COGNITIVE FUNCTION IN POST-MENOPAUSAL WOMEN WITH BREAST CANCER TREATED WITH AROMATASE INHIBITORS

by

Patricia M. Clark

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Doctoral Committee:

Associate Professor Bernadine E. Cimprich, Chair
Professor Jill B. Becker
Professor Anne F. Schott
Associate Professor Barbara A. Therrien

DEDICATION

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ABSTRACT

Introduction: Cognitive function changes reported as distressing by women diagnosed with breast cancer have been of interest to clinicians and researchers. The majority of post-menopausal women diagnosed with early stage breast cancer are treated with anti-estrogen therapies, usually aromatase inhibitors (AI). Estrogen is essential for brain function that supports everyday activities requiring cognitive functions of controlled attention and working and verbal memory. Post-menopausal breast cancer survivors are vulnerable to age-related cognitive decline which may be compounded by treatment-associated estrogen deprivation adversely affecting their roles at home, work, school, and society. This study explored effects of AI therapy on cognitive function in post-menopausal women treated for early stage breast cancer. The biological theory of treatment-associated estrogen deprivation was linked to neurobehavioral theory underlying basic cognitive processes of controlled attention and working and verbal memory.

Methods: Fifty post-menopausal women, 21 with breast cancer treated with AI, 10 with breast cancer receiving no AI and no other systemic therapy, and 19 healthy controls were enrolled in this longitudinal, non-randomized, comparative study. Established neuropsychological measures (Digit Span, Controlled Oral Word Association Test, Attention Network Test) and self-report of cognitive function (Attentional Function Index) were administered at two time points coincident with pre-AI and 3 months of AI therapy. Comparative and repeated measures statistics were used to examine between and within group changes over time.

Results: The AI group perceived worsening of cognitive function with more attentional lapses after three months of AI therapy in contrast to improvement in objective cognitive measures. There were no significant differences between AI and non-AI groups in objective or subjective measures of cognitive function. In comparison to healthy controls, the AI group demonstrated greater difficulty in high demand attention and working memory tasks. Similar group differences were noted in perceived cognitive function with greatest differences between the AI and healthy groups. The AI group perceived more attentional lapse over time than healthy controls.

Conclusion: Post-menopausal breast cancer survivors treated with AI perceive cognitive decline despite objective improvement in attention and working memory. Nurses are instrumental in supporting these women and helping them to recognize and manage effects of cognitive decline in everyday life.

CHAPTER I

INTRODUCTION

Breast cancer continues to be a significant health issue for post-menopausal women. An estimated 232,670 new cases of breast cancer will be diagnosed in 2014 with 79% occurring in women over the age of 50 (Anderson, Chatterjee, Ershler, & Brawley, 2002; American Cancer Society, 2013, 2014). In the majority of post-menopausal women diagnosed with breast cancer, the disease is found at an early stage (Stage 0 - II), is estrogen receptor positive (ER+), can be treated with oral systemic estrogen depriving therapy (EDT) after surgery and radiation therapy, resulting in a five year survival rate of 99% (American Cancer Society, 2013). The recommended EDT for use in treating post-menopausal women with early stage ER+ breast cancer is an aromatase inhibitor (e.g., anastrozole, letrozole, or exemestane) (Burstein et al., 2010). The duration of estrogen depriving therapy (EDT) may be a long as 10 years if the combination of a selective estrogen receptor modulator (SERM, e.g., tamoxifen) and an aromatase inhibitor (AI, e.g., anastrozole) is employed (National Comprehensive Cancer Network, 2014). Successful treatment of early stage breast cancer has resulted in nearly 3 million breast cancer survivors alive today (American Cancer Society, 2013).

A significant proportion of breast cancer survivors returning to their roles at home, work, school, and society may have difficulty doing so due to the cognitive side effects of treatment-associated estrogen deprivation (Hewitt, Greenfiled, & Stovall, 2006). The literature suggests that treatment-associated estrogen deprivation may have an independent detrimental effect compounding the natural effects of aging on cognitive function (Bender et al., 2008; Bender et

al., 2007; Breckenridge, Bruns, Todd, & Feuerstein, 2012; Eberling, Wu, Tong-Turnbeaugh, & Jagust, 2004; V. Jenkins, Shilling, Fallowfield, Howell, & Hutton, 2004; Lejbak, Vrbancic, & Crossley, 2010; Paganini-Hill & Clark, 2000; K. A. Phillips et al., 2011; K. A. Phillips et al., 2010; Schilder et al., 2010; Shilling, Jenkins, Fallowfield, & Howell, 2003). This is congruent with the location of estrogen receptors in areas of the brain (prefrontal cortex and hippocampus) involved in selective attention, working memory and verbal memory (B. S. McEwen, Akama, Spencer-Segal, Milner, & Waters, 2012). These domains of cognitive function allow focus on relevant information, inhibition of irrelevant stimuli, and active maintenance of information relevant to ongoing and future behavior (Kandel, 2013). There is a need to determine the effect of treatment-associated estrogen deprivation on specific cognitive processes because they are relevant to the way knowledge is recalled and used in daily life. If women experience significant cognitive decline with EDT, they will have difficulty using relevant information to understand and participate in treatment decisions and to adhere to long-term treatment plans. In addition, their ability to recognize and manage side effects may be compromised. These activities are central to successfully living with a breast cancer diagnosis.

Potential mechanisms of cognitive decline in post-menopausal women with breast cancer treated with aromatase inhibitors include: 1) further deprivation of already low post-menopausal estrogen levels resulting in less available estrogen in the brain for cognitive tasks; and 2) the increased cognitive demands of a breast cancer diagnosis and their effect on cognitive capacity in an older population of women already vulnerable to cognitive decline.

Breast cancer in post-menopausal women is most often estrogen receptor positive (ER+) and even naturally reduced circulating estrogen levels due to aging remain possible contributors to breast cancer growth (American Cancer Society, 2013). Current clinical practice guidelines

suggest two pharmacological approaches to breast cancer treatment in this population: 1) a drug that competes with estrogen for its receptor (a selective estrogen receptor modulator or SERM, e.g., tamoxifen) or 2) a drug that blocks the biosynthesis of estrogen by inhibiting a key enzyme, aromatase (aromatase inhibitor or AI, e.g., anastrozole, letrozole, or exemestane) (Burstein, et al., 2010; National Comprehensive Cancer Network, 2014). The effects of these drugs on serum estrogen differ. Tamoxifen has no significant effect on serum estrogen (estradiol) (Wilking, Carlstrom, Skoldefors, Theve, & Wallgren, 1982) while anastrozole decreases serum estradiol levels by 81 - 88% (Buzdar, et al., 2002) suggesting that anastrozole is the more intense therapy. Estrogen receptors are not unique to breast tissue (Pfaff, 1980) and these drugs have the capacity to act on tissues containing estrogen receptors in various parts of the body including the brain (Miyajima et al., 2013). Aromatase, the enzyme that converts androgen precursors into estradiol, is present throughout the brain (Azcoitia, Yague, & Garcia-Segura, 2011; Fester, Prange-Kiel, Jarry, & Rune, 2011) including the hippocampus and prefrontal cortex, areas of the brain involved in cognitive performance including attention, working memory, and verbal memory (Buwalda & Schagen, 2013). Therefore, because aromatase inhibitors circulate in the periphery and cross the blood brain barrier, resulting in aromatase inhibition in the brain, already low estradiol levels are further decreased both in the periphery and in the brain leaving less estradiol available for crucial, everyday cognitive functions such as controlled attention, working memory, and verbal memory.

Decreased availability of estrogen for cognitive functions required in everyday life occurs in post-menopausal women with breast cancer at a time when they are dealing with increased cognitive demands that require the use of these cognitive functions. Increased cognitive demands in this setting may include incorporating new and relevant information to make treatment

decisions, adhering to long-term oral estrogen depriving therapy, managing side effects of therapy, and adjusting to cancer-related role changes at home and at work. Research by Cimprich (Cimprich, 1992, 1998; Cimprich & Ronis, 2001; Stark & Cimprich, 2003) and others (Munir et al., 2011) has suggested that women treated for breast cancer are at risk for cognitive impairment as a result of loss of capacity to direct attention, that is, to focus on the task at hand and decline in working memory. In this setting, cognitive impairment may compound difficulty in dealing with increased cognitive demands, undermining confidence in the ability to perform everyday activities at home and at work. Nurses have an active role in helping cancer survivors integrate long-term treatment into their lives and are in a pivotal position to identify cognitive decline, evaluate cognitive demands, and to design practical, effective interventions.

STATEMENT OF THE PURPOSE

The purpose of the study was to examine the effect of aromatase inhibitors (AIs) on cognitive function, specifically on attention, working memory, and verbal memory, in post-menopausal women treated for early stage breast cancer.

SIGNIFICANCE OF THE PROBLEM

Attention, working memory, and verbal memory are functionally related processes that are fundamental to higher level cognitive function and relevant to the way that knowledge is gained, recalled, and used in daily life (Kandel, 2013). These cognitive functions are used throughout the day in planning and carrying out everyday activities: arriving at work on time; planning and executing projects at work, home, or school; conversing with colleagues at work or friends and family at home; performing commonplace household tasks such as cleaning and cooking; driving a car; taking public transportation; handling financial transactions; planning

family gatherings; and managing work and/or family conflict. In brief, controlled attention, working memory, and verbal memory support cognitive functions that post-menopausal breast cancer survivors use every day to successfully live their lives.

Functionally, these processes are subserved by areas of the brain rich in estrogen receptors and aromatase, the key enzyme for estrogen production in post-menopausal women. Aromatase inhibitors, the gold standard of treatment for breast cancer in these women, further lowers their naturally low estrogen levels. Combined with increased cognitive demand exacted by coping with a breast cancer diagnosis, important decisions about treatment, and self-monitoring for symptoms associated with treatment, post-menopausal women receiving AIs may experience estrogen deficiency related decline in key cognitive processes of controlled attention, working memory, and verbal memory. In the setting of vulnerability to decline in these key cognitive processes by natural aging, it is important to better understand the potentially additive effects of AI therapy in order to design practical, effective interventions to help women integrate long-term treatment into their lives.

STUDY AIMS AND RESEARCH QUESTIONS

The specific aim of the study was to determine whether AI therapy in post-menopausal women treated for breast cancer is associated with alteration in cognitive function over time as determined by objective and subjective measures of directed attention, working memory, and verbal memory. The specific questions for investigation were:

1) Is there a measureable decline in cognitive function, as assessed by objective and subjective measures of controlled attention, working memory, and verbal memory, in

post-menopausal women treated for breast cancer at 3 months after initiation of AI therapy?

2) Compared with women treated for breast cancer without AI, do women treated with AI for breast cancer show greater impairment at 3 months in controlled attention, working memory, and verbal memory?

3) Compared with healthy controls, do women with breast cancer – both AI treated and non-AI treated show greater impairment at Time 1 (prior to AI treatment for the AI group) and Time 2 (3 months)?

THEORETICAL FRAMEWORK

Attention, Working Memory, and Verbal Memory in Estrogen Deprivation

This study is based on a theoretical framework that links the biological theory of treatment-associated estrogen deprivation in post-menopausal women treated for breast cancer to the neurobehavioral theory underlying basic cognitive processes specifically, controlled attention, working memory, and verbal memory. Long-term estrogen deprivation is a key component to successful treatment of breast cancer in women diagnosed with estrogen receptor positive (ER+) disease. Estrogen receptors are not unique to breast tissue; they are present in various tissues throughout the body, including the brain. The vast majority of ER+ breast cancers are diagnosed in women who are post-menopausal and who already have low levels of endogenous estrogen. Further lowering estrogen levels in this population of women who are already at risk for cognitive decline due to age could have an adverse effect on cognitive function. This is especially true for those domains related to the location of estrogen receptors in the brain (prefrontal cortex and hippocampus) (B. S. McEwen, et al., 2012), specifically,

controlled attention, working memory, and verbal memory. Furthermore, because these functionally related cognitive processes are relevant to the way knowledge is gained, recalled, and used in daily life (Kandel, 2013), they are crucial to the ability of women with breast cancer to use relevant information to understand and participate in treatment decisions, to adhere to long-term treatment plans, and to recognize and manage treatment side effects.

Definition of Terms

The terms used in the theoretical framework are defined as follows:

Attention. Attention, specifically directed or controlled attention, is the ability to successfully exert mental effort to focus on information relevant to the task at hand while actively inhibiting information that is irrelevant (James, 1892; S. Kaplan & Berman, 2010; S. Kaplan & Kaplan, 1989; Posner, 1995). It is used when trying to work in distracting surroundings, taking on difficult work, or when trying to make a decision about a complex situation (S. Kaplan, 1995a). Attention requires continued use of mental effort and active inhibition, and is functionally constrained by a limited capacity (S. Kaplan & Berman, 2010; S. Kaplan & Kaplan, 1989).

Working memory. Working memory temporarily maintains information (visual, spatial, or verbal) in order that it may be mentally manipulated for some purpose (Baddeley, 1986, 2012; Smith & Jonides, 1999). It allows one to maintain and actively manipulate a limited amount (seven plus or minus two items) of information for a few seconds until it is used, or acquired and stored for longer term use (M.M. Mesulam, 2000). Working memory is functionally related to directed attention and cannot function without the inhibitory control that directed attention provides (Awh, Vogel, & Oh, 2006).

Verbal memory. Verbal memory includes memory of facts about people, places, things, and the meaning associated with this information including memory of words, letters, or numbers. It requires purposeful, deliberate effort, i.e., attention. Verbal memory can be very short term such as working memory or function in the longer term (M. M. Mesulam, 1998). For example, verbal working memory is employed to keep the name of a new acquaintance in mind while carrying on a conversation.

Attention, working memory and verbal memory deficits. Attention, working memory, and verbal memory are basic cognitive processes crucial to the success of breast cancer survivors' ability to manage self-care activities. Deficits in attention and working memory result in an inability to focus on the task at hand, retain relevant information, and inhibit competing stimuli (Cimprich, 1992; S. Kaplan & Kaplan, 1989). As a result, an individual with these deficits cannot exert the cogntive effort needed to think clearly, follow a train of thought, set goals, plan and initiate new tasks, solve problems, comprehend new information, or perform executive functions even at a basic, everyday level (Cimprich, 1995; S. Kaplan & Kaplan, 1989). Deficits in verbal memory hinder the association of new facts and experiences to existing knowledge which interferes with recall of new information (M. M. Mesulam, 1998).

CHAPTER II

COGNITIVE DEFICITS IN THE SETTING OF ESTROGEN DEPRIVATION IN WOMEN WITH BREAST CANCER

The distressing effects of cancer and its treatment on cognitive function have been of interest to researchers for the last three decades (Silberfarb, 1983). Much attention has been focused on cognitive changes related to chemotherapy, commonly called "chemo-brain", a term first coined by women receiving treatment with chemotherapy for breast cancer (Hurria, Somlo, & Ahles, 2007). Advances in breast cancer detection have made it possible to diagnose many cancers at an earlier stage, obviating the need for chemotherapy although adjuvant systemic estrogen-depriving therapy is often advised (National Comprehensive Cancer Network, 2014). Most women diagnosed with breast cancer are post-menopausal at diagnosis and have breast cancer that over-expresses the estrogen receptor (estrogen receptor positive, or ER+) making even naturally reduced levels of circulating estrogen possible contributors to breast cancer growth. While estrogen levels are low in post-menopausal women, they are not absent due to the synthesis of estrogen from androgens in the periphery and in the brain (Simpson, 2003). Thus, most post-menopausal women with early stage breast cancer may avoid chemotherapy but must undergo systemic treatment with an effective estrogen-depriving therapy in the adjuvant setting to decrease the risk of disease recurrence (Burstein, et al., 2010).

The gold standard of estrogen-depriving therapy for post-menopausal women with early stage breast cancer blocks the synthesis of estrogen from its androgenic precursors by inhibiting the key enzyme, aromatase. Aromatase inhibitors (AIs, e.g., anastrozle, letrozole, and

exemestane) lower circulating estrogen (estradiol) by as much as 88% either for the duration of treatment (anastrozole, letrozole) or permanently (exemestane) (Buzdar, Robertson, Eiermann, & Nabholtz, 2002). AIs act peripherally and cross the blood-brain barrier (Biegon et al., 2010) affecting peripheral and brain concentrations of estrogen. Therefore, AIs have the potential to alter cognitive function in a population of women who are already vulnerable to cognitive function due to normal aging.

This chapter will present an overview of the role of estrogen deprivation in breast cancer treatment, discuss the effects of estrogen deprivation on cognitive function, and review current thought about the cognitive effects of estrogen-depriving breast cancer therapy in women with breast cancer. A biobehavioral theoretical framework linking the biological theory of treatment-associated estrogen deprivation in post-menopausal women treated for breast cancer to neurobehavioral theory underlying the basic cognitive processes of controlled attention, and working and verbal memory will be discussed.

Estrogen Deprivation as Treatment for Breast Cancer

In early stage ER+ breast cancer, that is cancer that does not extend to the lymph nodes or beyond the breast, reducing or eliminating the role of circulating estrogen to prevent recurrence of breast cancer is a goal of adjuvant therapy. In post-menopausal women, two pharmacological approaches are used. The first approach exploits the over-expression of the estrogen receptor in ER+ disease by targeting the receptor using a selective estrogen receptor modulator or SERM (e.g., tamoxifen). Tamoxifen does not directly lower circulating estrogen levels but rather competes with estrogen to bind to the estrogen receptor (Wilking, et al., 1982). The second approach is to directly lower circulating estrogen levels by interfering with synthesis. In post-

menopausal women, estrogen is produced in the mesenchymal cells of adipose tissue (including the breast), osteoblasts and chondrocytes of bone, vascular endothelium and aortic smooth muscle cells, and multiple sites in the brain (Simpson, 2003). These extra-ovarian sites of estrogen production result in local tissue concentrations that are high and biologically active even if peripheral estrogen concentrations remain low (Simpson, 2003). A key enzyme in this process is aromatase. Aromatase inhibitors (AI, e.g., anastrozole, letrozole, or exemestane) reduce circulating estrone (E1), estradiol (E2), and estrone sulfate (E1S) by 81%, 84 - 88%, and 98% respectively (Buzdar, et al., 2002; Geisler, Haynes, Anker, Dowsett, & Lonning, 2002) and have been shown to cause a precipitous drop in estradiol and estrone concentrations within breast cancer tumors (de Jong et al., 1997). Aromatase inhibition occurs either by binding and inactivating aromatase or competing with endogenous substrates to reduce estrogen production (Williams & Lin, 2013). Current clinical practice guidelines suggest the use of an AI either alone for 5 years or sequentially with tamoxifen for two to three years. (Burstein, et al., 2010; National Comprehensive Cancer Network, 2014).

Estrogen receptors are not unique to malignant or normal breast tissue and are targets for drug therapy in various parts of the body, including the brain (B. S. McEwen, et al., 2012; Pfaff, 1980). In addition to areas of the brain that regulate the reproductive and endocrine systems, estrogen receptors are located in the prefrontal cortex and hippocampus, areas of the brain that support attention, and working and verbal memory (B. McEwen, 2002; B. S. McEwen, et al., 2012; Pfaff, 1980). This suggests that deficits in attention and working and verbal memory, key aspects of cognitive function, could be observed in an estrogen deprived environment.

