Subscale T3	.68**
FACT-Social and Family T3	.08
BDI T3	-.55*
MOS-36 Physical Function T3	.62**
Estradiol T3	.04
Hemoglobin T3	-.11

*p < .05 level, two-tailed. **p < .01, two-tailed; T3 = Post-treatment; BCPT = Breast Cancer Prevention Trial; MOS = Medical Outcomes Study; FACT= Functional Assessment of Cancer Treatment; BDI = Beck Depression Inventory

Table 17

Partial Correlations of Post-Treatment BDI with Baseline Predictor Variables Partialing Out Baseline BDI

Scale	BDI T3
BCPT Cognitive Problems T1	.41
BCPT Hot Flash T1	-.61 **
BCPT Weight Problems T1	.03
BCPT Nausea T1	.08
FACT-Social & Family T1	-.33
FACT-Functional T1	-.29
FACT-F T1	-.29
MOS-36 Physical Function T1	.06
Estradiol T1	.10
Hemoglobin T1	.29
Age	.18
Education	.25

*p < .05 level, two-tailed. **p < .01, two-tailed; T3 = Post-treatment; BCPT = Breast Cancer Prevention Trial; MOS = Medical Outcomes Study; FACT= Functional Assessment of Cancer Treatment; BDI = Beck Depression Inventory

Table 18

Partial Correlations of Post-Treatment BDI Scores with Post-Treatment Predictor Variables Partialing Out Baseline BDI Scores

Scale	Beck Depression Inventory Scores T3
BCPT Cognitive Problems	.13
BCPT Hot Flashes T3	.00
BCPT Weight Problems T3	.35
BCPT Nausea T3	.38
FACT-Functional Subscale T3	-.73**
FACT-Social & Family T3	-.29
FACT-F Subscale T	-.60**
MOS-36 Physical Function T3	.30
Estradiol T3	.45
Hemoglobin T3	.07

*p < .05 level, two-tailed. **p < .01, two-tailed; T3 = Post-treatment; BCPT = Breast Cancer Prevention Trial; MOS = Medical Outcomes Study; FACT= Functional Assessment of Cancer Treatment; BDI = Beck Depression Inventory

Table 19

Partial Correlations of Post-Treatment BCPT Hot Flash Subscale with Baseline Predictor Variables Partialing Out Baseline BCPT Hot Flash Subscale

Scale	BCPT Hot Flash Subscale T3
BCPT Cognitive Problems T1	.22
BCPT Weight Problems T1	.05
BCPT Nausea T1	.36
FACT-Social & Family T1	-.23
FACT-Functional T1	-.26
FACT-F T1	.11
BDI T1	.51*
MOS-36 Physical Function T1	-.06
Estradiol T1	-.49*
Hemoglobin T1	-.26
Age	.21
Education	.41

*p < .05 level, two-tailed. **p < .01, two-tailed; T3 = Post-treatment; BCPT = Breast Cancer Prevention Trial; MOS = Medical Outcomes Study; FACT= Functional Assessment of Cancer Treatment; BDI = Beck Depression Inventory

Table 20

Partial Correlations of Post-Treatment BCPT Hot Flash Subscale with Post-Treatment Predictor Variables Partialing Out Baseline BCPT Hot Flash Subscale

Scale	BCPT Hot Flashes Scale
BCPT Cognitive Problems T3	.15
BCPT Weight Problems T3	.27
BCPT Nausea T3	.25
FACT-F Subscale T3	-.01
FACT-Social & Family T3	-.45
FACT-Functional T3	-.44
BDI T3	.43
MOS-36 Physical Function T3	-.12
Estradiol T3	.02
Hemoglobin T3	-.31

*p < .05 level, two-tailed. **p < .01, two-tailed; T3 = Post-treatment; BCPT = Breast Cancer Prevention Trial; MOS = Medical Outcomes Study; FACT= Functional Assessment of Cancer Treatment; BDI = Beck Depression Inventory

APPENDIX B

FIGURES

Figure 1

Mean Baseline SF-36 Physical and Mental Health Summary Scores between subjects and newly diagnosed Breast Cancer patients (Ganz, 2004)