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ABSTRACT

Title of Thesis: **Tamoxifen and aromatase inhibitors: Cognitive function in occupationally active breast cancer survivors**

Lynn Marie Breckenridge, MS, 2010

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Previous research has suggested that endocrine therapy to inhibit growth of breast cancer tissue is positively associated with cognitive limitations in breast cancer survivors (BCS). Whether this relationship exists in occupationally active survivors is unknown. This study examined endocrine therapy and cognitive function in working BCS, an average of 3 years post-primary treatment. Seventy-seven BCS with past or current exposure to endocrine therapy (tamoxifen or aromatase inhibitors) and 56 BCS with no history of endocrine therapy completed measures of perceived and performance-based cognitive function, physical fatigue, anxiety and depression. Exposure to endocrine therapy was moderately related to perceived attentional problems at work (ß=-0.198, $CI_{.95}$ = -2.75, -0.25) and perceived cognitive functioning in overall life (ß=0168, $CI_{.95}$ = 0.33, 11.47) in excess of what could be explained by symptom burden measures. Symptoms of physical fatigue, depression and anxiety were positively associated with self-reported general cognitive limitations, and symptoms of depression and anxiety were positively associated with perceived cognitive limitations at work.

Tamoxifen and Aromatase Inhibitors: Cognitive Function in Occupationally Active Breast Cancer Survivors

by

Lynn Marie Breckenridge

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INTRODUCTION

Based on 2004 to 2006 rates of breast cancer, it is estimated that one in eight women born in the United States today will be diagnosed with breast cancer. Currently, over 2.5 million women in the United States have a history of breast cancer (American Cancer Society, 2007). The five-year relative survival rate for all forms of breast cancer is approximately 90.3%, and the five-year relative survival rate for non-metastasized breast cancer is 100 percent. In comparison, in 1979 the five-year relative survival rate for all stages of breast cancer was just under 75%, and in 1989, the five-year relative survival rate was 84.3% for all stages of breast cancer (American Cancer Society, 2007; Jemal, 2005). This drastic increase in survivability is due mostly to early detection, but also due to advancements in medical treatment (Hind, Ward, De Nigris, Simpson, Carroll, & Wyld, 2007).

Neurocognitive Deficits in Breast Cancer Survivors

When diagnosed with breast cancer, most women and their doctors have a variety of options, including adjuvant chemotherapy, radiation therapy and surgery to remove or kill cancerous cells. These primary treatments are often followed by targeted therapies such as trastuzumab, a monoclonal antibody that reduces proliferation of cancerous cells in patients whose tumors are human epidermal growth factor receptor 2 positive, and adjuvant endocrine therapy for patients whose tumors are estrogen receptor positive (Hind, Ward, De Nigris, et. al, 2007; Visvanathan, Chlebowski, Hurley, Col, Ropka, Collyar et. al., 2009). The most common types of adjuvant endocrine therapy include the selective estrogen receptor modulator (SERM) tamoxifen, and aromatase inhibitors (AIs) such as exemestane or arimidex. Both chemotherapy and adjuvant

therapies result in substantial improvements in overall survival for women with breast cancer (Jemal, Thun, Ries, Howe, Weir, Center, et. al. 2008; Winer, Hudis, Burstein, Wolff, Pritchard, Ingle, et. al. 2005). However, as the rate of survivorship has increased, there have been increasing reports of cognitive dysfunction and chronic fatigue in breast cancer survivors (Castellon, Ganz, Bower, Peterson, Abraham, & Greendale, 2004; Wefel, Witgert, & Meyers, 2008).

In the United States, approximately 5% of working age women, roughly defined as under the age of 60, have or have had breast cancer (American Cancer Society, 2007). A study of breast cancer survivors reported that more than 80% of women who were working at the time of diagnosis returned to work between 12 and 18 months after diagnosis (Bradley, Bouknight and Luo, 2006). In addition, the number of women working at the time of diagnosis is growing, and there are increasingly more breast cancer survivors present in the workplace (Chirokos, 2001). Several studies report growing concerns amongst breast cancer survivors with regard to possible cognitive deficits associated with treatment (Schagen & van Dam, 2006; Ahles & Saykin, 2002; Nelson, Nandy & Roth, 2007). These concerns may negatively impact their quality of life (Ahles & Saykin, 2002), and may have a negative effect on their ability to make informed treatment decisions, or to pursue occupational and academic ambitions (Nelson, Nandy & Roth, 2007). Further, despite the increased survival benefit of endocrine therapy drugs, breast cancer survivors who wish to remain occupationally active may be less likely to adhere to their prescribed treatment regime. Research indicates that side effects, such as fatigue, “mental fogging,” and cognitive deficits, are cited by breast cancer survivors as the leading reason for non-adherence to adjuvant therapy drugs (Grunfeld, 2005).

A negative relationship between chemotherapy and neurocognitive dysfunction has been suggested in several studies (Falleti, Sanfilippo, Maruff, Weih & Phillips, 2005; Schagen, van Dam, Muller, Boogerd, Lindeboom, & Bruning, 1999; Wieneke & Dienst, 1995; Wefel et. al., 2008), although the mechanism of action in this relationship remains unclear. On performance-based measures, one study suggested that approximately 75% of survivors display deficits (up to two standard deviations below the mean) in one or more areas, including speed of processing, visual and verbal memory, mental flexibility, attention span, concentration, visuo-spatial ability or motor function after chemotherapy and adjuvant endocrine therapy, despite high-normal estimated pre-morbid intelligence (mean FSIQ=113; Wieneke & Dienst, 1995). Another investigation (Von Ah et al., 2009) reported that 25% of breast cancer survivors (BCS) had scores suggestive of cognitive detriments on the Rey Auditory Verbal Learning Test. Further, on self-report and performance-based measures of cognitive function, 16-50% of BCS with a history of adjuvant chemotherapy are reported to have cognitive limitations that are significant up two years after treatment (Bender et. al., 2005; Fan et. al., 2005), compared with 5% of healthy controls (Fan et. al.), particularly in the domains of memory, attention, concentration, executive function and psychomotor efficiency (Bender et. al.).

However, other studies suggest that there may not be a direct association between cancer treatments and cognitive deficits. Quesnel and colleagues (2009) reported that some cognitive deficits (impaired capacity for recruiting verbal information) existed in breast cancer survivors regardless of whether or not they received either chemotherapy or radiotherapy. This study also reported that in some breast cancer patients, attention deficits existed prior to the initiation of treatment (lower Digit Span

forward score in one group, and lower than average Symbol Digit Modalities Test scores in another group; $p<0.05$). Ahles and colleagues (2008) also reported that prior to any treatment, Stage 1-3 breast cancer patients scored significantly lower than Stage 0 patients and healthy controls on several neuropsychological tests. The study reported that 22% of these patients were classified as having lower than expected cognitive performance, compared to 0% of Stage 0 patients and four percent of healthy controls ($p<0.005$), even after accounting for symptom burden (Ahles, Saykin, & McDonald, et. al., 2008). Further, Wefel and colleagues (2004) indicated that baseline cognitive deficits existed in approximately 35% of patients with breast cancer, particularly in verbal learning and memory (18-25% of patients) prior to chemotherapy. These results suggest that cognitive deficits reported by BCS may not be directly accounted for by exposure to cancer treatment.

Adjuvant Endocrine Therapy

In addition to primary treatment methods (radiation therapy, surgery, and/or chemotherapy to remove cancer from the breast), about 60% of women diagnosed with breast cancer are candidates for endocrine therapy (Berry, Corrincione, Henderson, et. al., 2006). Endocrine therapy is used in women with tumors that express estrogen receptors. Most estrogen target tissues such as breast, endometrium, liver and bone express estrogen receptors in their cells. Normally, estrogen and its receptors have beneficial roles, such as programming breast and uterine tissue for reproduction. When estrogen binds with its receptors, it initiates cell proliferation. Cell proliferation naturally occurs in areas such as the lining of the milk glands, preparing the breast to produce milk when necessary. Cancer occurs when there are DNA mutations in the genes that regulate cell growth and

division. These mutations may be inherited, may be the result of carcinogens, or may occur spontaneously as the result of a mistake that is made when a cell duplicates its DNA prior to cell division. When DNA mutations are acquired in specific genes that regulate proliferation, such as proto-oncogenes or tumor suppressor genes, these changes are duplicated with each new division of cells. These mutations can lead to uncontrolled proliferation of cells and the onset of cancer. Although estrogen does not appear to cause the DNA mutations that trigger breast cancer, it does stimulate cell proliferation, leading to an increased number of mutated cells if the cells are estrogen receptor positive (National Cancer Institute, 2006). Endocrine therapy is utilized to impede estrogen-induced proliferation of cells, either by eliminating estrogen in the body with aromatase inhibitors, or by antagonizing estrogen in target tissues. However, because estrogen has several important benefits, concerns exist regarding possible unintended negative effects associated with its depletion or antagonism in other target tissues. One of these concerns is with regard to possible cognitive deficits in the brain, another estrogen target tissue (Cella & Fallowfield, 2008).

While the relationship between cognitive dysfunction and traditional treatments such as chemotherapy remains unclear, the relationship between adjuvant endocrine therapy and cognitive function in breast cancer survivors has received even less attention (Cella & Fallowfield, 2008). Although some studies report that use of adjuvant endocrine therapy is associated with cognitive dysfunction in excess of what is typically related to chemotherapy (Castellon et. al., 2004; Castellon, Silverman, & Ganz, 2005; Jenkins, Ambroisine, Atkins, Cuzick, Howell, & Fallowfield, 2008), other studies have reported that adjuvant endocrine therapy is not associated with any additional

cognitive deficits (Jenkins et. al, 2008; Fan, et. al., 2005; Hermelink, Henschel, Untch, Bauerfeind, Lux, & Munzel, 2008, Paganini-Hill & Clark, 2000). In fact, it has been suggested that certain estrogen-like drugs may have a neuroprotective effect in the brain (Ernst, Chang, Cooray, Salvador, Jovicich, Walot, et al. 2002; Schilder & Schagen, 2007). In a proton magnetic resonance spectroscopy (MRS) study of elderly women receiving tamoxifen or estrogen, it was observed that both groups had lower concentrations of myo-inositol in their basal ganglia than control subjects, and that these concentrations were inversely correlated with the duration of tamoxifen treatment (Ernst, et al., 2002). In previous studies, increased levels of myo-inositol were reported in patients with Alzheimers disease (Miller, RA, Shonk, Ernst, Woolley, & Ross, 1993), brain injuries (Garnett, Blamire, Corkill, Cadoux-Hudson, Rajagopalan, & Styles, 2000), and multiple sclerosis (Fernando, et al., 2004). Higher myo-inositol levels were associated with diminished cognitive abilities in adults with Down Syndrome (Beacher, Simmons, Daly, Prasher, Adams, Margallo-Lana, et al., 2005), and also were associated with neuropsychological impairment and distress in recently detoxified alcoholics (Schweinsburg, Taylor, Videen, Alhasson, Patterson, & Grant, 2006). While further research is required, it has been suggested that estrogen and estrogen-like drugs (such as tamoxifen) may work through the inositol pathway or similar mechanisms to produce a neuroprotective effect (Ernst, et al., 2002). Further, both a meta-analysis and a longitudinal study reported that cognitive impairment due to adjuvant chemotherapy and/or adjuvant endocrine therapy tended to decline with time after treatment, and is often undetectable within a year after treatment (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Quesnel, Savard & Ivers, 2009).