Estrogen Deprivation and Cognitive Function

Evidence of cognitive function decline after estrogen deprivation comes primarily from studies of pre-menopausal women undergoing total abdominal hysterectomy and bilateral oophorectomy (TAH-BSO) and studies of estrogen replacement in post-menopausal women. With dramatic decreases in plasma estrogen levels (TAH-BSO) (S. M. Phillips & Sherwin, 1992; Sherwin, 1988), women commonly report the inability to concentrate and memory problems. Prospective studies of estrogen replacement in young women (37 - 50 years) showed that in the short term, working and verbal memory performance was positively correlated with estrogen levels independent of age (S. M. Phillips & Sherwin, 1992; Sherwin, 1988; Sherwin & Tulandi, 1996). However, effects of estrogen treatment in older women do not agree with these findings. The Women's Health Initiative Memory Study reported an increased risk of dementia and mild cognitive impairment in the estrogen-alone and estrogen-plus-progestin trials in women between 65 and 70 years of age (Espeland et al., 2004; Shumaker et al., 2004) as measured by the Modified Mini-Mental Status Exam. Further inconsistency was found in a randomized, double-blind experiment in which hysterectomized women (median age of 64 years) received placebo, estrogen, or estrogen/progesterone treatment. This study showed no difference among groups in attention, working, verbal, or visual memory at 4 and 24 weeks after initiation of treatment (Wolf, Heinrich, Hanstein, & Kirschbaum, 2005). A similarly designed study of older women randomized to estrogen alone or placebo (median age of 74 years) showed no change in verbal memory, attention, or executive functions (Almeida et al., 2006).

The different effects of estrogen deprivation on cognitive function could be due to depressed mood state and symptoms such as fatigue and sleep quality that have been reported by post-menopausal women. In one study, menopausal subjects receiving placebo had an increase in

hot flushes that correlated negatively with scores on a cognitive measure of immediate verbal recall but with no other measures. There was no difference in sleep quality between the groups and no relationship between sleep quality and cognitive function (S. M. Phillips & Sherwin, 1992). These results, confirmed by others (Almeida, et al., 2006; Shumaker, et al., 2004), suggest that hot flushes and resulting sleep disturbance that contribute to cognitive dysfunction in post-menopausal women not treated with HRT could not account for impaired cognitive function in menopausal women (Hogervorst, Williams, Budge, Riedel, & Jolles, 2000).

The inconsistencies in these studies may demonstrate a window of opportunity in which the addition of estrogen is beneficial (MacLennan et al., 2006). Three recent observational studies formally tested this timing hypothesis. The Multi-Institutional Research on Alzheimer Genetic Epidemiology Study (MIRAGE) concluded that initiation of estrogen therapy at age 50 - 63 years reduced the risk of dementia but women initiating this therapy at ages 64 - 71 or 72 - 99 years of age did not benefit (Henderson, Benke, Green, Cupples, & Farrer, 2005). A Kaiser Permanente study revealed that mid-life treatment with estrogen (median age 49 years) reduced risk of dementia but those women who started estrogen later in life (median age 76 years) had an increased risk of dementia (Whitmer, Quesenberry, Zhou, & Yaffe, 2011). Further confirmation came from a study that compared women starting estrogen plus progesterone therapy within five years of menopause to those starting more than five years after menopause, those starting after age 65, and never users. Women beginning therapy within five years of menopause had 30% lower incidence of Alzheimer's disease (AD); women starting therapy more than five years after menopause had no change in risk; and those starting over age 65 had an increased risk of developing AD (Shao et al., 2012).

Differences in subject and comparison populations, dose and type of hormone replacement used make it difficult to arrive at any firm clinical recommendations. Lack of clarity is fueled by the variety and sensitivity of instruments used to assess cognitive function and differences in the way the same instruments were administered in different studies. While some of these studies of replacement estrogen, especially placebo-controlled, randomized clinical trials, may provide indirect insight, it is difficult to extrapolate these findings directly to the effects of estrogen-depriving therapy on cognitive function in women with breast cancer.

Chemotherapy and Estrogen Deprivation Effects on Cognitive Function in Breast Cancer

Chemotherapy and estrogen-depriving therapies (EDT) are often given sequentially in the adjuvant setting, making it difficult to separate the independent effects of EDT on cognitive function in these studies. Studies of the combined influence of EDT and cytotoxic chemotherapy on cognitive function have been both cross-sectional and longitudinal in design and many have included effects of both tamoxifen and aromatase inhibitors. Eight studies (Ahles et al., 2002; Bender, et al., 2007; Breckenridge, et al., 2012; Castellon et al., 2004; Donovan et al., 2005; Schagen et al., 2002; Schagen et al., 1999; Schilder et al., 2009) addressing combined effects were cross-sectional in design and five (Ahles, et al., 2002; Bender, et al., 2007; Breckenridge, et al., 2012; Donovan, et al., 2005; Schilder, et al., 2009) included post-menopausal women. Five studies (Ahles, et al., 2002; Breckenridge, et al., 2012; Donovan, et al., 2005; Schagen, et al., 2002; Schagen, et al., 1999) showed no additive effect of EDT on cognitive function in women with breast cancer receiving adjuvant chemotherapy.

In contrast, Castellon and colleagues (Castellon, et al., 2004) showed a significant negative effect of chemotherapy plus tamoxifen on cognitive function when compared to

chemotherapy alone two to five years after treatment. In a cross-sectional study of 31 postmenopausal women, some with prior chemotherapy treatment, Bender (Bender, et al., 2007) found that anastrozole users had worse visual and verbal learning and memory than women receiving tamoxifen after taking EDT for at least three months. The Tamoxifen and Exemestane Multicenter (TEAM) trial was an open label, randomized multi-center comparative trial of five years of exemestane versus 2.5 years tamoxifen followed by 2.5 years of exemestane after standard adjuvant chemotherapy. In a cross-sectional sub-study, significantly more patients complained of memory problems than healthy controls but there was no difference in memory complaints between those receiving exemestane (n = 50; mean age 58) or tamoxifen (n = 30; mean age 58). Objective measures of cognitive function were not different between the patient groups but patients were significantly worse than controls (n = 48; mean age 60) in measures of verbal fluency and processing speed (Schilder, et al., 2009).

There are also seven published longitudinal studies of chemotherapy plus EDT on cognitive function (Bender et al., 2006; Bender, et al., 2007; Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009a; H. G. Fan et al., 2005; Hermelink et al., 2008; Hurria et al., 2006; V. Jenkins et al., 2006; K. A. Phillips, et al., 2010) with mixed results. In a study designed to assess the cognitive effects of induced menopause in women receiving neoadjuvant chemotherapy for breast cancer, cognitive function was assessed at three time points: prior to chemotherapy, at completion of chemotherapy, and about one year after the baseline assessment (Hermelink, et al., 2008). Women taking estrogen-depriving therapies (mean age 50 years) were on therapy (either tamoxifen n = 49, anastrozole n = 9, or letrozole n = 4) for approximately four months at the third time point of testing. No significant effects of EDT were reported in the results of the study. Fan and colleagues (H. G. Fan, et al., 2005) reported no difference in cognitive function between

groups receiving chemotherapy alone or chemotherapy plus tamoxifen at one and two years after initiation of chemotherapy. In another study, decline in visual, verbal, and working memory and increase in subjective memory complaints in women receiving both chemotherapy and tamoxifen were reported at an 18 month assessment (Bender, et al., 2006). Bender and colleagues conducted another cross-sectional study of women with early stage breast cancer comparing those who received tamoxifen with those who received anastrozole for a minimum of three months. In this study, women receiving anastrozole exhibited poorer verbal and visual learning and memory than women treated with tamoxifen (Bender, et al., 2007).

The four longitudinal studies that included post-menopausal women (Collins, et al., 2009a; Hurria, et al., 2006; V. Jenkins, et al., 2006; K. A. Phillips, et al., 2010) had contradictory findings. Jenkins and colleagues (V. Jenkins, et al., 2006) compared 85 women receiving chemotherapy to 43 women receiving EDT (SERM or AI) alone and 49 healthy controls, testing them prior to systemic therapy and at three time points after treatment initiation. Those receiving chemotherapy plus EDT did not differ in performance from those receiving EDT alone or from healthy controls at 18 months. In Hurria's study (Hurria, et al., 2006) 31 women over 65 years with early stage breast cancer were tested prior to therapy and 6 months after therapy was completed. Of the 28 women completing testing, 25 received EDT after chemotherapy; 25% of this group had significant decline in visual memory, spatial function, psychomotor function, and attention. Collins (Collins, et al., 2009a) examined post-menopausal women only and found that those receiving chemotherapy plus EDT had worse scores than those receiving chemotherapy alone on composite measures of processing speed and verbal memory. Phillips and colleagues (K. A. Phillips, et al., 2010) report results of a cognitive function sub-study (n = 120; median age 63) of the Breast Cancer International Group 1-98 (BIG 1-98) trial in which women were

randomized to receive 5 years of letrozole or tamoxifen or a sequential dosing of these two drugs. Women taking letrozole in this study were more likely to have had prior chemotherapy (35% prior chemotherapy vs. 24% no prior chemotherapy). Objective measures of cognitive function included attention and working memory, visual learning and memory, speed of psychomotor function, and visual attention; a composite cognitive function score consisting of the average standardized score of each of these tasks was the primary endpoint in the sub-study. The letrozole group had significantly higher composite cognitive function scores when compared with the tamoxifen group after 5 years of treatment, suggesting no negative impact on cognitive function in the setting of an aromatase inhibitor. Taken together, these studies provide an inconsistent picture of the combined effects of chemotherapy and EDT in the adjuvant setting. This is likely due to differences in treatment regimens, cognitive measures, testing intervals, and in some cases, small group numbers, making it difficult to generalize results.

Independent Effects of EDT on Cognitive Function

Seven studies involved women treated with EDT alone without chemotherapy. Four of these studies were cross-sectional in nature and all included post-menopausal women. Eberling and colleagues (Eberling, et al., 2004) found in a small study (N = 40) that women taking tamoxifen (n = 10) performed significantly worse on measures of verbal memory than women taking unopposed estrogen (n = 15) or women taking no hormonal therapy (n = 15). In one large (N = 1163) study, 58% of subjects were current or past users of tamoxifen. The remaining women had never taken tamoxifen and no subjects had been treated with chemotherapy. Tamoxifen users were twice as likely as never users to report seeing their physician for memory problems after diagnosis and made more errors in testing of visuospatial relationships, working memory and verbal memory (Paganini-Hill & Clark, 2000). In a subgroup of the randomized

ATAC (Anastrozole and Tamoxifen Alone and in Combination) trial, Shilling and colleagues (Shilling, et al., 2003) found significantly lower performance in women with breast cancer taking EDT compared with healthy women in processing speed and immediate verbal recall at 36 months. In a study of 65 post-menopausal women, 28 women with breast cancer taking either tamoxifen (78%) or anastrozole (22%) for at least one year were compared to 37 healthy age-equivalent controls. The group treated with EDT performed worse on measures of letter fluency, complex visuomotor attention and speed of manual dexterity but not measures of verbal memory or spatial ability (Lejbak, et al., 2010).

Three longitudinal studies have conflicting results. Two of these studies were initiated as a result of cross-sectional studies that revealed worse cognitive function in women receiving chemotherapy and EDT (Collins, et al., 2009a; Schilder, et al., 2009). Collins and colleagues conducted an unplanned extension of their prior study this time comparing post-menopausal women without breast cancer receiving estrogen-depriving therapy alone (tamoxifen n = 31; anastrozole n = 14) with healthy female volunteers (n = 28). Baseline neuropsychological testing was performed prior to estrogen-depriving therapy and again 5 - 6 months later. Both groups taking estrogen-depriving therapy performed significantly worse than healthy controls on measures of processing speed and verbal memory with the anastrozole group scoring the lowest (Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009b). A separate, repeated measures sub-study was also conducted in the TEAM Trial (Schilder, et al., 2010) in patients who did not receive chemotherapy. Participants in this second study were tested prior to beginning estrogen-depriving therapy (T1) and again after one year of treatment (T2). After adjustment for T1 performance, exemestane users (n = 99; mean age 68) did not perform significantly worse than healthy controls (n = 120; mean age 66) on any cognitive domain. In contrast, tamoxifen users (n

= 80; mean age 69) performed significantly worse than healthy controls on verbal memory and executive functioning and significantly worse than the exemestane group on information processing speed. There were no differences in working memory or other measures between the three groups in this study.

In a unique longitudinal study, cognitive performance was measured in a sub-study of the International Breast Intervention Study (IBIS-II), a double-blind placebo-controlled trial of anastrozole in women at high risk for developing cancer, with the aim of comparing outcomes on measures of attention and memory at baseline (prior to treatment for anastrozole group), six months and 24 months. All women in this study (anastrozole n = 77; placebo n = 74 at 24 months) were post-menopausal but none had a history of breast cancer. Performance on cognitive function measures did not differ between groups over time and scores on objective tasks were within normal limits for age of participants (V. A. Jenkins et al., 2008).

In summary, studies that have examined the combined effects of chemotherapy and EDT as well as studies that have attempted to assess the independent effects of EDT on cognitive function in women with breast cancer have been mostly cross-sectional in nature, have employed a variety of measures, and a variety of control groups. Some studies lack baseline (pre-treatment) measures and many include large batteries of neuropsychological tests that are difficult to interpret outside a theoretical framework and due to their length may fatigue participants. There are few longitudinal studies of post-menopausal women receiving aromatase inhibitors without the confounding effect of prior chemotherapy. Despite these limitations and conflicting results, there is some indication that aromatase inhibitors may affect estrogen-dependent cognitive functioning in post-menopausal women with breast cancer.

Theoretical Framework

Establishing a theoretical framework provides context for selecting and interpreting measures in scientific inquiry. The theoretical framework for this project links the biological theory of treatment-associated estrogen deprivation in the post-menopausal woman treated for breast cancer to neurobehavioral theory underlying basic cognitive processes, specifically controlled attention and working and verbal memory. These functionally related processes are fundamental to higher level cognitive function and relevant to the way that knowledge is gained, recalled, and used in daily life (Kandel, 2013).

Neurobehavioral theory of controlled attention, working and verbal memory

Controlled attention. Controlled attention is a form of voluntary attention requiring exertion of mental effort in situations such as working in distracting surroundings, taking on work that is difficult or uninteresting, or when trying to make a decision about a complex situation (S. Kaplan, 1995b). Controlled attention requires two activities that work in tandem: focusing on information relevant to the task at hand and actively inhibiting information that is irrelevant (de Fockert, 2005; James, 1892; S. Kaplan & Kaplan, 1981). There is evidence that nearly all tasks involving controlled attention can be characterized by metabolic activation of prefrontal and posterior parietal cortex (M.M. Mesulam, 2000). Controlled attention is crucial to the success of breast cancer survivors' ability to manage self-care activities. When controlled attention is compromised, distinguishing relevant from irrelevant information may affect self-care activities such as taking daily medications and planning a daily schedule to include follow-up health care appointments.

Working memory. Working memory is functionally related to controlled attention. It allows one to maintain and actively manipulate a limited amount (7 plus or minus 2 items) of information for a few seconds until it is used, or acquired and stored for longer term use (M.M. Mesulam, 2000). Working memory maintains information (visual, spatial, or verbal) in order that it may be mentally manipulated (de Fockert, 2005). Working memory cannot function without the inhibitory constraint that controlled attention provides. Deficits in working memory represent frustrating inefficiencies of daily life to those experiencing them. Complaints include forgetting the purpose of walking into a room, being unable to hold a list of two or three items in mind when grocery shopping, and forgetting a telephone number before dialing is complete. Areas in the dorsolateral prefrontal cortex and anterior cingulate control working memory (Smith & Jonides, 1999). Deficits in working memory may occur when capacity for short-term storage becomes limited and/or there is a compromise in controlled attention such as fatigue.

Verbal memory. Verbal memory is a type of explicit memory that requires purposeful, deliberate effort, i.e., controlled attention. It includes memory of facts about people, places, things, and the meanings associated with this information including memory of words, letters, or numbers. Verbal memory can be very short term such as working memory, or function in the longer term. The hippocampus sustains and nurtures the fragile and sparse connections between new facts/experiences and existing knowledge. As these connections strengthen, new information becomes easier to recall (M. M. Mesulam, 1998). For example, verbal working memory is used to keep the name of a new acquaintance in mind while carrying on a conversation. If the name can be associated with existing knowledge (for instance equating the new name with a familiar animal or place) the fragile connections of the new name to existing knowledge will be strengthened and the name more likely to be remembered.

Biological theory of treatment-associated estrogen deprivation.

Estrogen deprivation and breast cancer treatment. The effectiveness of treatment-associated estrogen deprivation in post-menopausal women with ER+ breast cancer has been firmly established (The Early Breast Cancer Trialists Collaborative Group, 2005). Post-menopausal women begin EDT with low estrogen levels but still experience side effects typical of the menopausal transition signaling an intensification of estrogen depletion. Incidence of reported side effects varies with the type of EDT. SERMS (e.g., tamoxifen) do not directly lower estrogen levels but competitively bind to estrogen receptors with antagonistic effects in some tissues and agonistic effects in others (AstraZeneca, 2004). AIs (e.g., anastrozole) directly lower estrogen levels by inhibiting aromatase, a key enzyme in the conversion of testosterone to estrogen and the major pathway for estrogen synthesis in post-menopausal women (Buzdar, et al., 2002). The varying effects of SERMs and AIs on serum estrogen levels suggest that AIs provide more intense treatment-associated estrogen deprivation than SERMs.

It is unknown whether this difference in EDT intensity affects cognitive function. Estrogen has specific effects in the brain and estrogen receptors are present in multiple areas of the brain including the prefrontal cortex and hippocampus (B. S. McEwen, et al., 2012) anatomical sites involved in controlled attention, working memory, and verbal memory. Theoretically, sustained intensification of an already low estrogen state could be detrimental to cognitive function especially in an aging population vulnerable to cognitive decline. There is some evidence that cognitive deficits experienced by estrogen deprivation in natural menopause stabilize or even improve over time (Ryan et al., 2012). It is unknown whether cognitive function declines, stabilizes, or improves with sustained estrogen deprivation in EDT.

Estrogen effects on controlled attention, working memory, and verbal memory

Post-menopausal women produce estrogen in a number of extra-gonadal sites including the mesenchymal cells of adipose tissue (including the breast), osteoblasts and chondrocytes of bone, vascular endothelium, aortic smooth muscle cells, and numerous sites in the brain. It is thought that while the total amount of estrogen produced in local tissue may be small, its concentration is high enough to powerfully influence local tissue biology (Simpson, 2003). The role of estrogen as a neurosteroid suggests that it is needed for effective brain function. Post-mortem studies of human brains have revealed that concentrations of estrogen in the prefrontal cortex are as much as two times higher than in the temporal cortex, seven times higher than in the hippocampus, and higher in pre-menopausal women compared to post-menopausal women. While this suggests that regional differences in concentrations of estrogen in the brain may reflect levels of serum estrogen (Bixo, Backstrom, Winblad, & Andersson, 1995; Simpson, 2003), estrogen is also synthesized in the brain from cholesterol precursors. This suggests that serum and brain concentrations of estrogen may be different (Ryan, et. al., 2012). The prefrontal cortex is critical to both controlled attention and working memory. It is innervated by dopaminergic and serotonergic inputs that originate in the brain stem. Estrogen has global effects in the brain involving these pathways as well as catecholamine and cholinergic pathways (Colazto & Hommel, 2014; Sherwin, 2003).