It is important to note that evidence for or against an association between adjuvant endocrine therapy and cognitive dysfunction is limited by the methodological problems of the majority of studies, such as lack of baseline measurements, inability to establish causality, inability to examine long-term outcome relationships, inability to account for or control for extraneous variables and interaction effects, lack of an appropriate control group, and dependence solely on either performance-based or self-report measures (Cella & Fallowfield, 2008; Falleti et. al., 2005). Also, there are few studies to date that account for change in occupational activity of breast cancer survivors pre- to post-treatment, and no known studies have examined the relationship between endocrine therapy and cognitive function solely in breast cancer survivors who have remained or returned to work.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators such as tamoxifen were first used in the 1950s and are frequently prescribed to patients with breast cancer and estrogen receptor positive (ER+) tumors. They also are used in prevention of breast cancer development, prevention of bone loss, gynecomastia, infertility in women with anovulatory disorders, bipolar disorder, and even for temporary chemical castration in sex offenders (Furr, 1984; National Cancer Institute, 2006). In mammary tissue, these drugs have an antagonist action, competitively binding to ER-α and ER-β estrogen receptors. These receptors are G protein coupled receptors, and when bound by estrogen they signal the transduction of proteins and transcription of genetic material, ultimately resulting in proliferation of cancerous cells. By competitively binding to estrogen receptors, drugs such as tamoxifen deny the tumor or cancerous tissue the estrogen necessary to stimulate cell growth

(Jenkins, Atkins, & Fallowfield, 2007). Tamoxifen is a pro-drug that is metabolized in the liver by the cytochrome P450 isoform CYP2D6 and CYP3A4 into active metabolites, which have 30-100 times more affinity with estrogen receptors than tamoxifen itself. In competition studies, tamoxifen completely inhibited estradiol binding in ER+ human mammary carcinomas with a relative binding affinity of 0.87 ±0.35% that of estradiol. In ER+ tumors, saturable, high affinity (K^d = 6.0 ± 1.6 nM) tamoxifen binding sites are present at 8.6 times the concentration of the high affinity estradiol receptor sites measured in the same tissue (Sutherland & Murphy, 1980).

However, the role of SERMs in the tissues of the brain is not as well understood. There is conflicting evidence suggesting whether tamoxifen acts as an agonist or antagonist to estrogen in the brain (Jenkins, Atkins, & Fallowfield, 2007; Cella & Fallowfield, 2008). It could be assumed that because tamoxifen is known to be an estrogen antagonist in some tissues of the body, it would also be in the brain. However, tamoxifen acts as an estrogen receptor agonist in bone (Nakamura et. al., 2007), and a partial agonist in endometrial tissue (Grilli, 2006). Tamoxifen's mechanism of mixed agonism/antagonism is not clear (Shang & Brown, 2002), but may be relative to the availability of endogenous estrogen as a competitor. If tamoxifen acts as a very weak partial agonist, it may appear as an antagonist relative to the amount of effect normally seen in tissues that reach ER binding saturation. However, in tissue that has little or no estrogen, such as in the cases of postmenopausal women, the weak partial agonist effect of estrogen may appear stronger than if no ligands bound with the estrogen receptors (National Cancer Institute, 2006).

Tamoxifen also may selectively act as a agonist or agonist in different tissues based on the recruitment of either coactivators or corepressor, based on the structural arrangement of the estrogen receptor induced by ligand binding in that particular cell type. Changes in conformation of the receptor dependent on the type of ligand bound may determine how strongly the ligand-receptor complex recruits coactivators relative to corepressors, resulting in either agonism or antagonism, respectively. In a study of transcriptional responses to tamoxifen binding in different cell types, differential stimulation in the expression of promoter genes was noted. Typically, estrogen activation of receptors is associated with the recruitment of coactivators, and tamoxifen binding with estrogen receptors is associated with the recruitment of corepressors. However, in some cell types, tamoxifen binding induced the recruitment of coactivator complexes. The study reported that this recruitment was explained by the over-expression of certain coregulator cells, and the ratio of coactivator to corepressor proteins, in the cell types in which tamoxifen recruited coactivators rather than corepressors (Shang & Brown, 2002).

However, in the brain, it has not yet been determined if tamoxifen acts as an agonist or antagonist, and may not act the same in all parts of the brain. In a study of postmenopausal women undergoing estrogen replacement, tamoxifen therapy, or neither, proton MRS measures of myo-inositol suggested that use of either estrogen or tamoxifen is associated with neurocognitive protective effects in the basal ganglia, frontal white matter and hippocampus, when compared with controls (Ernst, et al., 2002). In women taking either tamoxifen or estrogen, lower levels of myo-inositol in various areas of the brain were reported, and lower levels of myo-inositol were associated with better cognitive functioning (Ernst et. al., 2002; Beacher et. al., 2005). However, in another

study of postmenopausal women undergoing pharmacotherapy with estrogen, tamoxifen, or neither, positron emission tomography (PET) and magnetic resonance imaging (MRI) measures suggested that tamoxifen may act as an estrogen antagonist in the brain, with harmful antiestrogen effects such as hypometabolism of brain glucose in the inferior and dorsal lateral frontal lobes and reduction in hippocampal volume (Eberling, Wu, Tong-Turnbeaugh, & Jagust, 2004). Because estrogen receptors are found in both the hippocampus and frontal lobes, which play an important role in verbal memory, working memory, and retrieval (Sherwin, 2007), it is reasonable to hypothesize that cognitive deficits in these areas may be related to estrogen antagonism.

According to Castellon and colleagues (2004), breast cancer survivors who received tamoxifen exhibited detriments in verbal learning and language, visuo-spatial functioning and visual memory between two and five years after initial diagnosis and treatment, in excess of what was seen in patients who had chemotherapy without tamoxifen. Further, as shown in Table 1, studies report that tamoxifen is associated with difficulties in memory, fluency, visuo-spatial ability and processing speed (Palmer, Trotter, Joy, & Carlson, 2008), and semantic memory (Eberling et. al., 2004). However, Paganini-Hill and Clark (2000) reported no significant effect of past or present tamoxifen use on neurocognitive battery scores in patients less than five years from diagnosis, and Hermelink and colleagues (2008) reported that within the first year after diagnosis, there was no difference in scores of 101 BCS who had or had not had adjuvant endocrine therapy (tamoxifen or aromatase inhibitors), on twelve cognitive tests, including the Wechsler Memory Scale Revised, the Wechsler Adult Intelligence Scale Revised, and the Trail Making Test.

Aromatase Inhibitors

Aromatase inhibitors such as exemestane, letrozole, and arimidex are becoming more frequently prescribed for patients with breast cancer, and may result in a better survival ratio for breast cancer survivors (Hind, Ward, De Nigris, Simpson, Carroll, & Wyld, 2007). Like selective estrogen receptor modulators, aromatase inhibitors increase the disease-free survival of BCS by limiting estrogen binding with ER+ tumors. Unlike SERMs, which prevent estrogen from binding to its receptors, AIs work by almost completely inhibiting the action of the enzyme aromatase, which is needed for the conversion of testosterone and androstenedione to estrogen. This inhibition almost completely (99.9%) diminishes the circulating supply of estrogen (Schilder & Schagen, 2009).

Aromatase inhibitors were first developed in the 1970s as a non-surgical means of reducing estrogen in individuals with estrogen-reactive tumors of the breast and uterine tissue. Exemestane, letrozole and arimidex are all third generation AIs, which offer increased potency and higher selectivity than previous generations. This generation of AIs consists of two different types, with slightly different mechanisms of action. Type I AIs such as exemestane are androgen analogues, and are also known as aromatase inactivators. They interfere with the substrate-binding site of aromatase and block the enzymatic complex by producing a permanent covalent bond between the inhibitor and the enzyme protein, inactivating it (Brueggemeier, Hackett, & Diaz-Cruz, 2005). Type II, non-steroidal AIs such as letrozole and anastrozole act as competitive inhibitors by reversibly binding to the active enzymatic site, blocking the electron transfer chain in the cytochrome P450 prosthetic group of the aromatase enzyme (Nabholtz, 2008;

Brueggemeier et. al., 2005). Both types are completely effective in inhibiting aromatase's enzymatic action in converting testosterone and androstenedione to estradiol, the most potent endogenous estrogen (Schilder & Schagen, 2009).

Aromatase is most abundant in the ovaries of premenopausal women, in the placenta of pregnant women, and in the peripheral adipose tissues of postmenopausal men and women (Brueggemeier et. al., 2005), but also is naturally found at various sites in the brain, including the hippocampus and cortex, which subserve verbal memory, working memory and retrieval (Sherwin, 2007). Although it has been suggested that the extreme depletion of aromatase and circulating estrogen causes cognitive deficits, the biochemical consequences of inhibiting aromatase in these areas of the brain are not definitively known (Jenkins, Atkins, & Fallowfield, 2007). Some studies suggest that AIs are associated with cognitive deficits, as indicated by lower verbal learning, visual memory, and working memory scores in postmenopausal women with early-stage breast cancer, a minimum of 3 months after initiation of adjuvant endocrine therapy (Bender, et al., 2007). However, others report that AI use is not related to cognitive performance, as exhibited on cognitive test scores in a study of postmenopausal women at-risk for breast cancer, who had been taking anastrazole for a minimum of 24 months (Jenkins, Ambroisine, Atkins, Cuzick, Howell, & Fallowfield, 2008). Further, in a recent study, Ribi and colleagues (2009) reported that after 5 years of therapy with aromatase inhibitors, and despite lower levels of estrogen, early-stage, post-menopausal BCS displayed fewer cognitive deficits than BCS taking tamoxifen.

Symptom Burden

Another potential mechanism by which endocrine therapy drugs may be associated with cognitive deficit is through mood modulation. Between 7% and 46% of women with breast cancer report clinically significant levels of depression or anxiety within the first 6 months after diagnosis (Gallagher, Parle, & Cairns, 2002). Depression and anxiety, as well as pain, distress and fatigue (commonly referred to in breast cancer literature as the collective "symptom burden") are reported to have a negative relationship with cognitive performance in several studies of cancer survivors (Jenkins et. al., 2004; Bender et. al., 2008; Calvio, Feuerstein, Hansen, & Luff, 2009). Jenkins and colleagues (2004) reported that Beck Depression Inventory scores and General Health Questionnaire scores were positively associated with self-reported cognitive deficits, but not performance-based scores. Additionally, in Bender and colleagues' (2007) study, anxiety, depression and fatigue enhanced the relationship between perceived and performance-based cognitive function. In post-menopausal women, lack of estrogen or failure of estrogen to bind with its receptors in the brain may be associated with increased depression, anxiety and mood lability (Archer, 1999; Kase, 1976; McEwen, 2002). However, in a recent literature search, no studies of the relationship between symptom burden, adjuvant endocrine therapy, and cognitive performance in occupationally active BCS were found. Occupationally active BCS may be under additional workplace stress that could negatively impact their cognitive function. Because the majority of breast cancer survivors are occupationally active, it is important to understand the impact of therapy regimes, symptom burden, and cognitive impairment on occupationally active breast cancer survivors.

Employment After Breast Cancer

Bradley and Bednarek (2002) reported that approximately 88% of breast cancer survivors who were working at the time of cancer diagnosis continued to work six months after diagnosis. Other studies have estimated that approximately 80% of breast cancer survivors returned to work or continued to work between 12 months and 3 years after diagnosis (Bouknight, Bradley & Luo, 2006). Similarly, deBoer and colleagues (2009) and Maunsell and colleagues (2004) reported that approximately 65-80% of breast cancer survivors returned to work after diagnosis and treatment (de Boer, Taskila, Ojajarvi, van Dijk, & Verbeek, 2009; Maunsell, Drolet, Brisson, Brisson, Masse, & Deschenes, 2004). Many breast cancer survivors report that maintaining employment is important for their quality of life, including physical and mental health as well as financial well-being (Maunsell et. al., 2004). For many survivors, returning to work is an important measure of recovery and mastery and may represent a step towards regaining a "normal" life.