The effect of menopause-induced lowered endogenous estrogen on basic cognitive processes such as controlled attention and working and verbal memory has been studied most extensively in post-menopausal women receiving replacement estrogen. In comparison studies of post-menopausal women receiving replacement estrogen compared to untreated control groups, those receiving replacement estrogen showed better performance on a working memory task

(digit ordering and digit span backwards) with a verbal component than non-users (Grigorova & Sherwin, 2006). In this study, non-users made nearly 40% more errors and committed more errors of perseveration (inability to inhibit incorrect responses) suggesting prefrontal cortex dysfunction (Joffe et al., 2006; Keenan, Ezzat, Ginsburg, & Moore, 2001). Controlled attention helps to determine what information is acquired, recalled, and manipulated in working memory. Subsequently, the hippocampus, over a period extending from days to weeks, may process this information into long-term storage in the association areas of the neocortex. In randomized clinical trials of post-menopausal healthy women, those treated with estrogen (any type) performed better than women receiving placebo on 47% of memory measures including those of verbal memory (Zec & Trivedi, 2002). Case control studies also support the idea that estrogen maintains verbal memory as well as working memory (Gold et al., 2000). In a recent systematic review of endogenous estrogen and cognitive function in older adults (Boss, Kang, Marcus, & Bergstrom, 2014), higher estradiol was associated with better verbal memory in two cross-sectional studies (Hogervorst, De Jager, Budge, & Smith, 2004; Wolf & Kirschbaum, 2002). Longitudinal studies were mixed in their findings with some studies finding a positive relationship between estradiol and verbal learning and memory but a negative association with executive function over time (Drake et al., 2000). In a more recent study of 643 healthy postmenopausal women who were not using hormonal therapy, endogenous sex steroid levels (free estradiol, estrone, progesterone, free testosterone, and sex hormone binding globulin) were measured in women who were early in menopause (< 6 years) and in a second group that was in late menopause (10+ years after menopause). None of the endogenous sex steroids were associated with cognitive composite scores but sex hormone binding globulin was positively associated with verbal memory and progesterone concentrations were positively associated with

verbal memory in women in the early years of menopause (Henderson et al., 2013). Taken together, these studies represent contradictory findings in regards to the effects of estrogen on verbal memory and suggest that its effect may be modulated by other endogenous sex hormones such as testosterone and sex hormone binding globulin.

Summary: Controlled attention and working and verbal memory are functionally related cognitive processes relevant to the way knowledge is gained, recalled, and used in daily life. These processes are related to areas of the brain known to have estrogen receptors. Some studies suggest that estrogen deprivation has a detrimental effect on cognitive function specifically on controlled attention, working memory, and verbal memory. Many post-menopausal women treated for breast cancer will undergo sustained estrogen deprivation with EDT that will further reduce already low estrogen levels. Further reduction of estrogen needed to support basic cognitive processes may lead to reduced cognitive capacity in this population faced with increased cognitive demands in adjusting to the diagnosis of breast cancer and already vulnerable to age-related cognitive decline.

CHAPTER III

METHODS

This study was designed to examine the impact of aromatase inhibitors on cognitive function in post-menopausal women treated for breast cancer. This chapter describes the research design, the sample selection and setting, measures, data collection procedures, and data analysis procedures.

Research Design

A longitudinal, non-randomized, comparative design was used to explore changes over time in controlled attention, working memory, and verbal memory in post-menopausal women with breast cancer from pre- to three-months post-adjuvant treatment with an aromatase inhibitor (AI). Three groups of post-menopausal women were included in this comparative study: one group with breast cancer who were treated with an aromatase inhibitor (AI group); a second group with breast cancer who were not treated with AI or any other systemic therapy to control for treatment factors (non-AI group); and a third group of healthy post-menopausal women without breast cancer to control for disease and treatment factors (healthy group). Baseline (Time 1; T1) cognitive testing was conducted within two weeks after locoregional treatment (surgery and radiation therapy) was completed and prior to initiation of AI therapy in the AI group and within a two weeks of completing local therapy in the non-AI group. The healthy group had baseline testing within one year of a normal mammogram. Time 2 (T2) testing for all groups was planned to occur 3 months after Time 1 testing to allow for AI therapy to reach therapeutic

steady state blood levels and to coincide with the first follow-up symptom assessment visit in the medical oncology clinic.

Sample and Setting

The sample consisted of 50 postmenopausal women, 21 women diagnosed with Stage 0 - I breast cancer treated with adjuvant aromatase inhibitor therapy (AI group), 10 women diagnosed with Stage 0 - I breast cancer who received no aromatase inhibitor or other systemic therapy (non-AI group), and 19 women without breast cancer who were healthy controls. The two groups with breast cancer (AI and non-AI) were recruited from the University of Michigan Comprehensive Cancer Center's Breast Oncology Program. Women in the healthy control group were recruited through the University of Michigan UM Clinical Studies (www.umclinicalstudies.org), a public website coordinated by the Michigan Institute for Clinical and Health Research (MICHR) that matches potential study volunteers with studies for which they are eligible.

All subjects were required to meet eligibility criteria related to menopausal status and cognitive function. Specifically, all subjects met the following requirements: post-menopausal status as determined by the Stages of Reproductive Aging Workshop (STRAW) definition (experiencing amenorrhea for at least 12 consecutive months (Soules et al., 2001); sufficient command of the English language to permit testing; and a Mini-Mental State Exam (MMSE) score of at least 24, indicative of no cognitive impairment. Eligibility criteria specific to women in the AI group included a pathologically confirmed diagnosis of early stage (0, I, or II) breast cancer that was either estrogen receptor positive (ER+) or estrogen receptor negative (ER -) and a treatment plan for AI without chemotherapy. Eligibility criteria specific to the non-

AI breast cancer group included a pathologically confirmed diagnosis of early stage (0, I, or II) breast cancer that was either ER+ or ER- , lobular carcinoma in situ (LCIS) or atypical ductal hyperplasia (ADH), and a treatment plan that did not include an aromatase inhibitor, any other estrogen-depriving therapy, or chemotherapy. In addition to the menopausal status criterion noted above, the healthy control group was required to have a mammogram within the past year showing no suspicion of breast cancer.

Potential subjects were excluded if they had the following: a medical history of active cancer other than non-melanoma skin cancer in the past five years; current or prior treatment with anti-estrogen therapy or chemotherapy; secondary diagnosis of mental or psychiatric disorder, learning disability; history of traumatic head injury, or drug or alcohol abuse; secondary diagnosis of debilitating medical disorder such as progressive muscle paralysis or advanced cardiac, respiratory, renal disease, or AIDS; or if they were currently taking psychoactive medications for treatment of a diagnosed psychiatric disorder.

Measures

Cognitive Measures

The measures used in this study were carefully selected based on a biobehavioral conceptual framework of controlled attention, working memory, and verbal memory in the setting of sustained estrogen deprivation. The cognitive function measures include neuropsychological measures of controlled attention, working memory and verbal memory, and a self-report measure of perceived effectiveness in cognitive functioning.

Cognitive Function Indicators

The Mini-Mental State Exam. The Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975) is a standardized screening test that evaluates four key areas of cognitive function: orientation, memory, attention, and language use and construction. Scores range from 0 to 30 with a conventional cutoff score of 24, indicating no serious cognitive impairment. In this study, the MMSE was used as a screening test to ensure intact cognitive function. This measure has documented reliability and validity (Folstein, et al., 1975; Pangman, Sloan, & Guse, 2000). The MMSE may be found in Appendix A1 (pg. 99).

Neuropsychological Measures

Attention: The Attention Network Test. The Attention Network Test (ANT) is a computerized test that evaluates three attention networks: alerting, acquiring and maintaining a state of readiness; orienting, selecting the area or thing to be attended; and executive control, the inhibition of conflict among possible responses. Subjects use a computer mouse to indicate the direction of a central arrow (left or right) that appears above or below a fixation cross and may or may not be flanked with arrows and accompanied by a cue. There are three flanker conditions. In the neutral condition, the central arrow is flanked by straight lines. The congruent condition displays all arrows, including the central arrow, pointing in the same direction. The incongruent condition presents the central arrow flanked by arrows pointing in the opposite direction. There are four possible warning cues represented by an asterisk (*). The center cue is represented by the asterisk in the center of the fixation cross, the double cue by an asterisk above and below the fixation cross, spatial cue by an asterisk either above or below the fixation cross to indicate

location of anticipated flanker arrows, and a no cue condition in which there is no asterisk. (J. Fan, McCandliss, Sommer, Raz, & Posner, 2002).

Scores for the ANT are reaction time (RT) and accuracy (ACC) in each attention network and are calculated by examining differences in mean reaction times associated with specific cue conditions or flanking conditions. The alerting effect score is represented by subtraction of the mean RT of the double-cue conditions from the mean RT of the no-cue conditions. The orienting effect score is computed by subtracting the mean RT of the spatial cue conditions from the mean RT of the center cue condition. The executive control score is obtained by subtracting the mean RT of all congruent flanking conditions, summed across cue types, from the mean RT of incongruent flanking conditions. The ANT has shown reliability across two testing sessions that varies according to attentional network from .52 in the alerting network to .77 in the executive control network (J. Fan, et al., 2002). Instructions for the ANT may be found in Appendix A2 (pg. 100).

Working memory: Digit Span. Digit Span is a subtest of the Wechsler Adult Intelligence Scale and the Wechsler Memory Scale. It is a test of working memory that evaluates short-term holding capacity and verbal recall of numerical information. The test consists of two parts, Digit Span Forward (DSF) and Digit Span Backward (DSB) that differ in cognitive demand. For each of these measures, the examiner reads a sequence of numbers to the participant. When the examiner is finished, the participant repeats the sequence of numbers. DSF and DSB are scored separately; the score is the total number of sequenced numbers (the span) that the participant is able to recall prior to two failed attempts. DSF is the less demanding of the two measures but involves short-term storage of information. DSF requires that the subject remember and repeat the sequence of numbers exactly in the same order as it is read by the

examiner. A span of 6 is usually achieved by healthy adults without difficulty. A span of 5 is considered marginal; 4 is considered borderline (Lezak, Howieson, D.W., Hannay, & Fischer, 2004). DSB places more cognitive demand on the participant as it requires short-term storage of information as well as manipulation of the information. DSB requires that the subject remember and repeat a sequence of numbers exactly backwards from the way it was read by the examiner. A span of 4 or 5 is considered normal in the DSB with a span of 3 considered borderline. Digit Span has documented test-retest reliability from .80 to .92 in older men and women (Lezak, et al., 2004). DSF and DSB may be found in Appendix A3 (pg. 101).

Verbal memory: The Controlled Oral Word Association Test. The Controlled Oral Word Association Test (COWAT) measures verbal fluency, working memory, and daily life communication skills (Loonstra, Tarlow, & Sellers, 2001). This measure consists of using three word-naming trials of one minute each. The examiner asks the participant to name as many words as come to mind that begin with a given letter of the alphabet in one minute, without using proper nouns, numbers, or the same word with a different suffix. The score for this measure is the sum of all acceptable words produced in three trials. For adults, score of 34 words is considered average (Loonstra, et al., 2001), 28 borderline, and less than 25 considered deficient (Ruff, Light, Parker, & Levin, 1996). Test-retest reliability has been established and is consistently greater than .70 (Lezak, et al., 2004). In this study, the letters used in the word-naming trials were different at Time 1 and Time 2 to avoid practice effect. The letters F-A-S were used at the Time 1 measure and the letters C-F-L were used at Time 2. Findings from a study by Lacy and colleagues (Lacy et al., 1996) suggest that there is little difference in difficulty although a more recent comparison (Barry, Bates, & Labouvie, 2008) suggests that C-F-L may

be more difficult than the F-A-S letter combination. The COWAT may be found in Appendix A4 (pg. 102).

Self-reported Cognitive Functioning

The Attentional Function Index. The Attentional Function Index (AFI) (Cimprich, 1990) is a self-rating scale measuring perceived effectiveness in basic cognitive activities including planning daily activities, getting started on tasks, making decisions, keeping a train of thought, remembering to do important things, and attending to details. These functions involve attention, working memory, and higher executive functions. The original AFI was designed with 16 items rated on a visual analogue scale ranging from 0 (not at all) to 100 (extremely well or a great deal) with higher scores representing greater perceived effectiveness in executive functioning. This study used the 16 item scale rated on a 10-point Likert scale from 0 (not at all) to 10 (extremely well). Instructions to the participant are to circle the number that best describes her perceived functioning "today". The 16-item AFI has been demonstrated to correlate positively with objective measures of attention and working memory in healthy adults (D. A. Jansen, 2006; Tennessen & Cimprich, 1995) and has established reliability with internal consistency coefficients ranging from .76 to .94 (Cimprich, Visovatti, & Ronis, 2011). The AFI has been used in several studies of women with breast cancer (Cimprich, 1993, 1999; Cimprich, So, Ronis, & Trask, 2005; Jung, 2013; Lee, 2005; Lehto & Cimprich, 1999). Recently, the AFI has been modified to a 13 item scale with 3 distinct subscales: effective action (7 items), attentional lapses (3 items), and interpersonal effectiveness (3 items). Internal consistency coefficients for the revised AFI were 0.91 for the total scale and ranged from 0.75 to 0.93 for the subscales (Cimprich, et al., 2011). The 16 item instrument used in this study can be found in

Appendix A5. Internal consistency coefficients for the 16-item AFI used in this study were acceptable at .94 at both time points.

Demographics and Medical Characteristics

A demographic survey was completed by all subjects at Time 1 testing. Demographic characteristics in this survey included: age, marital status, household composition, education level, occupation, employment status, ethnicity, race, and household income (see Appendix A6).

Medical characteristics were collected at the onset of the study from subjects. For the AI and non-AI groups, information regarding the histology and stage of breast cancer, type of local therapy including specific surgical procedure performed, and duration and type of radiation therapy, past history of estrogen replacement therapy, concomitant medications, and current medical conditions was obtained. Selected information was obtained from subjects at Time 2 and included concomitant medication and current medical conditions.

Procedures

Recruitment Procedures

Prior to recruitment, this study was approved by the University of Michigan Comprehensive Cancer Center Protocol Review Committee and by the Institutional Review Board of the University of Michigan Medical School (IRB-MED). Subjects were recruited through the University of Michigan Breast Care Center clinics. The principal investigator (PI), in consultation with primary oncologists and nurses generated a list of potential study subjects meeting eligibility criteria at the beginning of the clinic session. The oncologist, nurse practitioner, or clinic nurse determined the potential participant's interest in hearing more about the study and gave potential subjects a brochure explaining the study during their clinic visit. Once the potential participant indicated an interest in the study, the PI discussed the study with the potential participant. This discussion included review of potential benefits and risks as well

as assurance that subjects could withdraw from or choose not to participate in the study without affecting their clinical care at UMCCC. After answering participant questions about the study, the PI obtained informed consent from willing subjects.

Healthy controls were recruited through the UM Clinical Studies website (www.umclinicalstudies.org). This website provides an opportunity for interested persons to search for clinical trials for which they might be eligible. Initial screening was conducted by the staff at UM Clinical Studies and interested subjects were encouraged to contact the PI by e-mail or by telephone. The PI confirmed eligibility and discussed the study with the potential participant via telephone. Potential subjects were assured that they could choose not to participate without compromising their care at the University of Michigan Health System or their ability to participate in other clinical trials through UM Clinical Studies.

Recruitment was conducted from 11/06/2009 to 8/28/2012. Although a sample of 90 women was planned, in the final sample, there were 50 post-menopausal women enrolled as subjects in this study: 21 in the AI group, 10 in the non-AI group, and 19 in the healthy control group. Enrollment in this study was hindered for several reasons: many potential subjects who had chemotherapy (an exclusion criterion) as part of their treatment plan; many potential subjects who met the criteria for the non-AI group did not continue follow-up at the UMCCC and did not wish to return to participate in the study, and interested healthy controls did not meet eligibility criteria.

Testing Procedures

The principal investigator (PI) was trained and experienced in administration of neuropsychological tests involved in this study. The PI had clinical experience in dealing with the emotional responses to breast cancer and its symptoms such as fatigue and anxiety.

Subjects were tested at two time points. Women in the AI group had Time 1 testing after local therapy (surgery and radiation therapy) and prior to starting aromatase inhibitor (AI) therapy. Women in the non-AI group had Time 1 testing within six weeks after local therapy. Women in the healthy control group had Time 1 testing at their convenience and within one year of a normal mammogram. Time 2 testing for all groups was planned for 3 months after Time 1 to coincide with AI group. For the AI group, Time 2 testing was approximately 3 months after starting the AI to ensure that the AI had reached therapeutic steady state levels and for convenience was scheduled at a planned follow-up clinic visit when possible. Time 2 testing for the non-AI group and the healthy control group proved challenging as subjects in these groups did not routinely have a follow-up appointment scheduled, therefore, Time 2 testing was scheduled as close to 3 months as possible. To facilitate testing, the PI met with participants in a quiet, private room in the Breast Cancer Clinic at UMCCC, at a local library, in their home, in their office or in the PI's office for either or both testing times. All testing sites were free from distracting stimuli such as noise or interruption from telephone.

Statistical Analysis

All procedures for statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21 for Windows. Prior to testing the main hypotheses of the study, initial descriptive analyses of the collected data were performed to describe the

demographic characteristics of the three groups (AI, non-AI, healthy controls), to assess the data for potential outliers or errors in data entry, to investigate measure of central tendency for outcome measures in each group, and to establish equivalency on possible covariates among the three groups. Comparison of demographic characteristics (i.e., age, education, marital status, race) among groups was performed to identify any covariates that were to be controlled for in future multivariate analyses.

Research Question 1: Is there a measureable decline in cognitive function, as assessed by objective and subjective measures of attention, working memory, and verbal memory, in post-menopausal women treated for breast cancer at 3 months after initiation of AI therapy?

To determine changes over time in cognitive function in the AI group, a two-sided, paired-samples t-test was performed to determine whether the mean change on a given cognitive functioning outcome from baseline to three months was significant at the 0.05 level of statistical significance. Outcomes included in this analysis were the objective measures ANT, DSF, DSB, COWAT and subjective (AFI) measures of cognitive function. To increase statistical power of this observation, a composite cognitive function score was created that consisted of the sum of the z scores of the DSF, DSB, and COWAT measures.

Research Question 2: Compared with women treated for breast cancer without AI, do women treated with AI for breast cancer show greater impairment at Time 2 in directed attention, working memory, and verbal memory?

To answer research question 2, independent t-tests were performed to determine differences in the AI and non-AI groups at each time point. A repeated measures analysis of variance (ANOVA) was performed using a 2 X 2 factorial design, AI vs. Non-AI by Time 1 and

Time 2 to determine significant group by time interaction and any main effects of group and time.

Research Question 3: Compared with healthy controls, do women with breast cancer – both AI treated and non-AI treated show greater impairment at Time 1 and Time 2?

To answer research question 3, a one-way analysis of variance (ANOVA) and independent t-tests were performed to determine differences in the study groups at each time point. A repeated measures analysis of variance was performed using a 3 X 2 factorial design, AI vs. non-AI vs. control by Time 1 vs. Time 2, examined possible significant group by time interaction effect and main effects of group and time.

Significant differences among groups were considered to be $p < .05$. Differences that were trending toward significance, i.e., $p < .10$ are also reported in this preliminary work.

CHAPTER IV

RESULTS

This chapter provides analyses of findings that answer the three main research questions posed by this study: 1) Is there a measureable decline in cognitive function, as assessed by objective and subjective measures of controlled attention, working memory, and verbal memory in post-menopausal women treated for breast cancer at 3 months after initiation of aromatase inhibitor (AI) therapy? 2) Compared with women treated for breast cancer without AI, do women treated with AI for breast cancer show greater impairment at 3 months in controlled attention, working memory, and verbal memory? 3) Compared with healthy controls, do women with breast cancer – both AI treated and non-AI treated – show greater impairment at Time 1 (T1) and Time 2 (T2)?

Sample Characteristics

Demographic Characteristics

The data were obtained from 50 post-menopausal women: 21 with breast cancer treated with an AI and tested prior to beginning AI therapy (T1) and approximately 3 months later (T2), 10 with breast cancer receiving no systemic treatment after radiation therapy (T1) and approximately 5 months later (T2), and 19 healthy controls within a year of a screening mammogram (T1) and approximately 7 months later (T2). Analysis of variance (ANOVA) was used to examine group differences between T1 and T2 testing intervals. As expected, there was a significantly longer testing interval for healthy controls (M = 218.9 days ± 91.95)

than for the AI group (M =119.8 days ± 5.76), F (2, 34), p = .003. There was 26% attrition between T1 (n = 50) and T2 (n = 37). Attrition occurred in all groups: AI 24%, non-AI 20%, and healthy controls 32%. There were no significant differences in demographics, medical characteristics, or baseline cognitive function measures when participants completing both time points of testing were compared to those participants completing only T1 testing using independent t-tests.

The mean age of all participants was 63.2 years (SD = 6.9) with a range from 49 to 81 years. The mean years of education was 16.1 (SD = 2.2) and ranged from 11 - 20 years. Most of the total sample was white (n = 45, 90%), married (n = 31, 62%), and employed outside the home (n = 30, 60%) with an income > $31,000 per year (n = 45, 90%). Table 1 (pg. 51) details these findings.

To determine differences in demographic characteristics among groups, a one-way analysis of variance (ANOVA) was conducted for continuous variables (age and education) and the Pearson chi square statistic was used to determine differences in categorical variables (race, marital status, employment, and household income). The non-AI patient group was on average the oldest although no significant differences in age F (2, 47) = 1.71, p= .191 were found among groups by ANOVA. Independent t-tests revealed that there was a trend for education to be different among the three groups F (2, 47) = 3.08, p = 0.06. Post-hoc comparisons using the Tukey HSD test indicated that the mean education level for the non-AI group (14.8 yrs ± 2.0) was significantly lower (p = .04) than that of the healthy control group (16.8 yrs ± 1.9) but not the AI group (16 yrs ± 2.4). No significant differences were found among groups in race χ^2 (2, n = 50) = 6.72, p = .151, marital status χ^2 (2, n = 50) = 2.79, p = .248, employment outside the home χ^2 (2, n = 50) = 2.26, p = .323, or income χ^2

(12, n = 50) = 9.754, p = .638. Demographic data may be found in Table 1.

Table 1. *Demographics*

	Total Sample (N = 50)	**AI Group (n= 21)**	**Non- AI (n = 10)**	**Healthy Control (n = 19)**
	M ± SD (Range)	**M ± SD (Range)**	**M ± SD (Range)**	**M ± SD (Range)**
Age (years)*	63.2 ± 6.9 49 - 81	63.3 ± 6.3 49 - 80	66.3 ± 8.8 50 - 81	61.4 ± 6.0 53 - 76
Education (years)**	16.1 ± 2.2 11 - 20	16.0 ± 2.3 11 - 20	14.8 ± 2.0 12 - 18	16.8 ± 1.9 12 - 20
Number of family members	1 ± 1 0 - 3	1 ± 1 0 - 2	1 ± 1 0 - 3	1 ± 1 0 - 2
Interval * ** Time 1 to Time 2 (days)	164.5 ± 81.92 76 - 341	119.8 ± 5.76 76 - 245	165.88 ± 74.69 97 - 304	218.85 ± 91.59 101 - 341
	n (%)	**n (%)**	**n (%)**	**n (%)**
Race				
White American	45 (90)	20 (95)	9 (90)	16 (84)
Black American	3 (6)	0 (0)	0 (0)	3 (16)
Asian American	2 (4)	1 (5)	1 (10)	0 (0)
Marital Status				
Single[a]	19 (38)	6 (29)	3 (30)	10 (53)
Currently married	31 (62)	15 (71)	7 (70)	9 (47)
Employment				
Employed outside home	30 (60)	13 (62)	4 (40)	13 (68)
Unemployed	20 (40)	8 (38)	6 (60)	6 (32)
Annual household income[b]				
Less than $15,000	1 (2)	1 (5)	0 (0)	0 (0)
$15,000 - $30,000	3 (6)	1 (5)	1 (10)	1 (5)
$31,000 - $45,000	9 (18)	3 (14)	2 (20)	4 (21)
$46,000 - $60,000	3 (6)	0 (0)	1 (10)	2 (11)
$61,000 - $75,000	11 (22)	3 (14)	4 (40)	4 (21)
More than $76,000	22 (44)	12 (57)	2 (20)	8 (42)

[a] including never married, divorced, widowed, and separated; [b] missing n = 1 AI Group;
*p<.10 (AI vs. Non-AI: Interval T1 - T2); p<.10 (non-AI > healthy: Age)
** p<.05 (Non-AI < Healthy: Education); p<.05 (AI vs. Healthy: Interval T1 - T2

General Health Characteristics

Table 2 displays the general health characteristics of the three groups in this study. All participants in the study were post-menopausal by self-report using the STRAW criteria (Soules, et al., 2001). One-way ANOVA revealed no differences among groups in age at menopause F (2, 46) = .173, p = .842, or in menopausal years (number of years in menopause) F (2, 47) = 1.49, p = .234. Groups did not differ in co-morbid conditions χ^2 (2, n = 50) = 3.09, p = .213. The most common co-morbid conditions were hypertension (n = 4, 8%), asthma (n = 3, 6%) and diabetes (n = 3, 6%). Use of medications that would affect cognitive functioning, including narcotics, antidepressants, and sedatives for insomnia were similar across groups at both T1 (n = 12, 24%) and T2 (n = 11, 22%).

Table 2.
General Health Characteristics

	Total Sample (N = 50)	AI Group (n= 21)	Non AI (n = 10)	Healthy Control (n = 19)
	M ± SD (Range)	M ± SD (Range)	M ± SD (Range	M ± SD (Range)
Age menopause (years)	48 ± 7 30 - 57	48 ± 7.6 30 - 56	47 ± 6.9 33 - 54	49 ± 6.6 38 - 57
Years in menopause (years)*	15 ± 9 2 - 37	15 ± 10 2 - 37	19 ± 8.6 6 - 34	12 ± 8.4 2 - 30
		n (%)	n (%)	n (%)
Comorbid conditions				
Yes	12(24)	7 (33)	3 (30)	2 (11)
No	38 (76)	14 (67)	7 (70)	17 (89)

* p < .10 (Non-AI > Healthy)

Breast Cancer Characteristics

Breast cancer specific characteristics for the AI and non-AI patient groups are found in Table 3 (pg. 53). The difference between groups in the time interval between diagnosis and T1

testing and number of surgeries was determined using the independent t-test. Pearson chi square was used to determine the differences in categorical variables of type and stage of cancer, type of surgery (mastectomy vs. lumpectomy), presence of sentinel lymph node biopsy, and treatment with radiation therapy. Participants in the AI group were tested at T1 after completing surgery and radiation therapy and before starting AI therapy. Participants in the non-AI group underwent T1 testing after completing surgery and after their consultation appointment with medical oncology during which it was established that they would not be receiving an AI. There were no significant differences between groups in the time interval from diagnosis to T1 testing $t(29) = 1.27$, $p = .229$ (AI group: M = 134 days SD 62; non-AI group: M = 190 days, SD 132). No significant group difference was found in number of surgeries ($t(29) = .781$, $p = .441$). The AI group had significantly more cases of invasive ductal carcinoma than the non-AI group $\chi^2 (3, n = 31) = 10.79$, $p = .013$ and significantly more women with Stage I cancer than the non-AI group $\chi^2 (1, n = 31) = 18.79$, $p < .01$. This is clinically congruent with a treatment plan that includes an AI. There were no differences between groups in type of surgery (mastectomy vs. lumpectomy) $\chi^2 (1, n = 31) = .465$, $p = .495$, presence of sentinel lymph node biopsy $\chi^2 (1, n = 31) = 1.92$, $p = .166$, or treatment with radiation therapy $\chi^2 (1, n = 31) = .136$, $p = .713$.

Table 3.

Breast Cancer Specific Characteristics

	Total Sample (N = 31)	AI Group (n = 21)	Non-AI (n = 10)
	M ± SD (Range)	M ± SD (Range)	M ± SD (Range)
Time since diagnosis (days)*	152 ± 92 33 - 474	134 ± 62 33 - 302	190 ± 132 78 - 474
	n (%)	n (%)	n (%)
Type of cancer *			
DCIS	12 (39)	4 (19)	8 (80)
Invasive ductal carcinoma	16 (52)	14 (67)	2 (20)
Invasive lobular carcinoma	2 (6)	2 (9)	0 (0)
Other type	1 (3)	1 (5)	0 (0)
Stage of cancer*			
0	10 (32)	1 (5)	9 (90)
I	21 (68)	20 (95)	1 (10)
Number Surgeries			
1 surgery	21 (68)	16 (76)	5 (50)
> 1 surgery	10 (32)	5 (24)	5 (50)
Type of surgery			
Lumpectomy	24 (77)	17 (81)	7 (70)
Mastectomy	7 (23)	4 (19)	3 (30)
Sentinal Node Biopsy			
Yes	27 (87)	20 (95)	7 (70)
No	4 (13)	1 (5)	3 (30)
Radiation therapy			
Yes	23 (74)	16 (76)	7 (70)
No	8 (26)	5 (24)	3 (30)

* $p<.05$

Summary of Sample Characteristics. The sample of 50 post-menopausal women consisted of mostly white, married, well-educated, post-menopausal women. The women in the non-AI group were less educated and tended to be older though the age difference did not reach statistical significance. The AI and non-AI groups (patients) were newly diagnosed with early stage breast cancer and had been in good health prior to their diagnosis. As expected, the women in the AI group were more likely to be diagnosed with invasive ductal breast cancer and more likely to be Stage I; women in the non-AI group were more likely to

be diagnosed with ductal carcinoma in situ and, therefore, have Stage 0 disease. AI and non-AI groups were similar in the type of surgery (mastectomy vs. lumpectomy) and treatment with radiation therapy. The presence and type of comorbid conditions was consistent across groups as was the type of psychoactive medications taken.

Baseline Cognitive Function (Time 1)

Table 4 (pg. 45) details the findings at T1 for DSF, DSB, COWAT, composite cognitive function scores and AFI for the three study groups. Table 5 (pg. 46) details the ANT scores at T1 for the three study groups.

For Baseline (T1) assessment was conducted after primary therapy was complete (surgery and radiation therapy) and prior to beginning AI therapy. For the non-AI group, T1 assessment took place after primary therapy was complete. For healthy controls, T1 assessment took place after study consent was obtained.

Differences in objective and self-report measures of cognitive function at baseline were assessed using ANOVA. There were group differences trending toward significance in DSB at baseline with the healthy control group (M = 5.21, SD = 1.03) scoring higher (more digits recited backward in the correct order) than the non-AI group (M = 4.20, SD = 1.14), F (2, 47) = 2.56, p= .088. There were no differences among the three groups at baseline in DSF, COWAT, and there were no differences in the self-report of cognitive function, the AFI, at baseline. When the composite cognitive function score was calculated from the z scores of the DSF, DSB, and COWAT, there were no differences in objective cognitive function at baseline.

There was no difference in overall all reaction time or accuracy among groups at baseline (T1) in the ANT. When reaction time in individual networks (alerting, orienting and executive control) was assessed, the AI and non-AI groups did not differ at T1 in the alerting $t(28) = .679$, $p = .50$ and orienting $t(28) = 1.31$, $p = .202$ networks and neither group differed from the healthy control group. In the executive control network, however, there was a difference between the AI ($M = 124$, $SEM = 9.52$) and the non-AI groups ($M = 93.8$, $SEM = 13.15$) at T1 ($t(28) = 1.85$, $p = .08$) in reaction time with the AI group exhibiting a slower response than the non-AI group. Assessment of accuracy in the individual networks revealed no group differences.

Table 4.
Means and Standard Deviations of Attention and Memory Measures at Time 1

	Total Sample (N = 50) M ± SD	AI Group (n= 21) M ± SD	Non-AI (n = 10) M ± SD	Healthy (n = 19) M ± SD
MMSE	29.6 ± 0.64	29.5 ± 0.68	29.7 ± 0.68	29.5 ± 0.61
DSF	6.52 ± 1.14	6.38 ± 1.20	6.90 ± 1.37	6.47 ± 0.96
DSB	4.82 ± 1.19	4.76 ± 1.26	4.20 ± 1.14*	5.21 ± 1.03
COWAT	43.46 ± 12.30	40.38 ± 11.01	45.30 ± 13.18	45.89 ± 13.07
Composite Cognitive Function Score	.0000 ± 2.21	-.4204 ± 2.25	-.0402 ± 2.27	.4858 ± 2.15
AFI	8.13 ± 1.33#	7.99 ± 1.58	8.27 ± 1.29	8.21 ± 1.11
Attentional Lapse	7.95 ± 1.71	7.77 ± 2.26	8.2 ± 1.21	8.02 ± 1.30
Effective Interpersonal Relations	8.15 ± 1.65	7.87 ± 1.93	8.70 ± 1.27	8.16 ± 1.51
Effective Action	8.14 ± 1.41	8.02 ± 1.46	8.11 ± 1.67	8.28 ± 1.28

MMSE: Mini-Mental State Examination; DSF: Digit Span Forward; DSB: Digit Span Backward; COWAT: Controlled Oral Word Association Test; AFI: Attentional Function Index
Composite Cognitive Function Score: zDSF + zDSB + zCOWAT
*p < .10; non-AI < healthy controls
Missing n = 1 from AI group for AFI

Table 5.

Attention Network Test (N = 49) Time 1: Means and Standard Error of the Mean (SEM)

	AI Group (n = 20) Mean ± SEM (Range)	Non-AI (n = 10) Mean ± SEM (Range)	Healthy (n = 19) Mean ± SEM (Range)
	Accuracy		
Alerting network	.0007 ± ..0039 (-.03 - .03)	.0000 ± .0044 (-.03 - .01)	-.0005 ± .0031 (-.01 - .03)
No cue	.9860 ± .0034 (.96 - 1.00)	.9783 ± .0144 (.85 - 1.00)	.9770 ± .0135 (.74 - 1.00)
Double cue	.9853 ± .0029 (.95 - 1.00)	.9783 ± .0116 (.88 - 1.00)	.9775 ± .0152 (.71 - 1.00)
Orienting network	-.0098 ± .0035 (-.04 - .02)	-.0065 ± .0029 (-.03 - .00)	-.0021 ± .0021 (-.01 - .01)
Center cue	.9860 ± .0042 (.93 - 1.00)	.9823 ± .0012 (.88 - 1.00)	.9784 ± .0143 (.74 - 1.00)
Spatial cue	.9958 ± .0025 (.96 - 1.00)	.9888 ± .0098 (.90 - 1.00)	.9805 ± .0137 (.74 - 1.00)
Executive control network	-.0174 ± .0063 (-.11 - .01)	-.0272 ± .0193 (-.20 - .00)	-.0560 ± .0422 (-.81 - .02)
Congruent flanker	.9960 ± .0012 (.96 - 1.00)	.9926 ± .0207 (.88 - 1.00)	.9975 ± .0066 (.96 - 1.00)
Incongruent flanker	.9786 ± .0062 (.88 - 1.00)	.9654 ± .0258 (.75 - 1.00)	.9415 ± .0421 (.17 - 1.00)
Overall Accuracy	.99 ± .027 .96 - 1.00	.98 ± .012 (.88 - 1.00)	.98 ± .061 (.73 - 1.00)
	Reaction Time (msec)		
Alerting network	35.66 ± 4.90 (3.50 - 70.92)	29.40 ± 8.46 (-30.75 - 63.09)	44.81 ± 6.55 (-19.43 - 103.87)
No cue	739.93 ± 24.12 (588.53 - 958.07)	701.29 ± 27.93 (598.32 - 855.35)	694.75 ± 17.40 (556.10 - 844.69)
Double cue	704.27 ± 25.77 (536.60 - 951.83)	671.89 ± 31.90 (578.51 - 886.11)	649.94 ± 17.14 (516.83 - 777.15)
Orienting network	40.12 ± 4,80 (-0.85 - 86.19)	52.52 ± 9.45 (-22.71 - 84.37)	52.10 ± 7.73 (-25.72 - 98.03)
Center cue	718.13 ± 25.57 (569.88 - 955.87)	683.84 ± 28.51 (575.64 - 875.29)	676.63 ± 16.93 (540.73 - 832.64)
Spatial cue	678.01 ± 23.91 (537.99 - 869.68)	631.32 ± 26.10 (548.29 - 826.11)	624.53 ± 18.10 (451.10 - 769.39)
Executive control network	123.99 ± 9.52* (49.23 - 189.36)	93.78 ± 13.15 (23.58 - 175.00)	119.64 ± 12.67 (34.56 - 248.00)
Congruent flanker	664.28 ± 25.14 (512.53 - 934.88)	639.81 ± 33.33 (533.13 - 877.89)	617.36 ± 15.53 (579.05 - 922.95)
Incongruent flanker	788.27 ± 26.60 (619.38 - 986.88)	733.59 ± 24.24 (657.18 - 901.47)	737.00 ± 22.70 (579.05 - 922.95)
Overall Reaction Time	703.67 ± 24.48 (559.24 - 921.02)	663.93 ± 27.56 (588.86 - 853.79)	654.08 ± 73.54 (513.45 - 787.07)

* $p < .10$: Executive Control Network: AI > non-AI

Research Question 1

Research Question 1: Is there a measureable decline in cognitive function, as assessed by objective and subjective measures of attention, working memory, and verbal memory, in post-menopausal women treated for breast cancer at 3 months after initiation of AI therapy?

To answer research question one, data from the AI group were examined using the paired t-test for T1 and T2 for individual objective measures of cognitive function (DSF, DSB, and COWAT), composite cognitive function scores, and ANT scores (reaction time and accuracy overall and for each of the three networks measured) to determine the presence of a significant change in objective cognitive function measures over time. The paired t-test was also performed using the AFI mean scores to determine perceived changes in cognitive function over time. Attrition between T1 and T2 results in the total number of participants available to answer research question one is n = 16 for individual objective cognitive function measures, composite cognitive function scores and the AFI. There were 15 participants who completed the ANT at both time points; one participant's data was not collected due to a computer malfunction.

Paired t-tests revealed significant differences between T1 and T2 in the AI group with significant improvement over time in the DSF (paired $t(15) = 2.74$, $p = .02$) and in COWAT (paired $t(15) = 2.06$, $p = .06$). When individual objective measures of cognitive function were transformed into the composite cognitive function score (DSF, DSB and COWAT) there was no significant difference between T1 and T2 in the AI group (paired $t(15) = .08$, $p = .94$). These results are detailed in Table 4 (pg. 45) and Table 6 (pg. 48). Overall reaction time (paired $t(14) = .28$, $p = .78$) and accuracy (paired $t(14) = .000$, $p = 1.0$) on the ANT

was unchanged from T1 to T2 in the AI group. When considering the three individual networks measured by the ANT, the AI group demonstrated significantly faster reaction times in the executive control network at T2 testing (paired t (14) = 2.52, p = .03). There were no significant differences between T1 and T2 in the alerting or orienting networks in either reaction time or accuracy. Tables 5 (pg. 56) and 7 (pg 59) detail these findings.

Table 6.
Means and Standard Deviations of Attention and Memory Measures at Time 2

	Total Sample (N = 37) M ± SD	AI Group (n= 16) M ± SD	Non AI (n = 8) M ± SD	Healthy control (n = 13) M ± SD
DSF	6.76 ± 1.46	6.69 ± 1.25	6.50 ± 1.51	6.47 ± 0.96
DSB	5.35 ± 1.16	5.00 ± 1.03*	5.13 ± 0.99	5.92 ± 1.26
COWAT	43.54 ± 12.40	43.94 ± 12.60	44.75 ± 11.87	45.89 ± 13.07
Composite Cognitive Function Score	.0000 ± 2.38	-.5603 ± 2.31	-.5154 ± 1.39	1.01 ± 2.74
AFI	7.90 ± 1.36	7.38 ± 1.73	8.40 ± 0.97	8.32 ± 0.65
Attentional Lapse	7.53 ± 2.18	6.60 ± 2.61	7.79 ± 2.19	8.51 ± 0.87
Effective Interpersonal Relations	7.77 ± 1.86	7.21 ± 2.40	7.92 ± 1.70	8.38 ± 0.83
Effective Action	7.92 ± 1.29	7.60 ± 1.59	8.14 ± 1.24	8.22 ± 0.81

DSF: Digit Span Forward; DSB: Digit Span Backward; COWAT: Controlled Oral Word Association Test; AFI: Attentional Function Index; Composite Cognitive Function Score: zDSF + zDSB + zCOWAT
* p< .10: DSB: AI < Healthy control

Table 7.