However, a recent meta-analysis reported that breast cancer survivors were more likely to be unemployed than healthy control participants (35.6% vs. 31.7%, pooled relative risk 1.28; de Boer, Taskila, Ojajavarvi, van Dijk & Verbeek, 2009). According to Drolet and colleagues (2005), 3 years after diagnosis more survivors (21%) are not working than age-matched women who were never diagnosed with cancer (15%). This includes many BCS who returned to work immediately after treatment, but reported 3 years later that they valued their work less (42% of survivors, compared to 26% of healthy control; Drolet et. al., 2005). While the reason for this difference has not been empirically studied, it is often assumed that many women who stop working after a breast

cancer diagnosis do so because of lingering symptoms and symptom burden (Maunsell et. al., 2004).

Breast cancer survivors are more likely than women with no history of cancer to have symptoms of depression, anxiety and fatigue (Feuerstein, Harrington, & Hansen, 2008; Hansen, Feuerstein, Calvio, & Olsen, 2008). Studies suggest that both depression and fatigue are positively associated with the time taken to return to work after treatment (Spelten, et al., 2003), and that depression is positively associated with unemployment in non-cancer populations (Birnbaum, Kessler, Kelley, Ben-Hamadi, Joish, & Greenberg, 2009). Further, fatigue is more highly associated with workplace limitations in BCS than in healthy, age-matched women (Hansen, Feuerstein, Calvio, & Olsen, 2008). Additionally, fatigue, anxiety and depression were all reported to be related to greater workplace limitations in studies of other cancer survivors (Calvio, Feuerstein, Hansen, & Luff, 2009), suggesting that cancer survivors may be more impaired by symptoms of distress and fatigue. For breast cancer survivors, there may be desire to remain at or return to work, but if symptom burden exceeds the ability or desire to do so, quality of life may be substantially reduced. The negative impact of symptom burden and cognitive impairment is clinically relevant and warrants further investigation.

Bradley, Bouknight and Luo (2006) recently reported that return to work for breast cancer survivors was negatively associated with perceived employer discrimination due to cancer and lack of employer accommodation. One year after diagnosis, 13% of breast cancer survivors interviewed said that their employers were not accommodating, and 7% felt that they had been discriminated against because of their diagnosis (Bradley et. al., 2006). Considering the reported statistics regarding the

numbers of breast cancer survivors who experience fatigue, anxiety, depression, and cognitive deficits, as well as the report that 41% of breast cancer survivors express a need for special accommodation in order to keep working (Chirokos et. al., 2002), it is easy to see how uninformed employers could feel overly burdened by their BCS employees. Because employers and fellow employees who have never been closely exposed to breast cancer may not understand the impact of breast cancer treatments, and may not understand the BCS's changing needs, it may reflect poorly upon the breast cancer survivor. BCS may be perceived as being overly sensitive, complaining, or malingering in their symptoms. Therefore, it is important to accurately identify the symptoms breast cancer survivors are experiencing, to attribute these symptoms to causes or explanatory factors, and to disseminate information to BCS, clinicians, occupational specialists and employers.

Information about the risks of cognitive impairment associated with hormonal therapy is important to breast cancer survivors in making informed decisions about their treatment. However, for occupationally active breast cancer survivors, those who are often most likely to be negatively impacted by cognitive deficits, information on which to base their decisions is inadequate. In survivorship literature, the majority of breast cancer survivor studies have included a disproportionately large number of participants who have not returned to work, and may not be generalizable to breast cancer survivors. For instance, in Castellon and colleagues' (2004) study of cognitive deficits related to endocrine therapy in BCS, less than 60% of the participants were employed full-time between 2 and 5 years after initial diagnosis. Related to Maunsell and colleagues' (2004) findings or Bouknight, Bradley and Luo's (2006) findings that approximately 80% of

BCS return to work after diagnosis, Castellon's (2004) study may be disproportionate in its inclusion of occupationally active breast cancer survivors, and may be particularly low in numbers of those who attempt to return to their previous level of occupational functioning. This statement is also true of Palmer and colleagues' (2008) study, in which only about 65% of breast cancer survivor participants (mean age 45.8 years) were working full time, an average of 2.9 years following diagnosis. To our knowledge, no studies of cognitive functioning and association with a history of adjuvant endocrine therapy exposure have been conducted in working breast cancer survivors.

While it has been reported in other studies that use of adjuvant endocrine therapy is associated with greater detriments in memory, attention, processing and concentration, impairments associated with cancer therapy have been reported to dissipate in the years following diagnosis and treatment (Falleti et. al., 1999), most likely due to BCS's learned use of compensatory strategies to overcome deficits, or due to neuroplasticity effects (Tannock, Ahles, Ganz & van Dam, 2006; Johnson, 2009). In a workshop of breast cancer survivors, use of cognitive compensatory strategies such as avoidance of concurrent multiple task situations, frequent list-making, avoidance of high-pressure work situations through planning of workload, and recognizing increased need for sleep to overcome cognitive impairments at work was consistently endorsed by working breast cancer survivors (Tannock et. al., 2006). In other populations, it has been suggested that remaining cognitively engaged in volunteer or occupational work may be protective against cognitive dysfunction, with individuals showing a steeper trajectory of cognitive decline after retirement than before (Bieliauskas, Langenecker, & Graver, 2008; Carlson, et al., 2008). Further, in the vocationally active individual, repetitive

stimulation of synapses used in processes of working memory, executive function, multi-tasking, and attentional focus may result in neuroplasticity and long-term potentiation of relevant neurotransmission pathways (Johnson, 2009). Remaining cognitively engaged in activities such as occupational employment may reduce the appearance of cognitive deficits, either through learned, functional cognitive compensatory strategies, or through neuroplasticity mechanisms.

However, in the literature it is currently unclear whether occupationally active breast cancer survivors (OABCS) with a history of endocrine therapy differ from OABCS with no history of endocrine therapy exposure in symptoms of fatigue, anxiety and depression, and how these symptoms might interact with perceived and performance-based cognitive function. This information is important to breast cancer survivors in making informed treatment and occupational decisions, to clinicians and occupational specialists in screening and treatment of OABCS with symptoms of cognitive dysfunction, fatigue or distress, and to employers in understanding the needs and limitations of their breast cancer survivor employees. This study aims to:

1) Examine any differences in fatigue, anxiety and depression in occupationally active breast cancer survivors (OABCS) who have been exposed to adjuvant endocrine therapy versus OABCS who have never been exposed. In previous studies, lack of estrogen or failure of estrogen to bind with its receptors in the brain has been reported to be positively associated with increased depression, anxiety and mood lability (Archer, 1999; Kase, 1976; McEwen, 2002). Because both tamoxifen and aromatase inhibitors prevent estrogen from reaching its receptors (through different mechanisms), it is reasonable to believe that these drugs may have a similar relationship

with fatigue, anxiety and depression. Because fatigue, anxiety and depression may impact cognitive function (Bender et. al., 2007) as well as ability to return to and remain in employment (Spelten et. al., 2003; Birnbaum et. al., 2009), it is important to know if endocrine therapy is positively associated with fatigue and distress, and to make occupationally active breast cancer survivors and clinicians aware of any possible increased risk associated with the use of endocrine therapy.

2) Compare the perceived and observed cognitive functioning of OABCS with a history of adjuvant endocrine therapy with the perceived and observed cognitive functioning of OABCS who have never been administered adjuvant endocrine therapy. Cognitive deficits associated with endocrine therapy drugs have been reported in numerous studies (Castellon et. al., 2004; Palmer et. al., 2008, Eberling et. al., 2004; Bender et. al., 2007; Jenkins et. al., 2008; Ribi et. al., 2009). However, because most of these studies either did not include a large proportion of OABCS or did not include information on the working status of participants, and none of these studies were done specifically in OABCS, it is difficult to know whether the results are generalizable to the OABCS population. Information regarding the compensatory cognitive strategies of OABCS (Tannock et. al., 2006) and neuroplasticity associated with remaining occupationally active (Johnson, 2009) suggests that OABCS may appear to have fewer cognitive deficits associated with adjuvant endocrine therapy. However, it is important to know the extent to which these deficits do exist in association with endocrine therapy, so that OABCS can make informed decisions in treatment and in occupational planning, so that clinicians can screen for and treat symptoms, and so that employers can understand

OABCS's symptoms and provide reasonable accommodations to their OABCS employees.

3) *Examine the relationships among fatigue, anxiety, and depression and perceived and performance-based cognitive function in OABCS who have or do not have a history of adjuvant endocrine therapy.* A previous study of BCS found that symptoms of fatigue, depression, and anxiety enhanced the relationship between adjuvant endocrine therapy and perceived and performance based cognitive function (Bender et. al., 2007). Other studies have also reported that a positive association exists between symptoms of fatigue, depression, and anxiety and performance-based cognitive deficits (Jenkins et. al., 2004; Bender et. al., 2008). It is important for clinicians to be aware if such an association exists, in order to better screen for symptoms in BCS, and to develop interventions that target these symptoms and enhance OABCS's overall well-being and quality of life.

Hypotheses

Hypothesis 1: Occupationally active breast cancer survivors who have a history of exposure to adjuvant endocrine therapy will have more symptoms of depression, anxiety and fatigue than breast cancer survivors who have no previous exposure to adjuvant endocrine therapy.

Hypothesis 2: Occupationally active breast cancer survivors with a history of exposure to adjuvant endocrine therapy drugs will have greater cognitive limitations than those who have never been exposed to adjuvant endocrine therapy drugs, on both self-report and performance-based measures.

Hypothesis 3: In occupationally active breast cancer survivors, endocrine therapy exposure will be positively associated with perceived and performance-based cognitive limitations even after controlling for symptom burden as a potential confounder.

METHODS

Study Design

While many studies of endocrine therapy have not differentiated between BCS exposed to aromatase inhibitors, tamoxifen, or both, a few studies have raised concerns that there may be a difference in the deficits seen with tamoxifen versus the deficits seen with aromatase inhibitors (Schilder et. al., 2009; Bender, Sereika, Ryan, Casillo, Vogel, & Berga, 2005; Ribi, et al., 2009). However, other adequately powered studies have reported no statistically significant differences between cognitive deficits associated with either SERMs or AIs (Hermelink et. al., 2008; Jenkins et. al., 2004; n=101 and n=94, respectively). Based on the fact that both tamoxifen and aromatase inhibitors work through limiting estrogen (either through eliminating it or through blocking it from its target receptor), and evidence that estrogen is associated with cognitive deficits in BCS (Ernst, et al., 2002), it is rational to assume that any variations in cognitive deficits seen in either aromatase inhibitor users or SERM users would be minimal, if present at all. Further, because most of our participants had a history of both tamoxifen and aromatase inhibitors, and few had a history of only one or the other, we found it necessary to

combine the two drug groups. Our research goal was to examine adjuvant endocrine therapy as a whole, rather than to examine a specific drug, therefore, this was determined to be a reasonable study design. This study design is consistent with methods commonly used in the literature, such as Schilder and colleagues' (2009) study, which combined tamoxifen and exemestane users into the same group for analysis of relationships between cognitive function and symptom burden, as well as studies by Jenkins and colleagues (2004), Hermelink and colleagues (2008), Fan and colleagues (2005), and Shilling & Jenkins (2007).

Procedure

This study was part of a larger study that compared cognitive limitations, work performance, chronic fatigue and distress in 133 OABCS and 122 non-cancer control participants. Both the larger study and the current study were approved by the Uniformed Services University of the Health Sciences (USUHS) Institutional Review Board (Appendix A). In the current study, data from 77 OABCS who had had adjuvant endocrine therapy (tamoxifen or AI) and 56 OABCS who had not had adjuvant endocrine therapy were examined.