Attention Network Test (N = 36) Time 2: Means and Standard Error of the Mean (SEM)

	AI Group (n = 15) Mean ± SEM (Range)	Non-AI (n = 8) Mean ± SEM (Range)	Healthy (n = 13) Mean ± SEM (Range)
	Accuracy rates		
Alerting network	-.0020 ± .0035 (-.03 - .03)	.0000 ± .0036 (-.01 - .01)	-.0041 ± .0023 (-.03 - .00)
No cue	.9900 ± .0056 (.92 - 1.00)	.9917 ± .0035 (.97 - 1.00)	.9949 ± .0024 (.97 - 1.00)
Double cue	.9920 ± .0047 (.93 - 1.00)	.9917 ± .0035 (.97 - 1.00)	.9990 ± .0010 (.97 - 1.00)
Orienting network	-.0072 ± .0152 (-.04 - .01)	.0000 ± .0062 (.03 - .01)	.0000 ± .0021 (-.01 - .01)
Center cue	.9856 ± .0056 (.93 - 1.00)	.9917 ± .0043 (.97 - 1.00)	.9938 ± .0019 (.99 - 1.00)
Spatial cue	.9928 ± .0030 (.96 - 1.00)	.9917 ± .0035 (.97 - 1.00)	.9938 ± .0024 (.97 - 1.00)
Executive control network	-.0175 ± .0078 (-.12 - .01)	-.0150 ± .0057 (-.05 - .01)	-.0055 ± .0031 (0.01 - .02)
Congruent flanker	.9963 ± .0022 (.97 - 1.00)	.9990 ± .0010 (.99 - 1.00)	.9969 ± .0017 (.98 - 1.00)
Incongruent flanker	.9788 ± .0097 (.85 - 1.00)	.9840 ± .0052 (.95 - 1.00)	.9914 ± .0029 (.97 - 1.00)
Overall Accuracy	.9900 ± .0039 (.94 - 1.00)	.9888 ± .0023 (.98 - 1.00)	.9946 ± .0018 (.98 - 1.00)
	Reaction Time (msec)		
Alerting network	35.86 ± 7.31 (-18.83 - 74.67)	39.22 ± 6.07 (22.23 - 71.16)	52.72 ± 7.95 (10.60 - 107.79)
No cue	715.50 ± 35.20 (485.21 - 943.97)	679.39 ± 25.54 (611.84 - 826.46)	708.66 ± 15.73 (626.09 - 850.56)
Double cue	679.65 ± 34.33 (496.79 - 939.60)	640.17 ± 25.35 (587. 79 - 804.23)	655.94 ± 18.56 (551.82 - 785.67)
Orienting network	49.57 ± 5.10 (27.89 - 87.95)	52.23 ± 11.69 (1.84 - 94.92)	42.02 ± 7.68 (95.85 - 42.02)
Center cue	695.61 ± 36.96 (500.07 - 965.28)	664.11 ± 24.51 (597.28 - 807.25)	679.61 ± 16.00 (589.05 - 792.68)
Spatial cue	646.04 ± 34.85 (458.79 - 892.59)	611.89 ± 34.37 (534.00 - 741.90)	637.59 ± 18.02 (547.90 - 776.06)
Executive control network	107.50 ± 12.31 (28.92 - 232.00)	91.45 ± 19.01 (-.15.36 - 155.47)	117.73 ± 17.73 (50.92 - 292.11)
Congruent flanker	644.79 ± 34.29 (451.25 - 878.80)	618.96 ± 35.16 (533.42 - 817.55)	630.57 ± 14.15 (554.04 - 748.20)
Incongruent flanker	752.29 ± 38.99 (550.48 - 1028.07)	710.42 ± 19.67 (643.96 - 802.19)	748.30 ± 27.61 (622.50 - 980.82)
Overall Reaction Time	676.57 ± 35.06 (483.13 - 926.81)	641.49 ± 24.01 (585.72 - 784.35)	663.88 ± 16.69 (572.55 - 796.20)

Missing n = 1 from AI group

The paired t-test was performed using the AFI mean scores to determine perceived changes in cognitive function over time in the AI group. This group demonstrated a significant decrease in score on the AFI over time $t(15) = 2.488$, $p = .03$ suggesting that the AI group perceived a decline in cognitive function over time. Considering the three subscales of the AFI, the AI group demonstrated significant increase in perception of attentional lapses $t(15) = 2.386$, $p = .03$ at T2. There were no changes over time in the AFI subscales of effective action and effective interpersonal relations. Tables 4 (pg. 55) and 6 (pg. 58) detail these findings.

Summary Question 1

The AI group demonstrated improvement on selected objective measures of cognitive function, namely the DSF and the COWAT. When scores for these measures and the DSB were transformed to a composite cognitive function score, changes over time were not significant. Performance on the Attention Network Test (ANT) was unchanged between T1 and T2 for overall reaction time and accuracy however there was a significant increase in mean accuracy in the double cue condition of the alerting network (paired $t(14) = 2.36$, $p = .03$) and a decrease in mean reaction time for the executive control network (paired $t(14) = 2.52$, $p = .025$) of the ANT suggesting an improvement in performance.

Despite improvement over time in objective measures of cognitive function, the AI group demonstrated a perceived decrease in cognitive function only in the self-report AFI. Examination of the AFI subscales showed that there was a significant increase in perception of attentional lapses at T2. Taken together, these data suggest that while the AI group may experience improvement in select objective measures of cognitive function over time, this

was incongruent with their perception. They perceived that their cognitive function, specifically their ability to focus attention, was worsening over time.

Research Question 2

Research Question 2: Compared with women treated for breast cancer without AI, do women treated with AI for breast cancer show greater impairment at 3 months in directed attention, working memory, and verbal memory?

To answer research question 2, data from objective and subjective measures in the AI and the non-AI patient groups were examined. using independent t-tests to determine differences between groups at Time 1 (T1) and Time 2 (T2). Repeated measures ANOVA using a 2 X 2 factorial design, AI vs. non-AI by T1 vs. T2 was utilized where appropriate to determine significant group by time interaction and any main effects of group and time.

Objective Measures of Cognitive Function

At T1, the non-AI group performed better on the DSF and COWAT and the AI group performed better on the DSB but these mean differences did not reach significance. At T2, the AI group performed slightly better than the non-AI group in the DSF and the non-AI group had slightly better performance in the DSB and COWAT but again, none of these mean differences were significant.

The AI group improved over time in all three measures with significant improvements in the DSF (paired $t(15) = 2.74$, $p = .02$) and the COWAT (paired $t(15) = 2.06$, $p = .06$). Interestingly, the non-AI group worsened over time in both the DSF and COWAT but similar to the AI group, improved in the DSB. Changes in these objective measures in the non-AI group were not statistically significant.

Repeated measures ANOVA in a 2 (AI vs. non-AI group) X 2 (T1 vs. T2) design was used to evaluate group, time, and interaction effects. There was an interaction effect of time and group (Figure 1) for the DSF ($F(1,22) = 2.67$, $p = .07$) with the AI group improving over time but no time ($F(1,22) = .000$, $p = 1.0$) or group ($F(1,22) = .410$, $p = .529$) effects for the DSF. There were no time, group, or interaction effects noted for the DSB or COWAT.

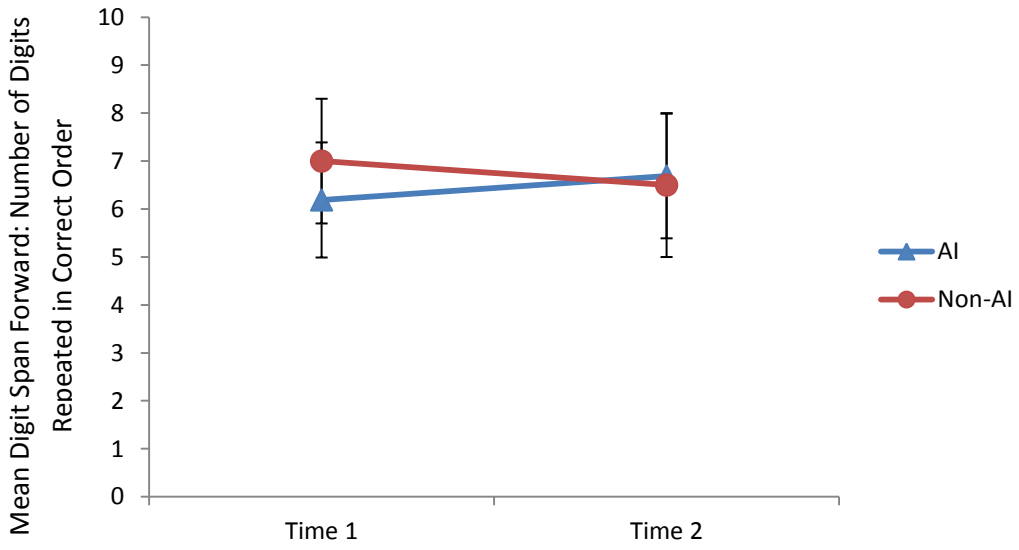


Figure 1: Mean Digit Span Forward T1 and T2 for AI and Non-AI Groups

When the z scores of the DSF, DSB, and COWAT were summed to produce the composite cognitive function score, independent-samples t-test were conducted to compare the composite cognitive function scores between patient groups and revealed no significant differences between the AI group (M = -.42, SD = 2.25) and the non-AI group (M = -.04, SD = .72) at T1. Similarly, no significant differences between the AI group (M = -.56, SD = 2.31) and the non-AI group (M = -.52, SD = 1.39; t (22) = -.050, p = .960) were noted at T2.

Figure 2 (pg. 54) illustrates that the objective composite cognitive function score for the AI group did not change significantly over time (paired t (15) = .078, p = .939) and

although the non-AI group worsens over time, this change is not statistically significant (paired t (7) = 1.039, p = .333). Repeated measures ANOVA revealed no interaction effect between group and time *F* (1,22) = 1.45, p = .242 and no main effect for either time *F* (1,22) = 1.6, p = .219 or group *F* (1,22) = .341, p = .565.

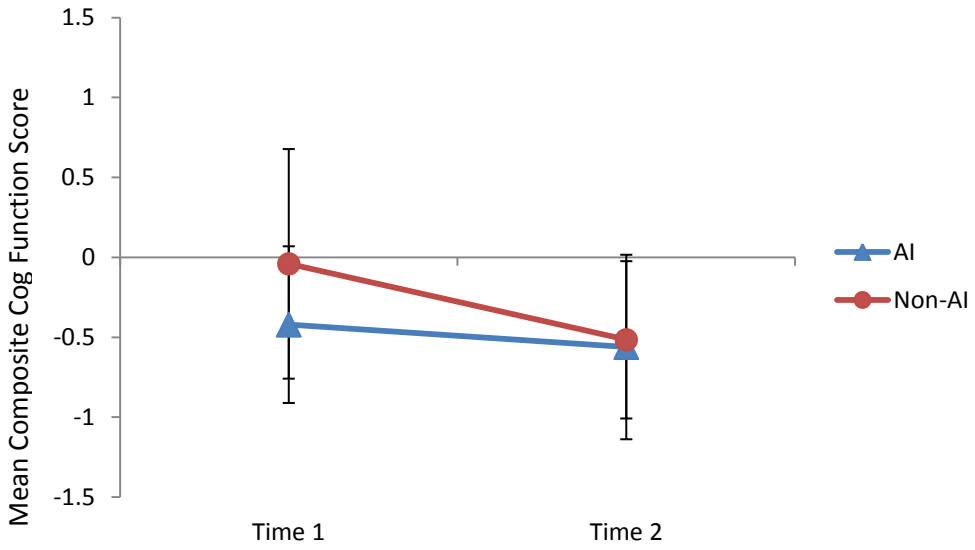


Figure 2: AI and non-AI Group Composite Cognitive Function Scores Over Time

Attention Network Test (ANT)

Differences in performance in the Attention Network Test between the AI and non-AI groups were examined first by assessing the differences at T1 and T2 in overall reaction times and accuracy. Subsequently, differences between the AI and non-AI groups were assessed in each of the three ANT networks (alerting, orienting, executive control). Behavioral performance (reaction time and accuracy) in the three networks and on the cue conditions used in each network were assessed in a manner consistent with the evaluation of overall reaction time and accuracy. Table 5 (pg. 46) and Table 7 (pg. 49) detail results for ANT at T1 and T2 respectively.

ANT: Differences in Overall Reaction Time and Accuracy

At T1, the AI group was slower in reaction time and had greater accuracy in response than the non-AI group but independent t-tests showed no significant differences in overall mean reaction time ($t(28) = .998$, $p = .327$) or accuracy ($t(28) = .647$, $p = .506$). Similarly at T2, the AI group was slower in reaction time and more accurate in response but there were no significant differences in overall mean reaction time $t(21) = .681$, $p = .503$ or mean accuracy $t(21) = .222$, $p = .827$.

There were no significant differences in reaction time between T1 and T2 in the AI group ($t(14) = .283$, $p = .781$) or in the non-AI group ($t(7) = .384$, $p = .712$). No significant change in accuracy over time was noted in either the AI ($t(14) = .000$, $p = 1.0$) or non-AI group ($t(7) = 1.9$, $p = .104$).

Repeated measures ANOVA examining reaction time revealed no interaction between group and time $F(1, 21) = .00$, $p = .996$ and no main effect for either group $F(1, 21) = .642$, $p = .432$ or time $F(1, 21) = .149$, $p = .703$. Repeated measures ANOVA examining accuracy revealed no significant interaction between group and time ($F(1,21) = 1.25$, $p = .277$ and no main effect for either group $F(1,21) = .078$, $p = .782$ or time $F(1, 21) = 1.25$, $p = .277$. Figure 3 (pg. 56) illustrates ANT reaction times for AI and non-AI groups in milliseconds (msec) at T1 and T2; Figure 4 (pg. 56) illustrates ANT mean accuracy for these groups.

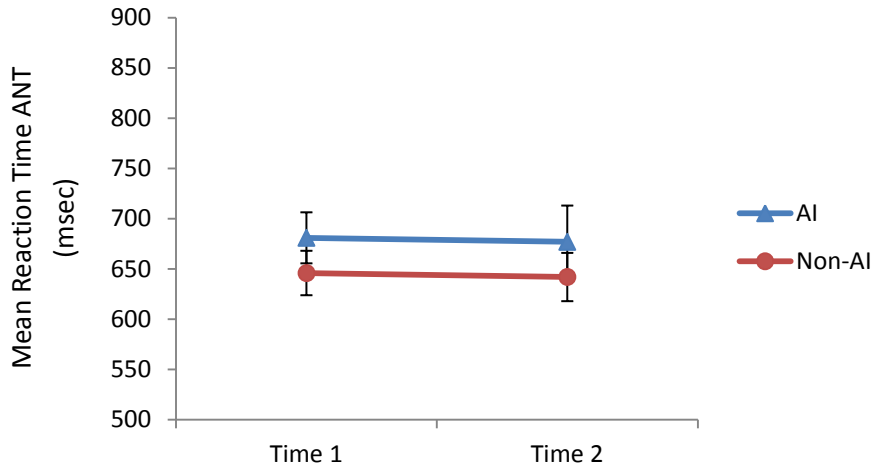


Figure 3: Attention Network Test: AI and non-AI Group Overall Mean Reaction Time. Error bars represent standard errors. Points represent reaction time.

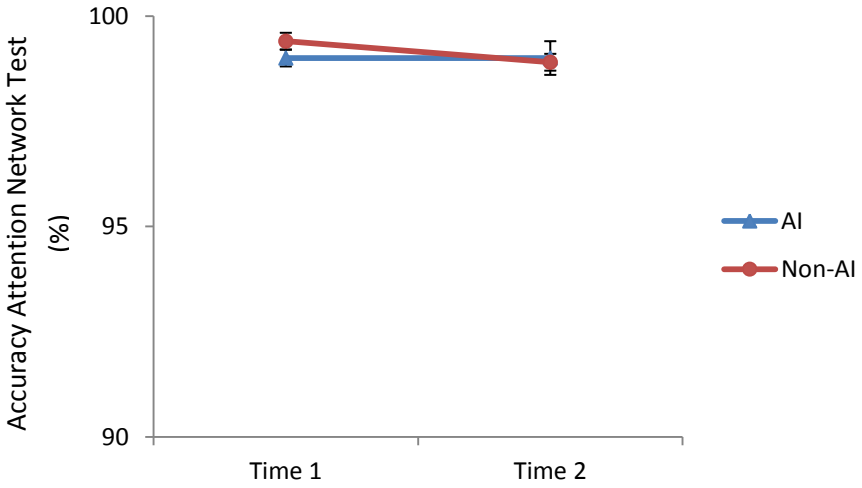


Figure 4: Attention Network Test: Accuracy for AI and non-AI Group. Error bars represent standard errors. Points represent percent of accuracy.

ANT: Group Differences in Alerting, Orienting and Executive Control Networks

Each of the three networks in the ANT were examined for group differences.

Alerting Network

The alerting network is represented by a contrast between double-cue and no-cue conditions. Functionally, this represents the extent to which cueing a participant for the impending appearance of the target stimulus affects reaction time and accuracy. To calculate the alerting network score, double-cue conditions are subtracted from no-cue conditions (J. Fan, et al., 2002).

Independent t-tests reveal no significant differences in reaction time between AI and non-AI groups in the alerting network at T1 ($t(28) = .679$, $p = .880$) or at T2 ($t(21) = .306$, $p = .763$). Similarly, there were no differences seen in accuracy between AI and non-AI groups in the alerting network at T1($t(28) = .104$, $p = .599$) or T2 ($t(21) = .368$, $p = .717$). The similarity of these two groups persisted for both reaction time and accuracy with no significant differences noted between groups when specific conditions of no-cue and double-cue were examined with independent t-tests (see Table 5, pg. 46).

Neither group showed significant changes over time in mean reaction time or mean accuracy in the attention network as a whole. In the no-cue condition, mean reaction time and mean accuracy improved in both groups over time but neither group demonstrated statistically significant differences. In the double-cue condition, both groups showed improved RT over time, though this was not statistically significant. Mean accuracy improved over time in both the AI and non-AI groups in the double-cue condition; the

increase in mean accuracy in the AI group over time was significant (paired t(14) = 2.36, p =.03).

Repeated measures ANOVA revealed a time effect in the double cue condition F(1,21) = 4.63, p <.05 with both groups increasing accuracy over time likely due to practice effect. No main effect for group or interaction effect between group and time was observed. This is illustrated in Figure 5.

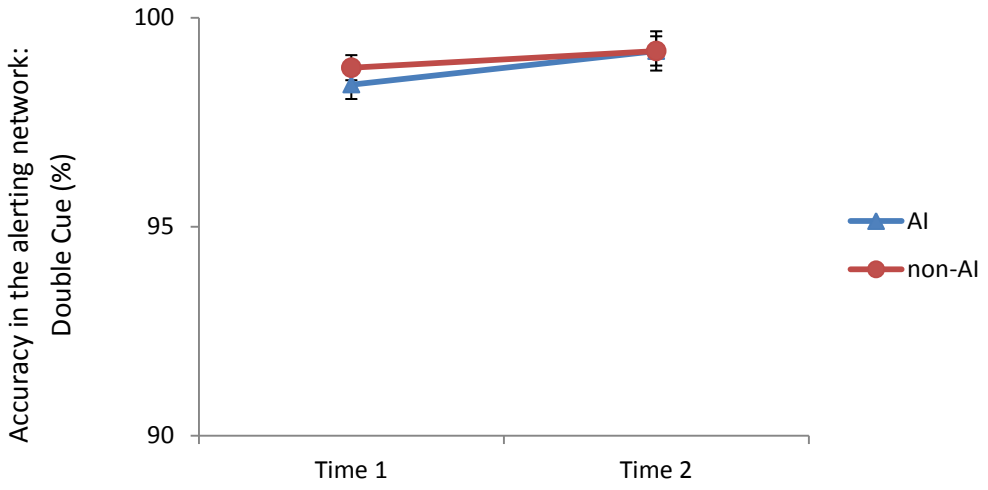


Figure 5: Accuracy of Double Cue Conditions. Error bars represent standard errors. Points represent percent of accuracy in double cue condition.