Participants were recruited in 2007, through ads and fliers placed at cancer clinics and centers, support groups and primary care centers across the United States. Newspaper ads, hospital bulletin boards, and websites also were utilized. All recruitment materials directed potential participants to a website hosted by SurveyMonkey® for screening. Exclusion criteria included a diagnosis of dementia, brain injury, adult attention deficit hyperactivity disorder (ADHD), epilepsy, drug or alcohol abuse, or metastatic cancer. Inclusion criteria consisted of female BCS, between

the ages of 18 and 65, who were working full-time at the time of assessment and who had been working prior to diagnosis. Potential participants needed to have access to a computer and the internet, and needed to be able to use a computer themselves. Recruited BCS were at least one year, but not more than ten years, from completion of primary treatment, and had no active cancer diagnosis. Potential participants who met the inclusion criteria were randomized to complete either the self-report measures or the neuropsychological probe first. Participants were each emailed an identification number and the portal address for the study's main website, also hosted by SurveyMonkey®.

Upon logging into the main website, participants were presented with an informed consent form (see Appendix B). In order to proceed, each participant had to click that she had read and understood the informed consent, and agreed to participate. Participants were randomly given instructions to either continue on SurveyMonkey, or to complete a neurocognitive measure remotely administered through a website hosted by CNS Vital Signs, LLC, a HIPAA compliant website. After completion of the first set of instructions, participants were given instructions to complete the portion of the study they had not previously completed (either SurveyMonkey or CNS Vital Signs).

The participants supplied demographic information including health and work history, and completed a series of self-report measures on cognitive limitations, depression, fatigue and work limitations. The health questionnaire included information about history of cancer, treatments and current medications, as well as other factors that could impact mental status and well-being, such as menopausal status, alcohol and caffeine use. The work history questionnaire asked for information about duration and

type of work currently, and prior to diagnosis. The information from these questionnaires is displayed in Tables 2-4.

Self-report measures used for this study included the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), the Multidimensional Fatigue Symptom Inventory- Short Form (MFSI-SF; Stein, Jacobsen, & Blanchard, 2004), the Pain Visual Analog Scale (Scott & Huskisson, 1979), the Functional Assessment of Cancer Therapy-Cognitive Scale Version II (FACT-Cog, Cella et al., 1993), and the Cognitive Symptoms Checklist-Modified (CSC; Feuerstein, Hansen, Calvio, Johnson, & Ronquillo, 2007; Hansen, Feuerstein, Calvio, & Olsen, 2008).

All database activities were conducted on SPSS 16.0 and data were stored at USUHS, on a password-protected computer in a secured office. While the participants provided sensitive information, all data were de-identified prior to analysis to ensure confidentiality.

Measures

Hospital Anxiety and Depression Scale (HADS)

The HADS (Zigmond & Snaith, 1983) is a self-assessment scale for measuring depression and anxiety in a general medical population. The HADS consists of 14 items on two subscales, one measuring anxiety (A-scale) and the other measuring depression (D-scale). The scales are scored separately and have independent validity. The HADS has been demonstrated as a valid assessment of depression and anxiety in cancer patients (Hopwood, Howell, & Maguire, 1991) and has been used extensively for this purpose (Poppelreuter, Weis, Kulz, Tucha, Lange, & Bartsch, 2004; Spiegel & Giese-Davis, 2003). Its effectiveness in detecting depression and anxiety in non-medical samples has

also been demonstrated. The HADS has high internal consistency (Cronbach's α= 0.88), stability (test-retest intraclass correlation coefficient= 0.94), and concurrent validity with the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI; 0.72 – 0.75; Micholpoulos et al., 2008; Zigmond & Snaith, 1983).

Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF).

The MFSI-SF (Stein et al., 2004) is a 30-item self-report measure of fatigue. It assesses five symptom domains: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor. In the current study, only the physical fatigue scale was used, in order to avoid multicollinearity with depression and anxiety in the regression models. The MFSI has been validated with the breast cancer population and has been able to detect differences in fatigue in breast cancer patients, related to different cycles of anthracycline-based chemotherapy, and to differences in levels of chemotherapy-induced inflammatory mediators (Mills, Parker, Dimsdale, Sadler, & Ancoli-Israel, 2005). The MFSI-SF also was reported to have excellent reliability (α coefficients from 0.87 to 0.96; Stein, Martin, Hann, & Jacobsen, 1998).

Depression can contribute to fatigue, and may negatively impact perception and self-reported measurement of fatigue (Jean-Pierre et al., 2007). Therefore, a multi-dimensional measure of fatigue seemed preferable to a single-item measure of fatigue. The MFSI allows for the measurement and separation of emotional and mental fatigue, both of which may be related to depressive symptoms, from physical fatigue. In an effort to ensure divergent validity (e.g., to avoid the redundancy of emotional and mental fatigue that is also being captured by the depression measure), the physical fatigue subscale of the MFSI-SF was used for our analyses.

Visual Analog Scale of Pain

The visual analog scale of pain (VASP) is a measure that consists of a single bar-line measure in which the patient may point to an area representing how much pain they are in. It is frequently used in the primary care setting; it has the advantages of being easily administered, and requires no verbal communication or literacy from the patient. In studies of trauma patients (Todd, Funk, & Funk, 1996), and emergency room patients (Kelly, 1998; Gallagher, Bijur, Latmer, C, & Silver, 2002), change in VAS pain score was reported to be strongly correlated with patients' verbal assessments of change in pain. In a recent study of reliability and validity in abdominal pain patients (Gallagher, Bijur, C, & Silver, 2002), intraclass correlation between VASP scores was reported as 0.99 (CI_{95}= 0.989, 0.992), and differences in scores increased linearly as the pain descriptors the patients used escalated from "much less" to "much more" pain ($p < .001$).

Measures of Cognitive Function

Currently, there are two modalities used in measuring cognitive function, self-report and neuropsychological battery. It is unclear which is the better estimate of clinically meaningful cognitive limitations. While examiner administered neurocognitive batteries are considered the "gold standard" for assessing cognitive deficits (Tannock et. al., 2004), they can be criticized for lack of ecologic validity, and may not be as sensitive to cognitive deficits in everyday life as self-report measures (Bender, Pacella, Sereika, Brufsky, Vogel, & Rastogi, 2008). Previous studies of cancer survivors (Calvio et. al., 2009; Hansen et. al., 2008) have suggested that self-report measures are more sensitive to cognitive limitations. However, some evidence suggests that these perceived deficits may not exist or may be related to other causes (Schagen, van Dam, Muller, Boogerd,

Lindeboom, & Bruning, 1999; Poppelreuter, Weis, Kulz, Tucha, Lange, & Bartsch, 2004). Further, a number of studies report that there is no correlation between objective measures of cognition and self-reported deficits (Cull, Hay, Love, Mackie, Smets, & Stewart, 1996; Klepstad, Hilton, Moen, Fougner, Borchgrevink, & Kaasa, 2002). Given the clear impact of both perceived and performance-based cognitive impairments on functioning and quality of life in BCS, assessment using both types of measures was warranted.

Functional Assessment of Cancer Therapy Cognitive Scale Version Two (FACT-Cog).

The FACT-Cog (Wagner, Cella, & Donninger, 2003) is a 50 question subjective measure designed to assess cognitive limitations and their effect on quality of general functioning in cancer survivors. A sample can be viewed at www.facit.org/qview/filedownload.aspx?file=**FACT-Cog**_us. The scale measures the frequency of positive and negative cognitive functioning events over the past seven days, based on self-report. The measure utilizes a five-point Likert-type scale (ranging from 0 to 4, 4 being the most frequent) to assess several different aspects of cognitive function. Lower scores are indicative of poorer perception of functioning. Jacobs and colleagues (2007) reported that the FACT-Cog demonstrated an internal consistency range of α = 0.97 (total score) to α = 0.58 (concentration subscale) in a sample of cancer survivors. The FACT-Cog assesses a broad range of cognitive domains (not just those specifically related to work) and provides a multidimensional view of the cognitive deficits often experienced by patients with cancer (Jacobs et. al, 2007). The Perceived Cognitive Impairment (PCI) and Impact of Perceived Cognitive Impairments on Quality of Life

(PCIQOL) subscales were used in this study as assessments of perceived cognitive performance and its impact on functioning and quality of life.

Cognitive Symptom Checklist-Modified (CSC)

The Cognitive Symptoms Checklist (CSC; Feuerstein, Hansen, Calvio, Johnson, & Ronquillo, 2007) was developed for use as a patient checklist to assist in orienting physicians to patients' cognitive difficulties. Unlike the FACT-Cog, which measures general functioning, the CSC is a specific measure pertaining to ability to function in an occupational setting, particularly in areas of work that require specific cognitive functions (O'Hara, Harrell, Bellingrath, & Lisicia, 1993). These areas of functioning include attention/concentration, memory, visual processes, and executive function. In a previous study (Feuerstein et al., 2007), the number of items on the CSC was reduced from 100 to 59 based on a factor analysis (varimax rotation) that revealed a three-factor solution (working memory, executive functioning, and attention), followed by reduction of items to only those with a factor loading of 0.4 or higher on one of the three factors. The internal consistency of each of the scales is as follows: working memory (Cronbach's α= 0.93), executive functioning (Cronbach's α= 0.91), and attention (Cronbach's α= 0.86). This 59-item version of the CSC was used as a measure of perceived cognitive limitations encountered by breast cancer survivors in their daily occupational duties, particularly in the domains of memory, attention, and executive function. Higher scores indicate lower functioning.

CNS Vital Signs (CNSVS)

The CNSVS is a remotely administered neurocognitive battery that objectively measures memory, psychomotor speed, reaction time, complex attention, and cognitive

flexibility. The battery is comprised of several well-established neuropsychological tests, such as finger tapping, symbol digit coding, the Stroop test, and the continuous performance test. The CNSVS takes approximately 30 minutes to complete. The subscales have acceptable to good test-retest reliability: attention ($r = 0.65$), memory ($r = 0.66$), psychomotor speed ($r = 0.88$), cognitive flexibility ($r = 0.71$), and reaction time ($r = 0.75$; (Gualtieri & Johnson, 2006). The test has been standardized with a normative sample and has been used to detect mild and moderate cognitive limitations in numerous neuropsychiatric patient groups, including patients with mild and severe brain injury, early dementia, post-concussion syndrome, attention deficit hyperactivity disorder (ADHD), and depression (Johnson & Gualtieri, 2008; Gualtieri & Johnson, 2006). For this study, scaled scores of visual memory, verbal memory, composite memory and executive functioning were utilized to assess impairment in the domains of cognitive function that are most often reported in BCS (Bender et. al., 2008).

Measures of Potential Confounding Variables

A large number of variables were considered for possible predictive value in a model of cognitive functioning in breast cancer survivors (see Table 6). Our use of a variable reduction technique (Hosmer & Lemeshow, 2000, Tabachnick & Fidell, 1996; see Statistical Methods for more details) revealed that many of these variables did not reach a significance level of $p<0.1$ as a factor related to either perceived or performance-based cognitive function outcomes, and therefore were not included in the multivariate regressions for either perceived or performance-based cognitive function. A significance level of $p<0.1$ is used as a conservative "filter" of variables that have the potential to

meet a significance level of $p<0.05$ when the number of variables is reduced. The following confounders were considered.

Demographics and Work-Related Factors

Our variable reduction technique (described in detail in the Statistical Methods section) suggested that income and current job could be confounders in certain relationships with perceived cognitive performance. Current job was measured as a self-report item in which participants chose between managerial, non-managerial, or self-employed. Income was recorded as a categorical variable with $10,000 to $20,000 increments, from $0- $10,000 per year up to $100,000+ per year.

Treatment

For certain outcome variables, it was suggested that type of cancer treatment (e.g., chemotherapy or radiation) could be a possible confounder in the relationship between adjuvant endocrine therapy and cognitive performance. In previous studies, a negative relationship between chemotherapy and cognitive ability, exclusive of adjuvant endocrine therapy, has been reported (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Wieneke & Dienst, 1995). Cognitive deficits have been reported in BCS, across all types of treatment received (Ahles, et al., 2008). Because the cognitive deficits commonly reported in BCS have not conclusively been attributed to any particular treatment, it was necessary to control for type of treatment. In the current study, history of radiation therapy or chemotherapy was self-reported as a "yes" or "no" rather than as a measurement of duration of treatment or time since treatment. Our preliminary analyses indicated that with regard to performance-based measures, only chemotherapy reached a

significance level of $p<.1$, and with regard to self-reported measures, no treatments (excluding endocrine therapy) reached significance.

Mental Status at Test Administration

Distraction during testing, as well as caffeine and nicotine use the day of testing, all reached significance as possible covariates with regard to performance-based measures in our preliminary analyses. Distraction, or whether or not the participant felt distracted during the test administration, was measured as a subjective binomial (yes/no) variable. Nicotine use prior to testing was assessed based on information from the Behavioral Risk Factor Surveillance System Questionnaire. Caffeine use assessment was derived from the Caffeine Consumption Questionnaire, a measure commonly used to assess caffeine consumption, including use of various over-the-counter substances that include caffeine.

Caffeine can raise alertness, decrease reaction time, and improve concentration, but it also may increase symptoms of anxiety (Bell & McClellan, 2002; Peeling & Dawson, 2007). Nicotine in regular users has been noted to increase concentration and alertness (Newhouse, Potter, & Singh, 2004). Nicotine administration may improve recall of information in smokers (Rusted & Warburton, 1992), may result in small improvements in sustained attention and recognition memory in smokers and non-smokers (Ernst et. al., 1999), and may increase information processing in smokers and non-smokers (Davranche & Audiffren 2002). However, other studies have shown that spatial memory may be impaired by nicotine in young smokers (Park, Knopick, McGurk & Meltzer, 2000), and that short term memory may be unaffected by nicotine (Jones, Sahakian, Levy, Warburton & Gray, 1992).

Statistical Analysis

Variable Reduction

Due to the large number of potential confounding factors (Table 6) relative to the sample size, a variable reduction technique was employed (Hosmer & Lemeshow, 2000; Tabachnick & Fidell, 1996). This technique results in a model that is more likely to be numerically stable, and more easily generalized. Including fewer variables in a model reduces the standard error (Hosmer & Lemeshow, 2000) and reduces dependence of the model on the stability and reliability of observed data (Tabachnick & Fidell, 1996). By using a less conservative estimate of significance ($p<0.1$ instead of $p<0.05$ or $p<0.01$) and conducting a series of simple tests, we were able to predict variables likely to reach significance in our final model using a statistical "filter" method. In this method, Hosmer and Lemeshow recommend using up to a $p< 0.25$ significance level. However, with regard to the relatively small sample size (n=133), and in order to substantially reduce the number of possible variables, a more conservative significance level of $p<0.1$ was employed.

Stepwise univariate linear or logistical regressions were for each of the potential independent variables, listed in Table 5, were conducted to eliminate potential confounders that were not likely to be significant, in relation to each of the outcome measures (cognitive impairment measures) in the current study. A method of forward selection followed by a test for backward elimination was employed, using a modified algorithm described by Hosmer and Lemeshow (2000), to build a sequential model based solely on statistical criteria. In association with the relationship between drug status group (independent variable) and each cognitive function measure (dependent variable),

any variable that reached a significance of $p<0.1$ or greater for any perceived or performance-based outcome measure was retained for entry into the final multivariate regressions. Retained variables were then tested individually for fit by comparing the estimated coefficient of that variable with the coefficient from the model containing only that variable, and by comparing the estimated coefficient with the coefficient from the full model, before variable reduction, to ensure no marked changes in magnitude. A marked change would indicate that an excluded variable was important in adjusting the effect of an included variable, but none were found in our analyses.

Power analysis

Power analyses were run using nQuery Software. The sample size was fixed based on data availability, but a power analysis was conducted for each predictor variable to confirm adequate power. For hypothesis 1, assuming a two-tailed test with the current sample size (n=122) and the standard deviations from previous literature, an analysis confirmed that the current study had an 80 percent chance or greater of detecting differences with a moderate to large effect size. The analysis indicated that the study was adequately powered to detect a difference as small as 2.5 points of the MFSI-SF, 1.8 points on the HADS-D, and 1.6 on the HADS-A. These effect sizes are just slightly greater than the minimal clinically important differences of the scales found in the literature (Puhan, Frey, Buchi & Schunemann, 2008; Mills, Parker, Dimsdale, Sadler, & Ancoli, 2005; Stein, Jacobsen, & Blanchard, 2004; Mantovani et. al. 2007), and therefore are appropriate for our study.

For the multiple regressions, separate power analyses were conducted for perceived and performance-based cognitive function measures. For self-report measures

of cognitive function, we computed adequate power with an α of 0.05, assuming six covariates in addition to our variable of interest (drug exposure). The current sample size (n=114) had an 80 percent possibility of detecting a moderate effect size of f^2=0.07. For the performance-based measures, we computed adequate power with an α of 0.05, assuming three covariates in addition to our variable of interest (drug exposure). Our current sample size (n=116) had an 80 percent possibility of detecting a moderate effect size of f^2=0.06.

Analyses of Variance

Hypotheses 1 and 2 were tested using one-way analyses of variance. A univariate analysis was conducted to determine if there were between-group differences in anxiety, fatigue and depression based on exposure to adjuvant endocrine therapy. A multivariate analysis of variance was conducted to detect between-group differences in perceived and performance-based cognitive function, after accounting for anxiety, fatigue, and depressive symptoms.

Regressions

After the final regression model was determined, a hierarchical multiple linear regression was computed for each of the outcome variables. Variables were entered by block based on expected significance (least to most), as depicted in Tables 7, 8 and 9. All analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 16.0.

RESULTS

Participant characteristics

Seventy-seven breast cancer survivors who had previously used or were currently using adjuvant endocrine therapy (tamoxifen or AI) and 56 breast cancer survivors who had never had adjuvant endocrine therapy were included. Of the adjuvant endocrine therapy (SERM/AI) group, 57% (n=44) reported use of tamoxifen (but not an AI) at some point during their treatment, 19% (n=15) had reported use of an AI (but not tamoxifen) during their treatment, and 22% (n=17) reported use of both tamoxifen and an AI at some point during their treatment. Twenty-seven (35%) were currently taking tamoxifen, and 27 (35%) were currently using an aromatase inhibitor.

Participant Demographics

Table 2 presents participant characteristics and demographic information for BCS exposed to adjuvant endocrine therapy (n=77) and BCS who had never been exposed to adjuvant endocrine therapy (n=56). Analyses of variance and chi-square analyses indicated no significant differences between the two groups on any demographic variable. Both groups were primarily (87.3%) Caucasian. Both groups were highly educated, with 80.6% of the SERM/AI group and 73.2% of the non-SERM/AI group possessing an associates degree or higher. The mean age for both the SERM/AI and non-SERM/AI group was almost 45 years old.

Table 3 presents the job characteristics of participants in the study. Analyses showed that although between group differences neared statistical significance in a few categories, there were no significant differences between groups in work characteristics. Over 50% of participants reported an annual household income of over $100K. For both

groups, the majority of participants were in non-managerial jobs, approximately 69% in the SERM/AI group and 53% in the non-SERM/AI group. For both groups, the majority of participants reported that they had worked at their job for an average of between 2 and 10 years, with a median of 6 years at their current job.

Cancer and Treatment

A summary of cancer and treatment characteristics is included in Table 4. There was no significant difference in time since treatment for the two groups, with an overall mean of 3.08 (SD=2.37) years since last treatment. The majority of participants had had multiple treatments for cancer. Menopausal status neared, but did not reach, statistical significance.

Hypotheses

As shown in Table 5, **Hypothesis 1 was not confirmed**. There was no significant difference between groups in symptoms of fatigue, depression or anxiety. **Analyses for Hypothesis 2 indicated a significant difference between groups on the Cognitive Symptom Checklist- Attention subscale, and the FACT-Cog Perceived Cognitive Impairments subscale,** with BCS exposed to adjuvant endocrine therapy reporting significantly more cognitive limitations ($p<0.05$). Therefore, **Hypothesis 2 was accepted.**

Hypothesis 3 was partially confirmed by a series of regression analyses. Tables 7 and 8 display the covariates retained from the preliminary analysis of all possible variables (Table 6), as well as results from the multivariate linear regressions for perceived cognitive function outcome variables. In each regression, possible covariates were entered first (income, current job, and smoking today, followed by fatigue,

depression, and anxiety), followed by the variable of interest (use of a SERM or AI). No demographic variables were found to be significant for any measure of perceived cognitive function. Similarly, no medical or treatment history variables or substance use variables were found to be significant.

Symptom Burden Factors and Perceived Cognitive Function

On the Cognitive Symptom Checklist-Memory subscale, symptom burden factors accounted for 26.1% of the variance in the model (R^2 Change= 0.261, $p<0.01$). The Hospital Anxiety and Depression Scale (HADS) Depression subscale score ($\beta=0.251$; $p<0.01$), accounted for a substantially significant proportion of variance in working memory, and HADS-Anxiety subscale score also was significant ($\beta=0.241$, $p<0.05$). The overall model accounted for 32.5% of the variance in Cognitive Symptom Checklist-Memory subscale scores ($p<0.01$). On the Cognitive Symptom Checklist-Attention subscale, symptom burden accounted for 20% of the variance in scores (R^2 Change= 0.207, $p<0.01$). Both HADS-Anxiety ($\beta=0.253$; $p<0.01$) and HADS-Depression ($\beta=0.241$; $p<0.05$) scores accounted for a statistically significant amount of variance in the overall model. Analysis of Cognitive Symptom Checklist-Executive Function subscale scores revealed that symptom burden accounted for 28% of the variance (R^2 Change= 0.282, $p<0.01$). The overall model accounted for 32.2% of the variance in Cognitive Symptom Checklist-Executive Function subscale scores ($p<0.01$).

On the FACT-Cog Perceived Cognitive Impairment subscale, symptom burden accounted for 27.5% of variance in the model (R^2 Change=0.275, $p<0.01$). Depression, anxiety and fatigue were all statistically significant factors ($\beta=-0.267$, $p<0.01$ for HADS-Depression, $\beta=-0.188$, $p<0.05$ for HADS-Anxiety and $\beta=-0.225$, $p<0.05$ for MSFI-SF).

Symptom burden accounted for 36.5% ($p<0.01$) of the variance in FACT-Cog Perceived Cognitive Impairments Impact on Quality of Life (PCIQOL) scores. Fatigue, depression and anxiety all accounted for a statistically significant proportion of variance in the model ($\beta=-0.255$, $p<0.01$ for fatigue, $\beta=-0.320$, $p<0.01$ for depression, and $\beta=-0.207$, $p<0.05$ for anxiety).

Endocrine Therapy and Perceived Cognitive Function

Past or present use of a SERM or AI was significantly associated with reports of decreased attention on the Cognitive Symptom Checklist (CSC-A; $\beta=-0.198$, $p<0.05$), and with greater perceived cognitive impairment on the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog PCI; $\beta=0.168$, $p<0.05$). Use of a SERM or AI accounted for 3.8% of the variance in attention on the CSC-A (R^2 Change= 0.038). The overall model accounted for 23.9% of the variance in Cognitive Symptom Checklist-Attention subscale scores ($p<0.01$). On the FACT-Cog PCI, use of a SERM or AI accounted for 3% of the variance in perceived cognitive impairments (R^2 Change= 0.027, $p<0.05$). The overall model for the FACT-Cog PCI accounted for 34.2% of the variance in perceived cognitive impairments ($p<0.01$).