Orienting Attention Network

The orienting network function is defined by a cue presented just prior to the target stimulus that serves to direct the participants' attention to the location in space in which the target stimulus will be presented. Both center and spatial cues serve this function but only the spatial cue (up or down) gives the participant the spatial information needed to direct attention. The orienting network function is calculated by subtracting the mean of the spatial cue conditions from the mean of the center cue conditions (Fan et al., 2002).

Mean reaction times of the AI group vs. non-AI group at T1 ($t(28) = 1.307$, $p = .518$) and at T2 ($t(21)$, $p = .811$) reveal no significant differences between the groups at either time point in the orienting network. Similarly, independent t-tests comparing accuracy of the AI and non-AI groups at T1 ($t(28) = .626$, $p = .537$) and at T2 ($t(21) = 1.03$, $p = .313$) showed no significant differences between groups at either time point.

The AI group slowed in mean reaction time in the orienting network from T1 to T2 but this difference was not statistically significant (paired $t(14) = 1.44$, $p = .17$). Accuracy increased slightly over time in this group but the difference was not statistically significant (paired $t(14) = .29$, $p = .78$). The non-AI group showed no statistically significant difference between T1 and T2 in mean reaction time (paired $t(7) = .015$, $p = .99$) and improved slightly, but not significantly in mean accuracy (paired $t(7) = .814$, $p = .44$).

Repeated measures ANOVA showed no significant group ($F(1,21) = .842$, $p = .369$), time ($F(1,21) = .683$, $p = .418$) or interaction effect ($F(1,21) = .640$, $p = .433$) in reaction time. Accuracy showed a similar pattern with no significant group ($F(1, 21) = 1.37$, $p = .254$), time ($F(1, 21) = .586$, $p = .453$) or group X time interaction effects ($F(1, 21) = .162$, $p = .692$) noted.

The effect of center and spatial cues on reaction time and accuracy in the orienting attention network for the AI and non-AI groups was examined. At T1 and T2, the AI group was slower in mean reaction and less accurate than the non-AI group for the center cue condition but this difference was not significant at either time point. In the spatial cue condition, the AI group was slower and more accurate at both time points than the non-AI group but these differences were not statistically significant at either time point.

It is possible that these small differences suggest a subtle compromise in the AI group in which speed is traded for accuracy in the spatial conditions. At both time points, it seems that the AI group may rely more on the spatial cue condition to respond accurately to the stimulus.

In within group analyses, the AI group showed no significant change in mean reaction time between T1 and T2 for either cue type. Mean accuracy was affected slightly with a decrease over time in the spatial cue condition. This was trending toward statistical significance ($t(14) = 1.74$, $p = .104$), but it should be noted that the accuracy at both time points was on average between 99 and 100%. Likewise, the non-AI group demonstrated no significant differences in reaction time between T1 and T2 but did show an decrease in mean accuracy in the spatial cue condition that was statistically significant (paired $t(7) = 2.65$, $p = .033$). While both groups had lower accuracy over time, accuracy in the non-AI group significantly worsened over time and remained below the accuracy of the AI group. Again it should be noted that the accuracy at both time points was on average > 99%. The differences over time in accuracy for both groups in the ANT overall are very subtle and accuracy remains high. The high accuracy of performance by both groups may represent a ceiling effect that could limit the usefulness of accuracy in this population in this particular measure.

Executive Control Network

The executive control network responds to conflict in attention. In this task, the executive control network is represented by the degree to which incongruent flankers (arrows in the opposite direction) versus congruent flankers (arrows in the same direction) or neutral flankers (straight lines) interfere with the participant's response to the target stimulus. The

executive control network is calculated by subtracting the mean reaction time of all congruent flanker conditions summed across all cue types from the mean reaction time of incongruent flanking conditions also summed across all cue types. Accuracy is calculated in a similar manner (Fan et al., 2002).

Between group analyses of reaction time at T1 showed a trend toward significance ($t(28) = 1.85$), $p = .08$) with the AI group displaying a slower reaction time (M = 124 msec, SEM = 9.52) than the non-AI group (M = 93.78 msec, SEM = 13.15) (Table 5, pg. 46). This pattern is similar at T2 but the difference is not statistically significant ($t(21) = .736$, $p = .670$). Mean accuracy is slightly lower for the AI group at both time points but the difference is not statistically significant. (Table 5, pg. 46 and Table 7, pg. 49).

Both groups demonstrated significant improvement in reaction time from T1 to T2 but this was statistically significant only within the AI group. Mean accuracy was slightly lower in both groups at T2 when compared to T1 but not to a significant extent. This suggests that for the executive control network, there may be trade-off with greater speed leading to less accurate responses.

Repeated measures ANOVA showed a significant time effect ($F(1, 21) = 5.64$, $p < .05$) largely driven by the decrease in mean reaction time from T1 to T2 in the AI group. No significant group or interaction effects were noted.

An analysis of the effect of flanker conditions on reaction time and accuracy in the executive control network was performed for each flanker type (congruent, incongruent) to examine differences between the AI and non-AI groups Independent t-tests performed for mean reaction time and accuracy in the congruent (arrows same direction) condition showed

that there were no significant differences between the AI and non-AI groups in reaction time and accuracy in this condition of the executive control network at T1 or T2. Paired t-tests to examine within-group differences (AI and non-AI groups) over time showed no significant influence of the congruent flanker condition on reaction time or accuracy in either group.

The incongruent condition (arrows in opposite direction) was examined in a likewise fashion. Independent t-tests performed to compare the AI and non-AI groups at T1 and T2 show no significant difference between the groups for reaction time or accuracy at either time point. Paired t-tests to examine within-group differences over time revealed no significant influence of the incongruent condition on reaction time or accuracy in either group in the executive control network.

Summary Research Question 2

There were no statistically significant differences between the AI and non-AI groups at T1 (baseline) or T2 in the DSF, DSB, or COWAT. The AI group improved over time in all three measures with statistically significant improvement in DSF and COWAT. The non-AI group improved over time in the DSB but unexpectedly worsened over time in the DSF and COWAT although none of these changes reached statistical significance. Repeated measures ANOVA revealed a group X time interaction in DSF that was likely driven by the improvement in performance demonstrated by the AI group.

There were no statistically significant differences between or within these groups at either time point in the composite cognitive function score. Predictably, repeated measures ANOVA showed no main effect for group or time and no interaction effect.

The Attention Network Test (ANT) scores for overall mean reaction time and mean accuracy were not statistically different between the AI and non-AI groups at T1 or T2 although at both time points, the AI group was slower in reaction time but more accurate in response. Changes over time, were not significantly different in either group. Repeated measures ANOVA was performed for both reaction time and accuracy revealing no main effect for time or group and no interaction effect between time and group.

The three networks of the ANT, alerting, orienting, and executive control, were examined for between and within group differences in the AI and non-AI groups. In the alerting network, both groups improved over time with faster reaction times and higher accuracy at T2 but there were no significant differences between groups. The AI group significantly improved over time in mean accuracy in the double-cue condition. In the orienting network, the groups were similar and slowed over time but their mean accuracy improved. The cue conditions revealed only one significant change over time: the non-AI group decreased significantly in accuracy in the spatial-cue condition. In the executive control network, the AI group was significantly slower than the non-AI group at baseline. Over time, the AI group improved significantly in mean reaction time but still remained slower than the non-AI group. Both groups had decreased accuracy over time. There was a main effect for time largely driven by the improvement in reaction time in the AI group. Flanker condition did not affect performance by either group in the executive control network.

Research Question 3

Research Question 3: Compared with healthy controls, do women with breast cancer – both AI treated and non-AI treated – show greater impairment at Time 1 (T1) and Time 2 (T2)?

One-way ANOVA was used to explore differences among the AI, non-AI, and healthy control groups at T1 and T2. When group differences were established by ANOVA, post-hoc tests and independent t-tests were used to further explore differences. Paired t-tests were used to explore within-group differences over time in all three groups. Repeated measures ANOVA in a 3 (AI, non-AI, healthy group) X 2 (T1, T2) model was used to examine main effects of time, group, or interaction effects.

The only differences at baseline among groups was a trend toward significance in digit span backward (DSB) with the healthy control group scoring higher (more digits correctly repeated backwards) than the non-AI group (F (2, 47) = 2.56, p= .088). There were no differences among the three groups at baseline in digit span forward (DSF), controlled word association test (COWAT), and there was no difference among groups in the attentional function index (AFI) at baseline. When the composite cognitive function score was calculated from the z scores of the DSF, DSB, and COWAT, there were no differences in objective cognitive function at baseline.

There was no difference in overall mean reaction time (F (2, 48) = 1.51, p = .231) or mean accuracy (F (2, 48) = .254, p = .777) among the three groups at baseline (T1) in the ANT as assessed by ANOVA (see Table 5, pg. 46). The AI group had the slowest mean reaction time (M = 704 msec, SEM = 24.5) but was the most accurate in response with the

highest mean accuracy (M = 98.9%, SEM = .003); the healthy group had the fastest reaction time (M = 654 msec, SEM = 16.9) but the lowest mean accuracy (M = 97.9%, SEM = .061). When individual networks (alerting, orienting and executive control) were assessed, there remained no statistically significant difference among the three groups in mean reaction time or mean accuracy. As discussed in research question 2, in the executive control network, there was a trend toward a significant difference in mean reaction times between the AI and the non-AI groups at T1 (t (28) = 1.85, p = .08) with the AI group (M = 124 msec, SEM = 9.52) exhibiting a slower reaction time than the non-AI group (M = 93.8 msec, SEM 13.15) but no statistically significant difference in mean accuracy. Table 4 (pg. 45) details the findings at T1 for DSF, DSB, COWAT, composite cognitive function scores and AFI for the three study groups. Table 5 (pg. 46) details the ANT scores at T1 for the three study groups.

At T2, there were no significant differences among groups in the controlled oral word association test (COWAT) or the digit span forward (DSF). There was a difference among groups trending toward significance in the digit span backward (DSB) at T2 ($F(2,34) = 2.70$, p = .082). Post hoc comparisons using the Tukey HSD test indicated that the difference between the mean DSB score for the AI group (M = 5.0, SEM = .258) and the healthy control group (M = 5.92, SEM = .348) approached significance (p = .08). The non-AI group (M = 5.13, SEM = .350) did not differ significantly from either the AI or the healthy control group. When differences among composite cognitive function scores were assessed using one-way ANOVA, there were no statistically significant differences in composite cognitive function scores between the groups at T2 ($F(2, 34) = 1.88$, p = .168). Independent t-test performed to compare the AI to the healthy control group revealed a trend in the difference in the composite cognitive function score (t(27) = 1.67, p = .106) with the AI group showing a

lower mean composite score (M = -.560, SEM = .577) than the healthy control group (M = 1.01, SEM = .760).

Attention Network Test (ANT): Overall Reaction Time and Accuracy

The AI group remained slower (M = 676.57msec, SEM = 35.1) than the non-AI (M = 641.49 msec, SEM = 24.01) and healthy control (M= 663.9, SEM = 16.7) groups but there were no statistically significant differences among the groups (F (2, 33) = .317, p = .730) in mean reaction time. No group differences in mean accuracy were seen at T2 (F (2,33) = .91, p = .414) and all three groups had on average $\geq$ 98% accuracy.

All three groups improved in reaction time between T1 and T2 but these improvements were not statistically significant. The AI group maintained a stable mean accuracy over time and the healthy control group improved slightly in mean accuracy but this was not a statistically significant change. The non-AI group had a slight decrease in accuracy that trended toward significance (paired t(7) = 1.87, p = .104) but it should be noted that the accuracy at T2 was still high at about 98.9%.

Repeated measures ANOVA for reaction time (Fig. 6, pg. 67) demonstrated no significant main effect for group (F (2,33) = .450, p = .642), time (F (1,33) = 1.03, p = .319) and no interaction effect between group and time (F (2,33) = .264, p = .769). Similarly, for accuracy (Fig. 7, pg. 67), there was no significant main effect for group (F(2,33) = .175, p = .840) or time (F(1,33) = .365, p = .55) and no interaction effect between group and time (F (2,33) = .953, p = .396).

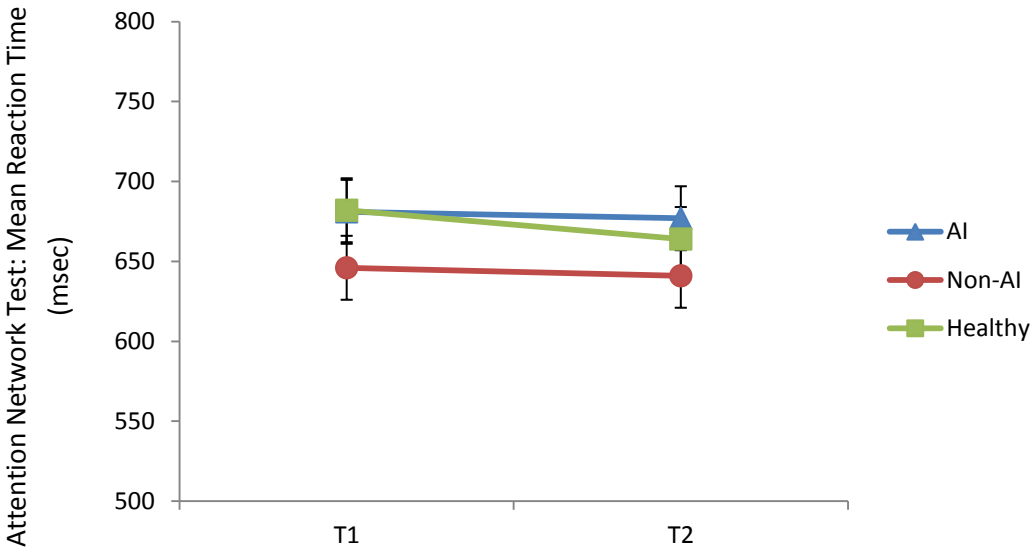


Figure 6: Attention Network Test (ANT): Mean Reaction Time All Groups. Error bars represent standard error. Points represent reaction time in milliseconds.

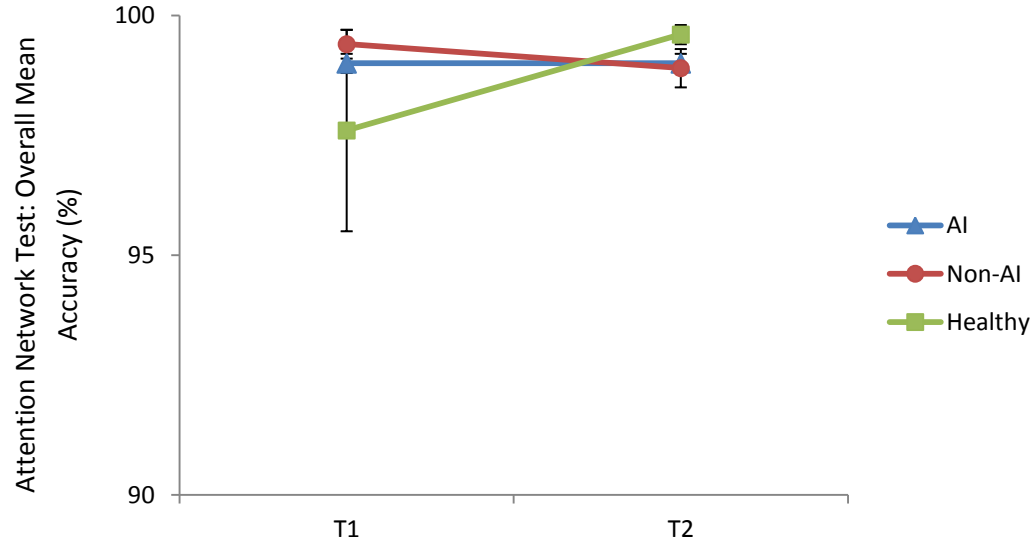


Figure 7: Attention Network Test (ANT): Mean Overall Accuracy All Groups. Error bars represent standard error. Points represent reaction time in milliseconds.

ANT: Group Differences in Alerting, Orienting and Executive Control Networks

Alerting Network

One-way ANOVA revealed no statistically significant difference among the three groups at T2 in reaction time ($F(2,33) = 1.5$, $p = .24$) or accuracy ($F(2,33) = .35$, $p = .71$). Paired t-tests used to determine significant changes in the alerting network over time within each group showed no significant changes in reaction time or accuracy between T1 and T2 in any of the three groups (Table 5, pg. 46 and Table 7, pg. 49) . Repeated measures ANOVA revealed no main effect for group or time and no interaction effect.

No group had a significant change over time in either cue condition of the alerting network in reaction time or accuracy and no significant differences were found among groups at T2. There was no main effect for group or time and no interaction effect in either condition for reaction time or accuracy.

Orienting Network

Analysis of the orienting network revealed no significant within-group differences in any group and no between-group differences at T2. Repeated measures ANOVA showed no significant main effect for time or group and no significant interaction effect between time and group for reaction time and accuracy in the orienting network.

Analyses of the effects of center and spatial cues on reaction time and accuracy revealed no significant differences in reaction time or accuracy among groups at T1 or T2 in either cue condition. However, within group differences were observed.

In the spatial cue condition, the AI group experienced a decrease in accuracy over time n trending toward significance ($t(14) = 1.74$, $p = .104$) while the non-AI group experienced an increase in accuracy that was statistically significant ($t(7) = 2.65$, $p = .03$). It should be noted that the accuracy remained on average > 98% at each time point in each of these groups. The healthy control group demonstrated a decrease in reaction time in the center cue condition over time that approached statistical significance ($t(12) = 1.86$, $p = .088$). This likely represents practice effect that was not observed in the patient groups. For both cue conditions, there was no evidence of main effect of group or time and no significant interaction effect.

Executive Control Network

The executive control network was examined in a similar way as the alerting and orienting networks. There were no significant differences among the groups in reaction time or accuracy in the executive control network at T2. No significant differences were found over time in mean reaction time or accuracy within the non-AI or healthy control groups. The AI group showed a significant decrease in mean reaction time in the executive control network (paired $t(14) = 2.52$, $p = .025$) but no significant difference in accuracy over time in this network. There was no main effect for group and no interaction effect for reaction time. There was a significant main effect for time in overall reaction time ($F(1,33) = 5.34$, $p < .05$), most likely due to the improvement in reaction time observed in the AI group (Fig. 8, pg. 70).