Performance Based Cognitive Function

Table 9 displays the results from the multivariate linear regressions for performance based cognitive function outcome variables. Possible covariates identified in the preliminary analyses (distractions during test, chemotherapy, and time since caffeine) were entered first, followed by the variable of interest (history of SERM/AI use). The analyses detected no statistically significant variables with regard to measures of performance based cognitive function. Further, the analyses indicated that use of a

SERM or AI was not a significant predictor of performance-based cognitive function in occupationally active breast cancer survivors, an average of three years after primary treatment.

DISCUSSION

This study indicated that BCS who were exposed to adjuvant endocrine therapy differed significantly from a group of BCS who had never been exposed to endocrine therapy on measures of perceived attentional difficulties in the workplace (CSC-A) and perceived cognitive impairments in everyday life (FACT-Cog PCI), with those exposed having higher levels of perceived cognitive limitations. No differences existed between the groups on any performance-based measure of cognitive function, and no confounding factors were indicated to be related to scores any performance-based measure. This study also indicated that symptom burden scores, including depression, anxiety and fatigue, were not significantly different based on exposure to adjuvant endocrine therapy. However, symptom burden did account for some, but not all, of the variance in cognitive deficits in all occupationally active breast cancer survivors.

The current study indicates that in occupationally active breast cancer survivors an average of three years post-primary diagnosis, most cognitive impairments associated with tamoxifen and aromatase inhibitors are limited. While significant results indicate that such impairments do exist, it is important to note that these impairments are

associated with, though not completely explained by, symptoms of fatigue, anxiety and distress for perceived cognitive deficits in everyday life, and symptoms of anxiety and distress for perceived cognitive deficits related to work.

Relationship to current literature

This study indicates that history of endocrine therapy was significant for two measures of perceived cognition, but none of the performance-based measures of cognitive function. Similar results have been reported in other studies of BCS and perceived cognitive function (Klepstad, Hilton, Moen, Fougner, Borchgrevink, & Kaasa, 2002; Poppelreuter, Weis, Kulz, Tucha, Lange, & Bartsch, 2004). However, Bender and colleagues (2007) reported statistically significant performance-based cognitive deficits in endocrine therapy patients, including difficulties in verbal learning, working memory, and processing speed, on a neurocognitive battery. Similarly, Jenkins and colleagues (2004) were able to detect memory and processing speed deficits using a neurocognitive battery. These studies indicate that there are neurocognitive measures capable of detecting deficits in cancer survivors, but that the measure of cognitive performance used in the current study may not be sensitive to OABCS-specific deficits. Further, the participants in Bender and colleagues' and Jenkins and colleagues' studies may have had more pronounced, easily detectable deficits, because all of their participants were currently taking estrogen inhibitors at the time of the study, and may not have had adequate time to recover from cognitive deficits related to treatment. In comparison, the participants in the current study included 54 (41%) BCS actively taking either tamoxifen or aromatase inhibitors, and 78 (59%) BCS who were previously exposed to adjuvant endocrine therapy, and all participants were at least 3 years post- primary treatment.

Additionally, not all participants in Bender and colleagues' and Jenkins and colleagues' studies were occupationally active, whereas the participants in the current study were all maintaining a daily level of cognitive activity via occupational tasks. Previous studies have suggested that maintaining cognitive activity can reduce cognitive slowing due to age and dementia (Bieliauskas, Langenecker, & Graver, 2008; Carlson, et al., 2008), and can increase rate of cognitive recovery from trauma (Noblett & Swain, 2003). This may be true in our participants as well. Additional research into the relationship between daily cognitive activity and cognitive impairments in BCS is warranted, and may be clinically relevant in symptom reduction.

In the current study, symptoms of depression, anxiety and fatigue were statistically significant with regard to perceived measures of cognitive function, but not to performance-based measures. Similar results are reported in Jenkins and colleagues' (2004) study, which indicated that Beck Depression Inventory scores and General Health Questionnaire scores (depression, anxiety and fatigue) were related to self-reported cognitive deficits, but not performance-based scores on neurocognitive testing. Other studies (Bender, Pacella, Sereika, Brufsky, Vogel, & Rastogi, 2008; Bender, et al., 2007) have reported some cognitive limitations in BCS using performance-based measures, but those were not indicated in the current study.

Limitations

This study employed a cross-sectional design with no baseline data, so we were not able to establish a causal relationship. Further, because it was not a randomized control trial, we were not able to control for amount of time the drug was taken, whether one or both drugs were taken, dose, or how long ago they were taken. Additionally, our

study was not adequately powered to separate past from present users of tamoxifen and aromatase inhibitors, or separate BCS with a history of aromatase inhibitors from BCS with a history of tamoxifen use. While these groups are often combined in the literature, this seems to be due to difficulty in obtaining the large number of participants needed for adequate power to study groups separately. Previous studies (Shilling, Jenkins, Fallowfield, & Howell, 2003; Bender, et al., 2007) suggested that length of time on endocrine therapy trial did not relate to cognitive deficits, but other studies suggested that current users of SERMs exhibited more cognitive deficits than those who had used but were no longer using the drugs (Paganini-Hill & Clark, 2000). While we hypothesized that the participants in our study may have experienced some recovery effect in time since primary treatment, it was beyond the scope of the data to determine the presence of any such effect. Our study indicated that time since primary treatment was not significant in relation to cognitive deficits, but data was not available regarding time since last exposure to endocrine therapy. Therefore, we could not ascertain whether there was an uncontrolled relationship between time since endocrine therapy, or current use of endocrine therapy, and cognitive limitations. Further, we could not be certain that differences did not exist between the cognitive limitations seen in BCS with a history of either tamoxifen or aromatase inhibitors.

Additionally, this study was reliant on self-report of medical history, including exposure to adjuvant endocrine therapy and other forms of treatment. While non-compliance is not an easily preventable issue (Waterhouse, Calzone, Mele, & Brenner, 1993; Ruddy, Mayer, & Partridge, 2009), several precautions were taken to decrease the risk of intentional or unintentional participant misrepresentation regarding

their cancer treatment and history. A review of self-report data indicated that participants reported their cancer history and treatment in a way that was consistent with a breast cancer diagnosis, and that participants were able to recount their treatment fairly accurately to what would seem plausible. Similar findings were reported by Maunsell and colleagues' (2005) study, which indicated that BCS could accurately report their medical history including cancer treatment, up to three years post-diagnosis. Schootman and colleagues (2005) also reported that elderly breast cancer patients could accurately report treatment history, with substantial agreement (kappa= 0.93 and 0.61 for chemotherapy and endocrine therapy, respectively) when compared with verified surveillance and epidemiology data, the gold standard in data collection. In addition, a number of other studies (Liu, Diamant, Thind, & Maly, 2009; Phillips, et al., 2005), all which reported high validity and consistency in self-report when compared to medical records of breast cancer survivors.

The current study's participants were mostly Caucasian, well educated, and of higher-than-average income. In comparison with demographics from recent cancer statistics (Jemal, et al., 2005; Jemal, et al., 2008), women of color and women of lower socioeconomic status are under-represented in this study. Because the study was Internet-based, it may have been subject to some selection bias. Not all BCS have access to the Internet, and those who do are likely younger, of higher income, more educated and better functioning (Pereira et al., 2000). However, a recent study indicated that over 75% of cancer survivors and their family members from various demographics access the Internet for health-related information (Simon & Schramm, 2008). Studies show that a demographically diverse group of individuals are increasingly seeking medical

information on the web (Whitehead, 2007). These reports suggest that while still present, selection bias in Internet studies may not substantial as it was once considered. Nonetheless, our sample was predominantly Caucasian and of high socioeconomic status, limiting the generalizability of our results.

While perceived cognitive deficits are related to mood and fatigue (Bender, et al., 2007), research completed within a larger study of occupationally active breast cancer survivors reported that perceived cognitive deficits, not performance-based deficits (as measured by the CNSVS neurocognitive battery) were more closely related to work limitations (Calvio, Peugeot, Bruns, Todd & Feuerstein, 2009). The present study included a web based neurocognitive battery as a proxy for face to face neuropsychological assessment, which is considered the "gold standard" for assessment of cognitive function (Tannock, et al., 2004). The measure employed in this study, the CNSVS, is based on conventional neuropsychological tests and has been correlated with other standard neurocognitive batteries (r= 0.65-0.88; Gualtieri & Johnson, 2006). While the CNSVS has been used to detect mild cognitive changes in other populations (Gualtieri & Johnson, 2008), the inability to account for a significant proportion of variance and wide confidence intervals found in this and other studies (Calvio, Feuerstein, Peugeot & Bruns, 2009; Hansen, Feuerstein, Calvio, & Olsen, 2008) indicates that it may lack sensitivity and specificity in measuring cognitive limitations in occupationally active BCS.

Implications

The current study has several important implications regarding cognitive deficits related to adjuvant endocrine therapy in breast cancer survivors at work. This study

provides preliminary evidence that there may be cognitive deficits associated with adjuvant endocrine therapy, but the mechanism and extent of these deficits remains undetermined. Nonetheless, clinicians must be aware that a substantial number of breast cancer survivors (17-50 percent, 1-2 years after chemotherapy treatment; Bender et. al, 2008; Fan, et al., 2005) report deficits related to adjuvant endocrine therapy, and that these perceived deficits are impacting BCS's ability to function in occupational settings and in everyday life. A better understanding of these deficits and the development of occupational interventions may be necessary.

The results also suggest that these perceived cognitive deficits are related to factors that may be mitigated, such as anxiety, depression, and fatigue. While this study was not designed to determine a causal relationship between cognitive impairments and distress, it is likely that the combination of these factors may have a compounded effect on the individual. Because treatments for cognitive impairments are limited, it is especially important for clinicians to be aware of any symptoms of distress that may be impacting patients' functioning. Early identification and treatment of fatigue and distress may be crucial in breast cancer survivors returning to work, and may prevent further exacerbation of cognitive impairments.

Future Directions

A substantial amount of evidence, including the results from this study, suggests that BCS experience cognitive limitations related to adjuvant endocrine therapy. However, the biobehavioral mechanisms of such a relationship remain unknown (Cella & Fallowfield, 2008), and the extent of these limitations remains undetermined (Bender et. al., 2008; Bender et al., 2007). While many studies report the presence of cognitive

deficits, this study could not account for a large proportion of the variance in cognitive limitations experienced by BCS, which is consistent with the literature as a whole (Wefel, Witgert, & Meyers, 2008). In our model, we were able to account for less than 50% of the variance in all cognitive measures, even after considering 21 possible factors. In order to accurately identify and mitigate factors related to cognitive impairment in breast cancer survivors, future studies should include a longitudinal design, and ecologically valid measurement of cognitive impairments in the work setting. Further, more sensitive, dynamic measurements of cognitive limitations and other potential factors related the etiology and exacerbation of cognitive limitations are required.

Additional research is necessary to examine the impact of maintaining an occupationally active lifestyle on mitigating cognitive limitations in BCS. Our study was unique in that the sample was comprised completely of occupationally active breast cancer survivors. It is not unreasonable to hypothesize that participants in our study exhibited fewer cognitive deficits than those reported in other studies of BCS in part because of their engagement in occupational activity; however, such a connection cannot be simply assumed. Occupational activity that involves the repetitive use of working memory, executive function, and attentional focus may facilitate plasticity in underlying neural processes, which is suggested to be related to improvement in cognitive functions over time (Johnson, 2009). This conjecture is simply a hypothesis at present. It is necessary to develop a better understanding of the impact of occupational activity on cognitive limitations in survivors, and to ultimately develop evidence-based approaches to optimize cognitive function, work performance, and overall quality of life.

Table 1. Evidence for cognitive impairments in previous studies of BCS				
Domain	Tamoxifen or AI?	Scale	Authors/Yr	Time After Diagnosis
Memory	Tamoxifen	Wechsler Memory Scale III, Logical Memory	Palmer et. al. (2008)	x=2.9 yrs
Visuo-spatial Ability	Tamoxifen	Mental Rotation Test	Palmer et. al. (2008)	x=2.9 yrs
	Tamoxifen	Wechsler Adult Intelligence Scale-III, Block Design	Castellon et. al. (2004)	2-5 yrs
Visual Memory	Tamoxifen	Wechsler Memory Scale Revised, Visual Reproduction	Castellon et. al. (2004)	2-5 yrs
	Tamoxifen	Rey- Osterrith Complex Figure Test	Castellon et. al. (2004)	2-5 yrs
	Tamoxifen	Rey- Osterrith Complex Figure Test	Palmer et. al. (2008)	x=2.9 yrs
	Aromatase Inhibitors	Rey- Osterrith Complex Figure Test	Bender et. al. (2007)	3+ mos
Processing Speed	Tamoxifen	Wechsler Adult Intelligence Scale-III, Digit Symbol Test	Palmer et. al. (2008)	x=2.9 yrs
	Both	Kendrick Digit Copying Task	Shilling et. al. (2003)	
Verbal Learning	Tamoxifen	California Verbal Learning Test	Castellon et. al. (2004)	2-5 yrs
	Aromatase Inhibitors	Rey Auditory Verbal Learning Test	Bender et. al. (2007)	3+ mos
Verbal Fluency	Tamoxifen	California Oral Word Association Test	Castellon et. al. (2004)	2-5 yrs
	Tamoxifen	Controlled Word Association Test	Palmer et. al. (2008)	x=2.9 yrs
Verbal Memory	Both	Wechsler Memory Scale, Paragraph Recall	Shilling et. al. (2003)	
Working Memory	Aromatase Inhibitors	Rivermead Behavioral Memory Test	Bender et. al. (2007)	3+ mos
Semantic Memory	Tamoxifen	Semantic Memory (Object Naming) Test	Eberling et. al. (2004)	current

Table 2. Participant Characteristics				
	SERM/AI group (n=77)		No SERM/AI group (n=56)	
	n	**%**	**n**	**%**
Age				
≤ 40 years old	21	30.4%	16	32.0%
41-50 years old	20	29.0%	20	40.0%
51-65 years old	28	40.6%	14	28.0%
Mean (SD)	44.93(9.99)		44.80(8.88)	
Race				
Caucasian	68	88.3%	48	85.7%
African American	6	7.8%	2	3.6%
Asian American/ Pacific Islander	3	3.9%	4	7.1%
Other	0	0.0%	2	3.6%
Ethnicity				
Hispanic	2	2.8%	2	4.2%
Non-Hispanic	69	97.2%	46	95.8%
Education				
Less than High School	1	1.3%	0	0.0%
High School Grad	6	7.9%	1	1.8%
Some College	8	10.4%	14	25.0%
Associates/Bachelors	27	35.1%	14	25.0%
Some Grad School	5	6.5%	6	10.7%
Graduate Degree	30	39.0%	21	37.5%
Marital Status				
Single	12	15.6%	8	14.3%
Cohabitating	5	6.5%	0	0.0%
Married	54	70.1%	41	73.2%
Divorced	5	6.5%	7	12.5%
Widowed	1	1.3%	0	0.0%
Note: Not all participants responded to all questions * No demographics were significant by group.				

Table 3. Job characteristics				
	SERM/AI group (n=77)		No SERM/AI group (n=56)	
	n	**%**	**n**	**%**
Current Job Characteristics				
Managerial	20	25.97%	19	34.5%
Non-Managerial	53	68.83%	29	52.7%
Self-Employed	4	5.19%	7	12.7%
Primary Occupation				
Clerical	7	9.3%	7	12.7%
Sales	6	8.0%	1	1.8%
Management/ Administration	22	29.3%	25	45.5%
Professional/Technical/ Science	37	49.3%	21	38.2%
Service Worker	3	4.0%	1	1.8%
Years at Current Job				
1 year or less	10	13.3%	11	21.6%
2-10 years	48	64.0%	36	70.6%
11-19 years	10	13.3%	10	19.6%
20+ years	7	9.3%	4	7.8%
Mean (Standard Deviation)	7.48(7.23)		7.13(6.68)	
Annual Income				
$10-19,000	2	2.6%	1	1.8%
$20-39,000	4	5.2%	1	1.8%
$40-59,000	7	9.1%	8	14.3%
$60-79,000	16	20.8%	6	10.7%
$80-99,000	9	11.7%	10	17.9%
$100,000+	39	50.6%	30	53.6%
Note: Not all participants responded to all questions * No demographics were significant by group.				

Table 4. Diagnosis and Treatment									
	SERM/AI (n=77)		No SERM/AI (n=56)			SERM/AI (n=77)		No SERM/AI (n=56)	
	n	%	n	%		n	%	n	%
Tumor Location					Time Since Primary Treatment				
Right Breast	39	51.3%	29	51.8%	1 year	26	34.7%	19	35.2%
Left Breast	33	43.4%	26	46.4%	2 years	10	13.3%	13	24.1%
Both Breasts	4	5.3%	1	1.8%	3 years	13	17.3%	6	11.1%
Tumor Stage					4 years	7	9.3%	6	11.1%
I	25	32.9%	22	39.3%	5 years	8	10.7%	4	7.4%
II	35	46.1%	27	48.2%	6 years	4	5.3%	0	0.0%
III	15	19.7%	7	12.5%	7 years	1	1.3%	3	5.6%
					8 years	0	0.0%	1	1.9%
Treatment (at any time since cancer diagnosis)					9 years	3	4.0%	1	1.9%
Chemotherapy	63	81.8%	47	83.9%	10 years	3	4.0%	1	1.9%
Radiation Therapy	62	80.5%	36	64.3%	Mean (S.D.)	3.31(2.51)		2.77(2.28)	
Surgery	75	97.4%	54	96.4%					
Herceptin (Trastuzumab)	12	15.6%	6	10.7%	Menopausal Status				
Tamoxifen (only)	45	58.4%	0	0.0%	Premenopausal	27	35.5%	13	23.2%
Both Tamoxifen and Aromatase Inhibitor	17	22.1%	0	0.0%	Post-menopausal	14	18.4%	24	42.9%
Aromatase Inhibitor (only)	15	19.5%	0	0.0%	Currently undergoing	35	46.1%	19	33.9%
*Not all participants answered all questions									

Table 5. Fatigue, distress, and cognitive symptoms in BCS exposed or not exposed to adjuvant endocrine therapy		
	SERM/AI (n=72)	No SERM/AI (n=50)
	Mean (SD)	Mean (SD)
MFSI Fatigue	5.67 (4.86)	5.60 (4.80)
HADS Depression	7.72 (2.98)	7.80 (3.16)
HADS Anxiety	4.42 (2.93)	4.74 (3.73)
CSC- Memory	8.97 (5.98)	8.35 (6.33)
CSC- Attention	5.50 (3.76)*	4.16 (3.62)*
CSC-Executive Function	3.96 (3.88)	4.58 (4.99)
Fact-Cog Perceived Cognitive Impairment (PCI)	51.53 (17.78)*	56.53 (16.93)*
Fact-Cog PCI Quality of Functioning	11.13 (4.67)	11.50 (4.24)
CNSVS- Visual Memory	102.76 (15.25)	102.96 (19.68)
CNSVS- Verbal Memory	101.62 (13.31)	97.24 (20.23)
CNSVS- Composite Memory	102.83 (15.28)	100.14 (21.58)
CNSVS- Executive Function	98.47 (9.325)	98.86 (9.01)
*= $p<0.05$		

Table 6. Potential Factors Related to Cognitive Function in Occupationally Active BCS	
Measure	Variable
Multidimensional Fatigue Symptom Inventory- Short Form (MFSI-SF)	Fatigue
Hospital Anxiety and Depression Scale (HADS-A)	Anxiety
Hospital Anxiety and Depression Scale (HADS-D)	Depression
Visual Analog Scale of Pain (VASP)	Pain
Visual Analog Scale of Distress (VASD)	Distress
Self-Report, Single Dichotomous Question	Distraction
Self-Report, Single Categorical Question from Caffeine Consumption Questionnaire	Caffeine
Self-Report, Single Categorical Question from Behavioral Risk Factor Surveillance System Questionnaire	Nicotine
Self-Report, Single Categorical Question	Alcohol Use
Self-Report, Single Categorical Question	Menopausal Status
Self-Report, Single Categorical Question	Education
Self-Report, Single Categorical Question	Income
Self-Report, Single Categorical Question	Race
Self-Report, Date of Birth	Age
Self-Report, Single Dichotomous Question	Ethnicity
Self-Report, Single Categorical Question	Job Characteristics
Self-Report, Single Categorical Question	Current Job
Self-Report, Single Dichotomous Question	Chemotherapy
Self-Report, Single Dichotomous Question	Radiation
Self-Report, Single Question	Years Since Primary Treatment
Self-Report, Single Question	Stage of Cancer

Table 7. Factors related to perceived cognitive function in occupationally active breast cancer survivors CSC (Cognitive function at work) scores, N= 114

	CSC-Memory		CSC-Attention		CSC-Executive Function	
	β	95% CI	β	95% CI	β	95% CI
Step 1: Demographic Factors						
Income	-0.134	(-1.470, 0.250)	-0.097	(-0.802, 0.265)	-0.167	(-1.142, 0.075)
Current Job	-0.163	(-3.575, 0.264)	-0.044	(-1.461, 0.919)	-0.026	(-1.546, 1.170)
	R^2=0.035		R^2=0.009		R^2= 0.027	
Step 2: Substance-Related Factors						
Smoking Today	0.157	(-0.258, 2.937)	-0.181	(-0.041, 1.932)	0.116	(-0.437, 1.836)
	R^2= 0.059 R^2 Change= 0.024		R^2= 0.041 R^2 Change= 0.031		R^2= 0.040 R^2 Change= 0.013	
Step 3: Symptom Burden Factors						
MFSI Fatigue	0.172	(-0.022, -0.450)	0.087	(-0.085, 0.212)	0.119	(-0.062, 0.270)
HADS Depression	0.251**	(0.110, 0.818)	0.241*	(0.045, 0.500)	0.330**	(0.182, 0.679)
HADS Anxiety	0.241*	(0.117, 0.843)	0.253**	(0.075, 0.542)	0.230*	(0.067, 0.578)
	R^2= 0.320** R^2 Change= 0.261**		R^2= 0.247** R^2 Change= 0.207**		R^2= 0.321** R^2 Change= 0.282**	
Step 4: Use of Endocrine Therapy						
SERM/AI	-0.073	(-2.885, 1.079)	-0.198*	(-2.748, -0.254)	0.033	(-1.112, 1.686)
	R^2= 0.325** R^2 Change= 0.005		R^2= 0.239** R^2 Change= 0.038*		R^2= 0.322** R^2 Change= 0.001	

*p<0.05
**p<0.01

Table 8. Factors related to perceived cognitive function in breast cancer survivors FACT-COG Scores, N=114