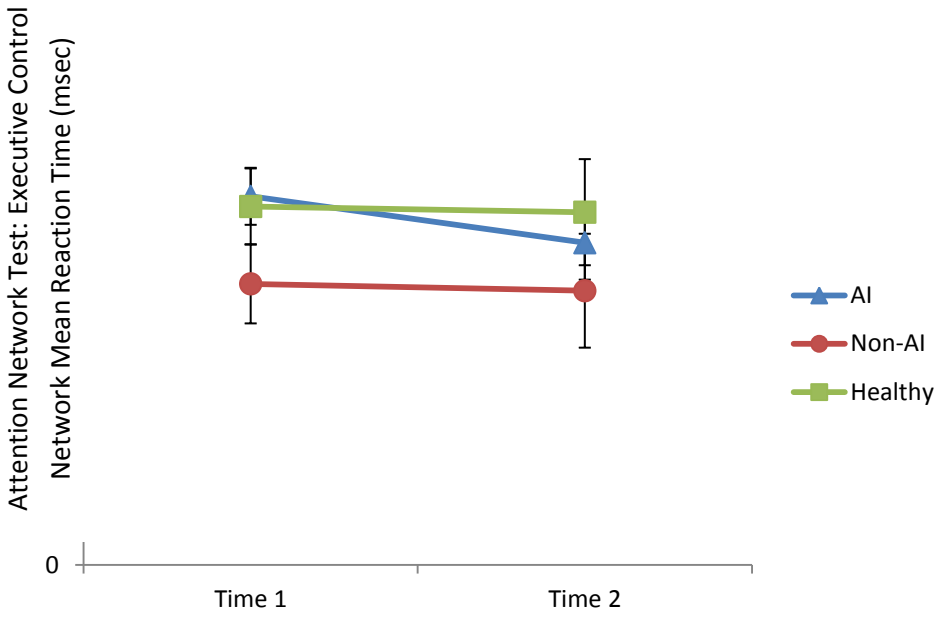


Figure 8: Attention Network Test: Executive Control Network Mean Reaction Time. Error bars represent standard error. Points represent milliseconds.

The effects of congruent and incongruent flanker conditions on reaction time and accuracy in the executive control network were examined. There were no significant within- or between-group differences at T2 in either flanker condition. In both flanker conditions, there was no main effect of time or group and no interaction effect for reaction time or accuracy.

Attention Network Test (ANT): Summary. Performance on the ANT did not differ significantly among groups at either time point in either mean reaction time or mean accuracy. The AI group was slower than the non-AI and healthy controls at both time points but this difference did not reach statistical significance. All groups improved in mean reaction time at T2 but within group changes over time were not significant. Within group differences in accuracy over time were not statistically significant although the non-AI group did have an decrease in mean accuracy at T2. There was no main effect for group or time and no interaction effect for mean overall reaction time and mean overall accuracy.

In the alerting network, no statistically significant differences in overall mean reaction time or mean accuracy were found among or within groups and there was no main effect for time or group and no interaction between time and group in mean reaction time or mean accuracy. In the double cue condition, the AI group had a significant improvement in accuracy over time that was not seen in the non-AI group. There were similar findings in the orienting network: overall mean reaction time and mean accuracy were similar among groups and there was no significant change within groups over time. The only influence of cue condition in this network was seen in improvement over time in mean accuracy for the non-AI group in the spatial cue condition. In the executive control network, there were no differences in overall mean reaction time or accuracy among groups at T2. Within group analysis revealed that the AI group had a significant decrease in mean reaction time between T1 and T2; this was not seen in the non-AI or healthy groups. There were no within group differences for accuracy in the executive control network. There was a main effect for time seen in this network but no group effect and no interaction effect was noted. When the congruent and non-congruent flanker conditions were assessed, there were no group differences at T2, no within group differences and no main effect for time, group and no interaction effect in either flanker condition. Overall, improvements over time in the ANT were present in both patient and healthy groups. In specific cue conditions, these improvements were statistically significant for the patients groups suggesting that there are subtle differences in the way patient groups benefit from specific cue conditions.

Research Question 3 Summary

There were two differences at baseline that trended toward significance among the three groups: a trend towards a significant difference in DSB with the healthy group scoring

higher than the non-AI group and a trend toward a significant difference in mean reaction times between the AI and non-AI groups. Neither of these groups was significantly different than the healthy group at T1.

At T2, there were two differences among the three groups. The AI group performed significantly worse than the healthy group on the DSB at T2 and had a lower (worse) composite cognitive function score at T2 than the healthy group that approached statistical significance. There were no significant group differences between the AI and non-AI groups or between the non-AI and healthy groups in these measures. All groups improved in overall mean reaction time at T2 in the ANT but these changes were not significant either among or within groups. The overall accuracy was not statistically different among groups at T2. When the individual networks of the ANT were examined at T2, there were no significant differences among groups in mean reaction time or mean accuracy in the three networks or in any of the cue conditions.

Comparison of Perceived Cognitive Function: Attentional Function Index (AFI)

At T1, the AI group had a slightly lower mean AFI score than the non-AI or healthy control groups (Table 4, pg. 45) but further examination with one-way ANOVA revealed that group differences in overall AFI score were not significant. Independent t-tests comparing groups at T1 confirmed that there were no significant differences in mean AFI score among groups. At T2 ANOVA revealed that group differences were trending toward significance ($F(2, 32) = 4.07$, $p = .109$). Independent t-tests revealed that the AI group AFI score at T2 was lower (perception of worse cognitive function) than the healthy control group ($t(27) = 2.01$, $p = .058$). There were no significant differences between the AI and non-AI groups or between

the non-AI and healthy groups in mean AFI scores at T2. Paired sample t-tests revealed significant differences between T1 and T2 AFI scores in the AI group (paired t (15) = 2.49, p = .025) representing perception of worse cognitive function over time, but no significant within-group differences for the non-AI or healthy control groups. Repeated measures ANOVA (3 groups X 2 time points) revealed no main effect for group or time and no interaction effect (Fig. 9).

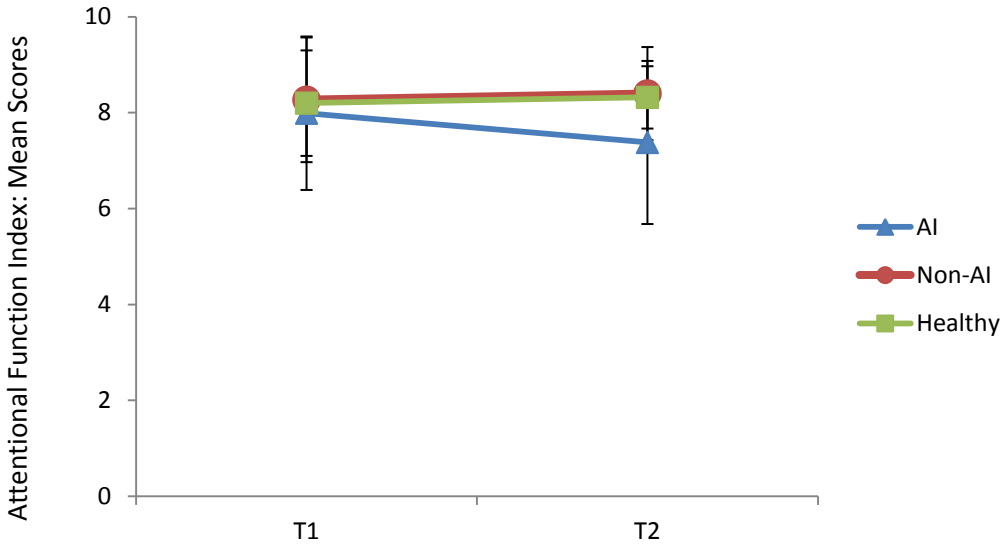


Figure 9: Attentional Function Index: Mean Scores. Error bars represent standard deviation. Points represent AFI score.

The AFI consists of three subscales measuring effective action, attentional lapse, and effective interpersonal relations. At T1, one-way ANOVA revealed no significant differences among groups in any of the three subscales.

Attentional lapse subscale. Repeated measures ANOVA demonstrated a significant interaction effect ($F(2, 34) = 10.25$, $p = .031$) in this subscale (Figure 10, pg. 75). Specifically, one-way ANOVA showed a difference among groups at T2, in the attentional

lapse subscale ($F(2,32) = 13.41$, $p = .056$) with post hoc independent t-tests between groups demonstrating statistically significant differences between the AI and healthy groups ($t(27) = 2.52$, $p = .013$) with the AI group reporting more attentional lapse. Paired samples t-tests revealed significant differences within the AI group with more reported attentional lapses reported over time (paired $t(15) = 2.39$, $p = .031$) but no significant differences over time for the non-AI or healthy control groups.

Effective interpersonal relations subscale. Repeated measures ANOVA revealed a trend toward a significant main effect for time ($F(1, 34) = 3.09$, $p = .101$) with no main effect for group and no interaction effect (Figure 11, pg. 75). There were no significant changes over time within any of the groups on this subscale, although both patient groups showed a slight decline in subscale mean scores at T2. One-way ANOVA revealed no significant difference among groups in the effective interpersonal relations subscale at T2, however, independent t-tests revealed differences in the mean effective interpersonal relation scores between the AI and healthy groups with the AI group reporting more difficulty in interpersonal relations ($t(27) = 1.67$, $p = .084$).

Effective action subscale. There was no main effect for group or time and no interaction effect for scores in the effective action subscale (Figure 12, pg. 76). One way ANOVA showed no group differences at T2 on the effective action subscale and this was confirmed by post hoc independent t-tests. Paired t-tests revealed a decrease in effective action for the AI group that approached significance ($t(15) = 1.75$, $p = .101$). The remaining two groups (non-AI and healthy controls) showed no significant changes in this subscale over time.

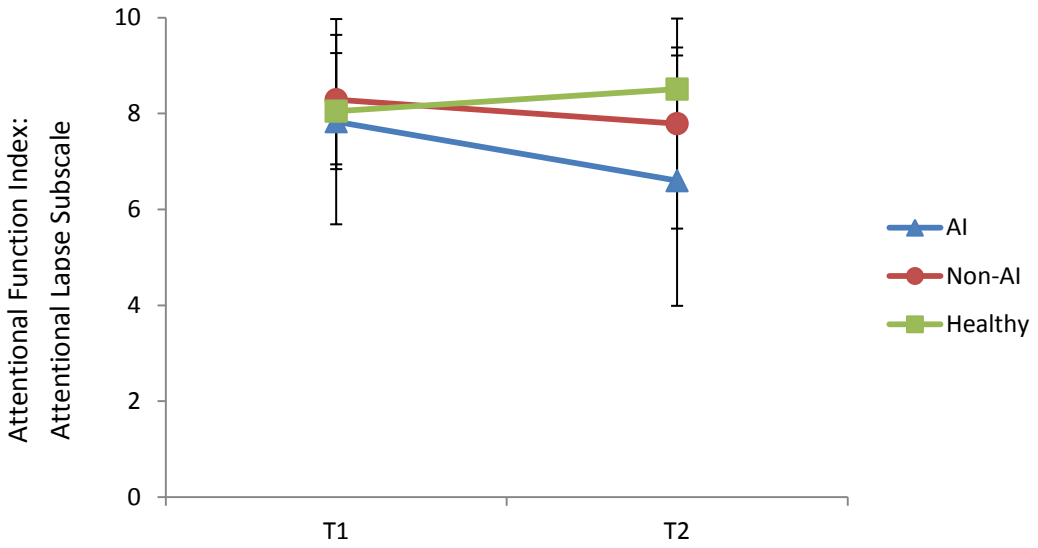


Figure 10: Attentional Function Index: Attentional Lapse Subscale. Error bars represent standard deviation. Points represent AFI subscale score.

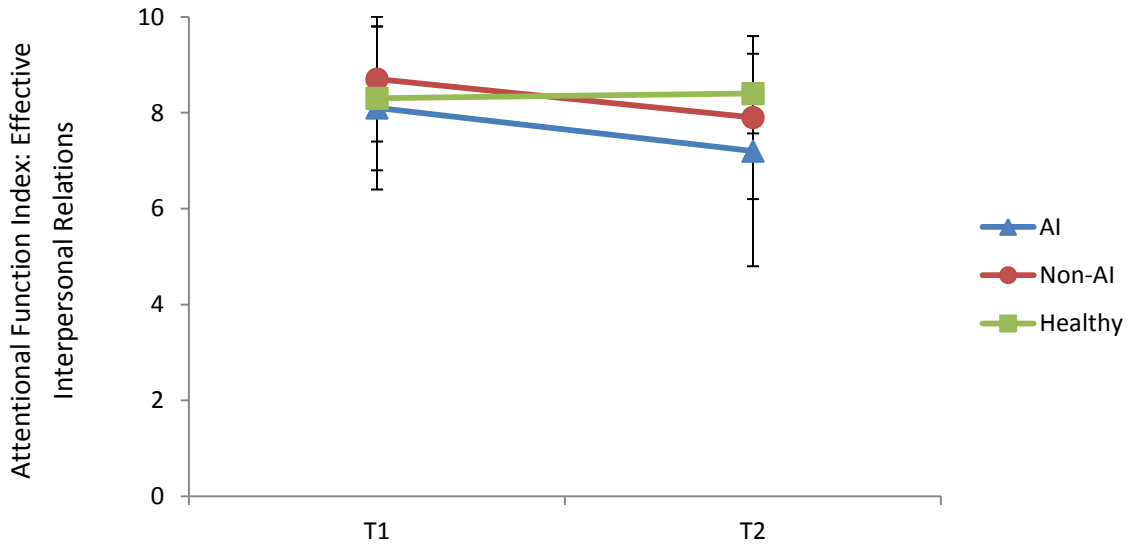


Figure 11: Attentional Function Index: Effective Interpersonal Relations. Bars represent standard deviation. Points represent AFI subscale score.

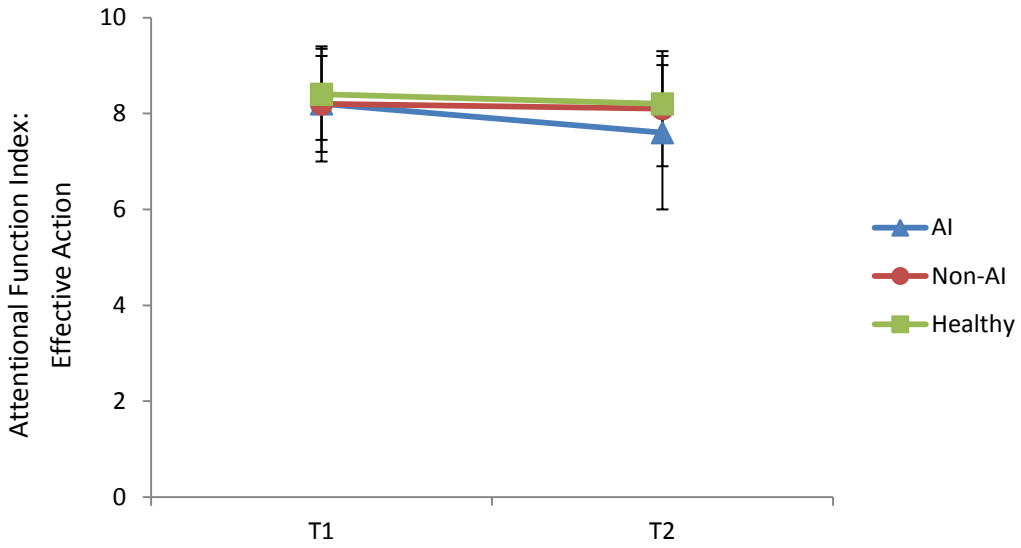


Figure 12: Attentional Function Index: Effective Action. Bars represent standard deviation. Points represent AFI subscale score.

Attentional Function Index Summary

At T2, both the AI and non-AI groups perceived an increase in cognitive difficulty compared to the healthy group as measured by the overall mean AFI score. The difference between the AI and healthy control groups in overall mean AFI scores trended toward significance at T2. When examining within group differences, between T1 and T2, the AI group had a significant drop in overall mean AFI score signifying the perception that cognitive function had worsened over time. The AI group worsened over time in all three subscales. The most significant difference between groups in subscale scores were between the AI and healthy groups. There was a significant interaction of group and time in the attentional lapse subscale and a trend toward a main effect for time in the effective interpersonal relations subscale. Post hoc analyses showed that the AI group perceived greater attentional lapses and less effective interpersonal relationships than the healthy group over time. The non-AI group also worsened over time in these measures but was not significantly different than either the AI or the healthy group.

Summary of Objective and Subjective Cognitive Function Data

Fifty post-menopausal women participated in this study. They were mostly white, married and well-educated. The groups differed in education and age with the non-AI group being less educated and older than the healthy group. Comorbid conditions and medications, including use of psychotropic medications, were similar across the three groups. As expected, there were differences between the groups of women with breast cancer in histology and stage of cancer with the AI group more likely to have invasive ductal carcinoma and to be diagnosed at Stage I than the non-AI group.

There were two differences in objective measures of cognitive function among groups at baseline (T1). The healthy group scored higher (more digits recited backward in the correct order) than the non-AI group in the DSB and the AI group demonstrated a slower reaction time in the executive control network of the Attention Network Test (ANT). The other objective measures of cognitive function, DSF, COWAT, and the ANT failed to demonstrate group differences at baseline. Self-report of cognitive function as measured by the Attentional Function Index (AFI) was not different among groups at baseline.

The first research question asked if there was a measurable decline in attention, working memory, and verbal memory in the AI group after 3 months of therapy. The AI group showed improvement in all objective measures over time with statistically significant improvement in the DSF, COWAT and executive control network of the ANT. When these individual scores were transformed to z scores and combined in the composite cognitive function score, there was no difference in performance over time. Despite the objective improvement in individual objective measures, the AI group demonstrated a perceived decrease in cognitive function as measured by the AFI with a statistically significant increase in perception of attentional lapses over time. These data suggest that although the AI group demonstrates objective improvement over time in attention, working memory, and verbal memory, their perception of their cognitive function, specifically their ability to focus attention, actually worsens over time.

The second research question asked if women treated for breast cancer with AI showed greater impairment in attention, working memory, and verbal memory at 3 months than women with breast cancer who did not receive AI. Overall, the AI group did not demonstrate greater cognitive impairment at T2 than the non-AI group. Interestingly, the

non-AI group worsened over time in two objective measures (the DSF and COWAT) while the AI group showed overall improvement in objective measures over time. The composite cognitive function score decreased slightly in both groups over time with the non-AI group experiencing the greater decrease. In the ANT, both groups slowed in overall reaction time over time and the AI group demonstrated an overall (but not statistically significant) improvement in accuracy when compared to the non-AI group. In the Alerting Network, both groups improved over time in mean reaction time and accuracy and the AI group showed a statistically significant improvement in accuracy in the double cue condition. The performance of these two groups was similar in the Orienting Network. The AI group performed worse in the Executive Control Network with statistically significant slower mean reaction times and non-significant but lower accuracy at T1 when compared to the non-AI group. This persisted at T2 but the differences were not statistically significant. Over time, both groups improved in reaction time but had worse accuracy; the AI group had a statistically significant improvement in mean reaction time. There was a main effect for time largely driven by the improvement in reaction time in the AI group. When comparing the AI and non-AI groups in overall performance on the ANT at T2, there were not significant differences but a closer examination of individual networks and cue conditions suggests that subtle differences do exist.

Research question 3 asked if women with breast cancer - the AI and non-AI groups - showed greater cognitive impairment at T1 and T2 when compared with healthy controls. The only difference among these groups at baseline was a trending difference between the healthy control group and the non-AI group in DSB with the healthy group scoring higher. There were no differences among groups in the other individual measures (DSF, COWAT)

and no differences in composite cognitive function score. In the ANT, differences in mean reaction time and mean accuracy were not significantly different among groups. There were no significant differences among groups at T1 in the individual networks of the ANT. At T2, significant differences among groups were limited to the DSB in which the AI group scored significantly lower than the healthy control group. Performance in the ANT at T2 revealed no significant differences among groups in mean reaction time or accuracy although the AI group was slower in reaction time than the non-AI and healthy groups. There were no group differences in the Alerting, Orienting, or Executive Control networks of the ANT in mean reaction time or mean accuracy at either T1 or T2. There were subtle changes over time in the non-AI group and the healthy group that were not present in the AI group in specific cue conditions but overall, the groups were similar in performance over time in the ANT. Differences among groups in perceived cognitive function were present at T2 where both the AI and non-AI groups perceived an overall increase in cognitive difficulty compared to the healthy group. Within group differences revealed a significant decline in mean overall AFI score in the AI group suggesting that this group perceived that their cognitive function was worsening over time. The most significant group differences were between the AI and healthy groups in attentional lapses and effective interpersonal relations with the AI group perceiving more difficulty than the healthy group.