	FACT-COG Perceived Cog Impairment		FACT-COG PCI Impact on Quality of Life	
	β	CI	β	CI
Step 1: Demographic Factors				
Income	0.052	(-1.800, 3.3152)	0.167	(-0.077, 1.164)
Current Job	0.121	(-2.044, 9.005)	0.067	(-0.894, 1.875)
	R^2=0.014		R^2=0.027	
Step 2: Concentration-related Factors				
Smoking Today	-0.162	(-8.547, 0.642)	-0.158	(-2.121, 0.183)
	R^2= 0.040 R^2 Change= 0.025		R^2= 0.051 R^2 Change= 0.024	
Step 3: Symptom Burden Factors				
MFSI Fatigue	-0.225*	(-1.470, -0.122)	-0.255**	(-0.385, -0.071)
HADS Depression	-0.267**	(-2.416, -0.395)	-0.320**	(-0.661, -0.190)
HADS Anxiety	-0.188*	(-2.106, 0.029)	-0.207*	(-0.537, -0.054)
	R^2= 0.315** R^2 Change= 0.275**		R^2= 0.416** R^2 Change= 0.365**	
Step 4: Use of Endocrine Therapy				
SERM/AI	0.168*	(0.330, 11.474)	0.043	(-0.941, 1.703)
	R^2= 0.342** R^2 Change= 0.027*		R^2= 0.418** R^2 Change= 0.002	

*p<0.05
**p<0.01

Table 9. Factors related to performance-based cognitive function in breast cancer survivors
CNSVS Scores

	Visual Memory Scaled Score		Verbal Memory Scaled Score		Composite Memory Scaled Score		Executive Functioning Scaled Score	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Step 1: Concentration-related Factors								
Distractions During	0.026	(-5.359, 7.114)	0.044	(-4.740, 7.699)	0.036	(-5.319, 7.902)	-0.066	(-4.587, 2.180)
	R^2= 0.001		R^2= 0.002		R^2= 0.001		R^2= 0.004	
Step 2: Treatment Factors								
Chemotherapy	-0.010	(-2.113, 1.894)	0.082	(-1.107, 2.875)	0.040	(-1.669, 2.574)	-0.147	(-1.936, 0.215)
	$R^{2=}$ 0.001 R^2 Change= 0.000		R^2= 0.009 R^2 Change= 0.007		R^2= 0.003 R^2 Change= 0.002		R^2= 0.026 R^2 Change= 0.009	
Step 3: Substance-related Factors								
Time Since Caffeine	-0.032	(-3.874, 2.755)	-0.033	(-3.860, 2.728)	-0.041	(-4.274, 2.745)	-0.067	(-2.408, 1.143)
	R^2= 0.002 R^2 Change= 0.001		R^2= 0.010 R^2 Change= 0.001		R^2= 0.005 R^2 Change= 0.002		R^2= 0.030 R^2 Change= 0.004	
Step 4: Use of Endocrine Therapy								
SERM/AI	0.049	(-4.762, 8.056)	-0.110	(-10.035, 2.644)	-0.037	(-8.124, 5.454)	0.049	(-2.537, 4.330)
	R^2= 0.004 R^2 Change= 0.002		R^2= 0.02 R^2 Change= 0.012		R^2= 0.006 R^2 Change= 0.001		R^2= 0.033 R^2 Change= 0.002	

Note: No analyses were statistically significant.
N=116

APPENDIX A. USUHS IRB Approval Letter

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799
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December 18, 2009

MEMORANDUM FOR 2LT LYNN BRECKENRIDGE, MS, USA, MEDICAL AND CLINICAL PSYCHOLOGY

SUBJECT: USUHS IRB #1 (FWA 00001628; DoD Assurance P60001) Approval of TO72LT for Human Subjects Participation

Congratulations! The Initial Review for your Minimal Risk human subjects research protocol was reviewed and approved for execution on December 18, 2009 by Margaret Pickerel as an EXEMPT protocol under the provision of *32 CFR 219*.101(b)(4). This approval will be reported to the USUHS IRB #1 scheduled to meet on January 14, 2010.

The proposed study will be using previously collected de-identified data from Project Number HU72JR. Please see pages 16 to 22 of Project Number HU72JR.

The proposed study will be using previously collected de-identified data from Project Number HU72JR. This study will examine the relationship between adjuvant endocrine therapy and cognitive ability in occupationally active breast cancer survivors, using measures of perceived cognitive function (the Functional Assessment of Cancer Therapy-Cognitive subscales and the Cognitive Symptoms Checklist-modified) and a remotely administered performance-based measure of cognitive function (the CNS Vital Signs) and will examine the role of symptom burden measures (the Hospital Anxiety and Depress Scale, the Multifunctional Fatigue Symptom Inventory-short form, and the Visual Analog Scale of Pain) in this relationship, using analyses of variance and a series of multivariate regressions.

You are required to submit amendments to this protocol, changes to the informed consent document (if applicable), adverse event reports, and other information pertinent to human research for this project in IRBNet. No changes to this protocol may be implemented prior to IRB approval. If you have questions regarding this IRB action or questions of a more general nature concerning human participation in research, please contact Margaret Pickerel at (301) 295-3836 or mpickerel@usuhs.mil.

Maraget Pickerel, CIP

Director, Human Research Protections Program

Exemption Determination Official

This document has been signed electronically.

"Electronic Signature Notice: In accordance with the "Government Paperwork Elimination Act" (GPEA) (Pub.L. 105-277; codified at 44 USC 3504); Federal and DOD applicable instructions, directives and regulations, documents have been electronically signed and authorized by all who have been required to do so. These signatures have the same effect as their paper-based counterparts. Verification is retained within our protected electronic records and audit trails."

APPENDIX B. INFORMED CONSENT

Consent for Participation in a Research Study

The following information is provided to inform you about the research project and your participation in it. Please read this form carefully and feel free to ask any questions you may have about this study and/or about the information given below.

It is important that you understand that your participation in this study is totally voluntary. You may refuse to participate or choose to withdraw from this study at any time. If, during the course of the study, you should have any questions about the study or your participation in it, you may contact:

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1. INDICATED BELOW ARE THE FOLLOWING:

    a. THE PURPOSE OF THIS STUDY
    b. THE PROCEDURES TO BE FOLLOWED
    c. THE APPROXIMATE DURATION OF THE STUDY

1a. THE PURPOSE OF THIS STUDY:

- Over 80% of breast cancer survivors return to work within months of diagnosis and treatment.
- Some survivors experience memory or concentration problems that may impact their ability to work.

- This study will look at how tests and questionnaires of memory, attention, and organization might relate to each other and to your performance at work.
- If you agree to participate in this study, you will be asked to take an online questionnaire and a short test of your memory, organization and attention. The study will take approximately one hour to one hour and fifteen minutes to complete.

1b. THE PROCEDURES TO BE FOLLOWED:

Individuals meeting qualifications below may be asked to participate in the study.

You may qualify for this study based on the following:

- Adult female ages 18 to 65 years old
- Currently working full-time
- Computer/Internet access and usage; computer speed faster than dial-up (Only people with an Internet speed connection faster than dial-up will be able to continue with the study.)
- **Breast Cancer Survivors Only**: Between 1 and 10 years since completion of primary treatment (surgery, chemotherapy, radiation); working 1 year prior to diagnosis of cancer, and currently working.

You are not qualified of you have any of the following:

- Metastasized Cancer
- Dementia or Brain Disorder (For Example: Traumatic Brain Injury or Epilepsy)
- Drug and/or Alcohol Abuse
- Existence of adult Attention Deficit Hyperactivity Disorder (ADHD) prior to Cancer treatment

Participation in this study includes completing

1. online questionnaire (approximately 30 minutes to complete)

   and

2. a short online test of memory, organization and attention (approximately 30 minutes to complete)

1c. DURATION OF THE STUDY

Approximately 1 hour to approximately 1.25 hours

2. THIS STUDY IS BEING DONE SOLELY FOR THE PURPOSES OF RESEARCH

There will be no direct benefit to you by participating in this study. It is the goal of this research to help other cancer survivors in the future related to their ability to work.

3. DISCOMFORTS AND/OR RISKS THAT CAN BE REASONABLY EXPECTED ARE:

- The risks associated with this study are minor
    - You may find the questionnaires ask questions that may make you uncomfortable
    - You may skip questions at any time
    - Also, you may decline to participate at any time and/or withdraw your participation at any time

- You may experience discomfort or fatigue while completing the test segment
    - There will be a ample opportunities to take a break built into the study, in between sections and after each test

- If you have any questions or concerns, you can reach the principle investigators:
    - By telephone (301)295-9660
    - By email: cogworkstudy@gmail.com
    - A researcher will get back to you within one business day

4. POSSIBLE BENEFITS TO YOU THAT MAY BE REASONABLY EXPECTED ARE:

- You may gain a better understanding of the relationship between your memory, organization and attention (perceived and actual) and your productivity at work.
- Through completing this study, you will be providing information that will be helpful in expanding scientific knowledge about work productivity and memory, organization and attention function in breast cancer survivors.
- Our long-term goal is to gain a better understanding of the measurement of memory, organization and attention limitations and its impact on work productivity, and ultimately, work towards improving work productivity in cancer survivors.

5. PRIVACY AND CONFIDENTIALITY:

- All information you provide as part of this study will be confidential and will be protected to the fullest extent provided by law.
- Information that you provide and other records related to this study will be accessible to those persons directly involved in conducting this study and members of the Uniformed Services University of the Health Sciences Institutional Review Board (IRB), which provides oversight for protection of human research volunteers.
- All questionnaires, results and forms will not have identifying information and will be kept in a restricted access, password protected computer, in a locked office. Data from questionnaires will be entered into a database in which individual responses are not identified.
- Paper copies of the data will not be kept.
- Personal information will be collected for payment purposes. This information will be kept separate from the database, in a password protected computer in a locked office at the Uniformed Services University of the Health Sciences.
- If you are a military member, please be advised that under Federal Law, a military member's confidentiality cannot be strictly guaranteed.

Note: YOU ARE FREE TO WITHDRAW THIS CONSENT AND TO STOP PARTICIPATING IN THIS STUDY OR ANY ACTIVITY AT ANY TIME FOR ANY REASON.

6. COMPENSATION

- You will be given the option of receiving a book on stress reduction for completing both phases of this study
- At the end of the study, you will be asked for some personal information (e.g., name, address, social security number, phone number)in order to receive the book.
- This information is collected for tax tracking information by our institution. We must receive this information in order to render compensation.
- This information will be stored separately from the study data and will be stored in a secure, password protected computer in a locked office with restricted access.

7. RECOURSE IN THE EVENT OF INJURY:

COMPENSATION TO YOU IF YOU ARE INJURED AND LIMITS TO YOUR MEDICAL CARE: This study should not entail any physical or mental risk beyond those described above. It is believed that complications arising from participation should not occur. If, for any reason, you feel that continuing this study would constitute a hardship for you, you may end your participation in the study at any time.

If at any time you believe you have suffered an injury or illness as a result of participating in this research project, contact the Director of Human Subjects Protection Program at the Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799 at (301)295-9534. This office can review the matter with you. They can provide information about your rights as a research volunteer. They may also be able to identify resources available to you. If you believe the government or one of the government's employees (such as a military doctor) has injured you, a claim for damages (money) against the federal government (including the military) may be filed under the Federal Torts Claims Act. Information about judicial avenues of compensation is available from the University's General Counsel at (301)295-3028.

Should you have any questions at anytime about the study you may contact the principal investigator, **Lisseth C. Calvio, M.S., Department of Medical and Clinical Psychology, USUHS, Bethesda, Maryland 20814-4799, at 301-295-9660.**

STATEMENT BY PERSON AGREEING TO PARTICIPATE IN THIS RESEARCH PROJECT:

I have read this consent form and I understand the procedures to be used in this study and the possible risks, inconveniences, and/or discomforts that may be involved. All of my questions have been answered. I freely and voluntarily choose to participate. I understand that I may withdraw at any time. By clicking on the "yes" button, you are agreeing that you have read the consent form and understand the procedures to be used in this study. You also agree that you freely and voluntarily choose to participate and understand that you may withdraw at anytime. If you wish you may print out a copy of this form for your records.

- **Yes, I agree to participate in this study.**

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