Overall, the findings indicate that the significant differences among the three groups at both T1 and T2 appear to be in measures of working memory with the healthy control group scoring higher than the AI group at T2. All three groups improve in mean overall reaction time from T1 to T2 in the ANT. Group differences existed at T2 in perception of cognitive function as measured by the AFI with both the AI and non-AI groups

demonstrating a perception of decreased cognitive function at T2 compared to the healthy group. The AI group decreased significantly in AFI score over time signifying a perception of worse cognitive function. The most significant difference between groups was that the AI group perceived less effective interpersonal relations and greater attentional lapse than the healthy group.

CHAPTER V

DISCUSSION

This longitudinal, non-randomized, comparative study explored cognitive changes over time in post-menopausal women with breast cancer from pre-to three-months post-adjuvant treatment with an aromatase inhibitor (AI). Three groups of post-menopausal women were compared: one group with breast cancer treated with an AI; one group with breast cancer not treated with an AI or any other systemic adjuvant therapy; and a third group of healthy post-menopausal women without breast cancer. Considering the potential impact of aromatase inhibitor (AI) treatment, specifically the lowering of estrogen levels in post-menopausal women who might already be vulnerable to cognitive changes due to age and decreased levels of estrogen, it was hypothesized that women with breast cancer treated with AIs would have measureable cognitive decline after three months of treatment. Hypotheses related to research questions 2 and 3 were that the AI group would have greater cognitive decline at 3 months when compared to the non-AI group (research question 2), and that both the AI and non-AI groups would have worse cognitive function at T1 and T2 when compared to healthy controls. In addition to measures of cognitive function, measures of potential covariates of depressed mood, sleep quality, symptoms, and fatigue were collected but are not included in this primary study.

Sample Characteristics

Fifty post-menopausal women were enrolled in this study: 21 with breast cancer treated with an AI, 10 with breast cancer receiving no systemic treatment after radiation therapy, and 19

healthy controls within a year of screening mammogram. Demographic and medical characteristics were consistent with previous studies of cognitive function in post-menopausal women receiving AI therapy for breast cancer (Lejbak, et al., 2010; K. A. Phillips, et al., 2010; Schilder et al., 2012). The mean age of the sample at 63 years was consistent with the age at which women are more likely to be diagnosed with breast cancer (American Cancer Society, 2013) but as expected was older than in studies comparing cognitive function between groups of women receiving AI and tamoxifen as these studies included pre-menopausal women (Bender et al., 2007; Breckenridge, Bruns, Todd, & Feuerstein, 2012; Hermelink et al., 2008; Jenkins et al., 2006). This sample was also better educated than most published studies probably reflecting the location at a major university health system. Most of the women in this sample were married and employed outside the home with an annual income that was higher than the US average with 66% of the sample earning more than $61,000/year (Bureau of Labor, 2014). This likely reflects the higher educational level attained by this sample of women.

The only statistically significant difference in demographics among the three groups in this study was education level. The non-AI patient group had a mean education level that reflected fewer years of college than the healthy control group. The non-AI group was on average the oldest of the three groups and the age difference between the non-AI and healthy groups approached but did not reach statistical significance. The three groups were similar in race, marital status, employment outside the home, and income.

General health characteristics were also similar among groups with no significant differences in age at menopause, menopausal years (number of years in menopause), or in the presence or type of comorbid conditions. Concomitant use of medications that could affect cognitive functioning including narcotics, anti-depressants, and sedatives for insomnia was

similar across groups. AI and non- AI patient groups were compared for differences in breast cancer characteristics and found to be similar in number of surgeries, type of surgery (mastectomy vs. lumpectomy), presence of sentinel lymph node biopsy, and treatment with radiation therapy. Expected differences were found in histology and stage of cancer with more women in the AI group diagnosed with invasive ductal breast cancer and at Stage I when compared with the non-AI group. This difference is consistent with the indications for treatment with AI therapy (National Comprehensive Cancer Network, 2014). As a whole, in health characteristics, these two groups represented the population of post-menopausal women diagnosed with breast cancer in the US (American Cancer Society, 2013).

Baseline Cognitive Function

Groups were similar in objective measures of cognitive function with two exceptions. The first was in the DSB in which the healthy group scored higher than the non-AI group but not the AI group. A score of 4 to 5 is considered to be within normal limits on the DSB (Lezak, et al., 2004). On average, healthy and AI groups scored in the normal range. When examining the upper and lower limits of the ranges, the non-AI group contained 3 women with a score of 3, which is below normal range and indicative of cognitive impairment and an upper limit of 6. The healthy group scores ranged from 4 - 7, all within normal limits. This difference may be attributed to educational differences between the groups as the non-AI group had significantly fewer college years than the healthy controls. In prior studies, post-surgical measures of DSB in women with breast cancer have been reported as similar to the non-AI group in this study; comparison to these studies is somewhat difficult as the interval between surgery and DSB measurement was shorter in published studies than in the current study (Cimprich, 1992; Cimprich & Ronis, 2001). The second difference was in the executive control network task of

the ANT in which the AI group was slower than the non-AI group in mean reaction time. These groups had no significant difference in accuracy in the executive control network which suggests that the AI group may be exhibiting a trade-off between speed and accuracy. Perceived cognitive function as measured by the AFI was not significantly different among groups.

These data suggest that there were subtle cognitive differences among groups before the start of AI therapy. While differences in education level influence objective cognitive function scores, it is also possible that these baseline differences are related to being a patient with breast cancer. This is consistent with published studies in which pre-treatment cognitive impairment has been reported in women with breast cancer (Cimprich et al., 2010; Cimprich, et al., 2005) and in patients with lung cancer (Lehto & Cimprich, 2009).

The Influence of AI therapy on Cognitive Function

It was hypothesized in research question one that the AI group would have a measureable decline in both objective and subjective measures over the three months of therapy. In contrast to the hypothesis, the AI group demonstrated improvement on selected objective measures of cognitive function, specifically the DSF and COWAT. There was no change over time in the DSB and when the z scores of the objective measures were summed in the composite cognitive function score, there was no change over time. Overall performance on the ANT was unchanged over time but there was a significant improvement in reaction time in the executive control network task of the ANT suggesting improvement in performance over time.

Improvement over time in cognitive performance in women treated with AI therapy also has been reported in the literature although study designs and study populations make comparisons challenging. In the International Breast Intervention Study - II (IBIS-II), women at

high-risk for breast cancer had improved cognitive function scores comparing 6 month to 24 month measures (V. A. Jenkins, et al., 2008). At the same time, in the large randomized trial comparing sequencing of letrozole and tamoxifen for breast cancer treatment (the Breast Cancer International Group or BIG 1-98 trial), women treated with the AI letrozole showed significant improvement in composite cognitive function scores after one year off therapy (K. A. Phillips, et al., 2010) suggesting some recovery. The improvement in objective performance by the AI group in this study may be related to several factors. Practice effect is one likely explanation as this is commonly seen in repeated measures of cognitive function. It is possible that the measures chosen for this study, while theoretically congruent, are not sensitive enough to identify cognitive changes over time in this population of women. The timing of measures may have affected the results of objective testing. Perhaps cognitive function changes would be noted if testing was done even earlier in the course of treatment while women are physiologically adjusting to the medication. It is possible that women experience objective changes in cognitive function for which they compensate over the first three months of therapy. If this is true, not only would earlier testing be appropriate, but later testing would also be appropriate to understand if potential compensatory brain mechanisms persisted, or more likely, would fail over time. Finally, it must be kept in mind that this is a small sample; it is possible that a different result would be reached with a larger sample of women on AI.

Although the AI group demonstrated at least stable performance and in some cases, improvement over time in objective measures of cognitive function, their *perception* of their cognitive abilities was different. Women treated with AI perceived a decrease in cognitive function as measured by the AFI with more perceived attentional lapses at 3 months after initiation of therapy. This suggests that the AI group's perception of their ability to focus

attention is incongruent with their performance on objective measures of cognitive function. For most symptoms thought to be related to cancer and its treatment, the clinician usually relies on patient perception to prompt further investigation and treatment. In this case, women may report cognitive difficulties that prompt testing but the results of testing may not support the presence of cognitive dysfunction making the need for intervention unclear. This makes the consideration of potential covariates such as worry, fatigue, depressed mood, sleep disturbance and other symptom concerns important. If one or more of these covariates predict how a women perceives cognitive function, they may provide a target for intervention to ease cognitive complaints.

An increase in self-reports of cognitive complaints has also been reported. A 3 year prospective study of the effects of adjuvant therapy on women with early stage breast cancer showed a steady increase over time in self-report of cognitive failures (V. Jenkins, et al., 2006). Caution should be taken in comparing this study with the current study as testing was done after therapy was started and there were few participants treated with AI therapy (V. Jenkins, et al., 2006). In the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial, chemotherapy-naive participants were tested before starting AI or tamoxifen therapy and again at 1 year. Complaints of memory difficulties assessed in a cognitive interview increased in the AI group over time while complaints of attention and concentration difficulties remained stable over time (Schilder, et al., 2012). Comparing the findings of these studies with the present study should be done with caution due to the heterogeneity of testing intervals and objective and subjective cognitive measures and lack of baseline measures in these studies. The finding that there is a incongruence between objective and subjective measures of cognitive function has been reported in the literature mostly as a lack of correlation in cross-sectional studies (V. Jenkins, et al., 2006; Schilder, et al., 2012).

The finding in this study that there is incongruence between objective performance and subjective measures, especially in attentional lapses, over time is important. First, the use of more sensitive testing, such as a task of attention and working memory during functional MRI, could detect changes in brain activity over time including the use of compensatory mechanisms to sustain cognitive function. Secondly, it is important for nurses and other clinicians to know that it is possible that post-menopausal women receiving AI therapy may experience an increase in cognitive difficulties at 3 months into treatment with even subtle changes making a difference. This knowledge gives clinicians the chance to educate patients at the beginning of treatment about this possibility and suggest ways to mitigate cognitive difficulties by suggesting life-style changes such as avoiding multi-tasking, making lists, and perhaps spending more time in nature (Cimprich, 1993). Future examination of the influence potential covariates such as fatigue, depressed mood, and other symptoms, on perception of cognitive function could also provide targets for intervention that could potentially improve perception of cognitive function in this population.

When comparing AI and non-AI patient groups in directed attention, working memory and verbal memory at the three-month assessment, there was little difference between groups. The AI group improved significantly over time in the DSF and COWAT but not in the more demanding DSB suggesting a lack of expected practice effect in this more demanding task. Lack of practice effect suggests that more mental effort was expended by the AI group in this task. Interestingly, the non-AI group did not significantly improve over time in any objective task also suggesting lack of practice effect. The composite cognitive function score was not different among groups at either time point and did not differ significantly over time within groups and, therefore, did not add important information in comparing patient groups.

Comparing the performance of the AI and non-AI groups in the ANT revealed no statistically significant differences between groups in overall mean reaction time or mean error rate although the AI group was on average slower at both time points. Analysis of the different aspects of attention (alerting, orienting, and executive control attention systems) revealed subtle group differences. In the alerting and orienting networks, groups were similar at both time points: both improved over time in RT with the AI group showing significant improvement in accuracy for the low-demand double-cue condition of the alerting network. In the orienting network, the AI group was slower with more errors over time in comparison with the non-AI group in the high demand center-cue condition. This suggests that the AI group had a more difficult time disengaging attention from the center cue, which did not signal a target location at which the stimulus would appear. Once engaged by the center cue, it is possible that attention could not be rapidly shifted to a different spatial location to respond to the stimulus. In the lower demand spatial cue condition, where attention is cued to an upper or lower location of the target, the AI group had slower reaction times but was more accurate at both time points than the non-AI group. Both groups improved in reaction time but had decreased accuracy over time that was significant in the non-AI group and approached significance in the AI group. The spatial cue is meant to help the participant anticipate the location of the target and therefore allow them to begin to shift their attention to that spatial location. These results suggest that both patient groups find it difficult to shift attention to spatial cues.

The executive control network revealed baseline differences between groups with the AI group significantly slower and with higher error rates than the non-AI group. The AI and non-AI groups did improve over time in reaction time but also had higher error rates over time. Flanker conditions (congruent or incongruent) did not influence group differences at either T1 or T2.

These results suggest that both groups may find this task effortful even in the congruent (no conflict/low demand) condition.

Taken together, these data suggest that although both AI and non-AI groups were within normal limits of testing, there may be subtle differences between them. The AI group may find higher demand tasks of attention and working memory such as the DSB more difficult than the non-AI group. Both groups had demonstrated subtle attention network difficulties in shifting attention in both low and high demand conditions.

Comparison of patients (AI and non-AI groups) to controls at baseline and 3 months indicated a trend toward differences particularly in the high demand DSB suggesting that the patient groups may have more difficulty in high demand attention and working memory conditions than healthy controls. There were no statistically significant differences among groups on performance in the ANT. The healthy group showed improvement in reaction time in the high demand center cue task of the orienting network that approached significance; the AI and non-AI patient groups did not improve over time in high demand tasks.

A significant difference between groups in *perceived* cognitive function was observed in AFI scores with the AI group perceiving significantly worse cognitive decline after 3 months when compared to the healthy control group. There was a significant interaction effect in the attentional lapse subscale in which the AI group reported significantly worsening attentional lapses over time when compared to the healthy controls. There was a trend toward group differences in the other two subscales with the AI group perceiving more impairment in effective interpersonal relations than the healthy group at three months and experiencing worsening perception of effective action over time. This suggests that while differences between groups in

objective performance may be subtle, there are more apparent differences in perceived cognitive function with the AI group perceiving significantly greater cognitive difficulty over time compared to healthy controls. The AFI has not yet been used in other studies of cognitive function in women receiving aromatase inhibitors but has been used in numerous studies of ill and healthy individuals. A cautious comparison could be made to other studies of women with breast cancer who were tested either prior to surgery or following adjuvant chemotherapy. Mean overall AFI was reported in the satisfactory range (6.2 - 7.0) in these studies. (Cimprich, 1999; C. E. Jansen, Cooper, Dodd, & Miaskowski, 2011; C. E. Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008; Merriman et al., 2011). The overall mean AFI for women treated with AI in the current study was similar, though slightly higher suggesting that women prior to and 3 months after initiation of AI therapy perceived higher cognitive functioning than women who have chemotherapy as part of their treatment regimen.

The findings in this comparative study were mixed and should be interpreted with caution due to the small sample size. In this study, post-menopausal women receiving AI therapy did not objectively change in measures of cognitive function over time, yet their perception of their cognitive performance worsened after three months of therapy. The reason for this is not clear. On one hand, the lack of objective change over time could be reassuring to clinicians and women receiving AI therapy; however, the perception of worsening cognitive performances cannot be ignored. These contradictory findings may indicate that measures in this study are not sensitive enough to pick up on cognitive changes over time. In future studies, the use of a measure of attention and working memory during functional MRI would be more sensitive to subtle neural alterations. It is possible that the perception of worsening cognitive function indicates use of more effortful compensatory brain processes to support task performance. Extending repeated

measures beyond three months of therapy might be useful in identifying this phenomenon. Again, the use of functional MRI would be helpful in identifying areas of brain activation that might be involved in a compensatory manner (Askren, MK,. et al, 2014). It also is possible that worsening of perceived function is related to potential covariates of fatigue, depressed mood, sleep quality, and symptom distress and that management of these conditions would mitigate this perception.

Findings suggest that women with breast cancer who are not receiving systemic therapy as part of their treatment are somewhat different both from those treated with AI therapy and from healthy controls. In this study, the non-AI group scored worse on the cognitively demanding DSB at baseline and performance worsened slightly over time in the less demanding DSF and in verbal memory as measured by the COWAT. Accuracy worsened over time in the executive control network of the ANT. These findings suggest that women receiving no systemic therapy for breast cancer may face challenges with demanding cognitive tasks. While these changes did not reach statistical significance in this small sample, they may be indicative of subtle cognitive changes that have not been studied in this group of women and deserve future consideration. Women who are not treated with AI or any other systemic therapy may experience symptom and psychological distress related to their breast cancer diagnosis that could affect cognitive function. It is possible that, because they are not on active therapy, they may have follow-up appointments scheduled at longer intervals than women on AI therapy and thus not have their concerns addressed in a timely way. This may affect their return to work, school and family life, thus affecting their quality of life.

Strengths and Limitations

This study reports longitudinal measurement of attention, working memory and verbal memory in post-menopausal women treated for breast cancer with AIs in comparison with women treated for breast cancer without systemic therapy and healthy controls. The longitudinal design of this study was a strength as was the inclusion of groups that controlled for AI treatment (non-AI group) and disease (healthy controls). There are few, if any trials that compare AI treated patients with non-AI patients on measures of cognitive function. One reason for this might be the difficulty in recruiting such a population in an academic setting. One cross-sectional study by Lejbak and colleagues (Lejbak, et al., 2010) tried to recruit a non-AI patient arm but was unsuccessful. Most studies compared AI treated patients with patients receiving other estrogen depriving therapies, usually Tamoxifen, another estrogen-reducing therapy. It is important to include women not receiving AI to better understand and intervene for subtle cognitive changes women treated with AI may experience. An additional strength of this study is that both objective and subjective measures of cognitive function were obtained in the AI group at baseline, prior to beginning AI therapy. Many studies of cognitive function in women receiving AI therapy have been cross-sectional in design and therefore have tested women with various durations of treatment. Testing women at approximately 3 months after initiating therapy allowed for drug levels to stabilize and coincided with a usual return clinic visit lessening participant burden. Finally, this study used measures that were congruent with a theoretical model linking biological theory of treatment-associated estrogen deprivation in post-menopausal women treated for breast cancer to the neurobehavioral theory underlying the basic cognitive processes of attention, working memory, and verbal memory.

The findings of this study should be interpreted with caution in light of study limitations. First, this is a small sample limiting the potential to generalize any findings. Although the longitudinal design is a strength, some attrition occurred in all groups in this study decreasing the power to make comparisons among and within groups over time. Although data for the non-AI group are included in this analysis, this is a small comparison group making effective comparison difficult. Findings from this initial study indicate that the non-AI group may have differences in cognitive function compared to both AI and healthy control groups but these differences, and all findings in this study, must be regarded as preliminary data. Additionally, the second time point of measurement is early in the course of AI treatment, which may extend for 5 or more years in the adjuvant setting. Results from this study cannot provide information about long term worsening (or improvement) in attention, working memory, or verbal memory in women with breast cancer in either the AI or non-AI group. Additionally, due to the small sample size, there was no differentiation made among types of aromatase inhibitor in the AI group and therefore no conclusions may be drawn between type of AI received and changes in cognitive function.

Recommendations for Future Research

Future studies are needed that include a larger sample overall and a larger group of women in the non-AI patient group. The current study revealed subtle differences in cognitive function in this group but due to the small sample size, it was difficult to draw meaningful conclusions. One solution to difficulty in recruitment of the non-AI group would be to recruit from multiple clinical sites, especially community oncology practices. It is likely that the women who do not require systemic therapy for breast cancer will return from the academic setting to a

local community oncologist for follow-up. Including community oncology practices in future recruitment could improve recruitment and retention of women in this study group.

Extending longitudinal assessment of attention, working memory and verbal memory would be beneficial in better understanding any patterns of cognitive function change over the course of AI therapy. The use of a test of attention and working memory in functional MRI would provide more sensitive testing over time and might help identify the presence of compensatory brain activity to maintain cognitive function. The use of sensitive assays of low-level circulating estrogen in combination with objective and subjective measures could be helpful in elucidating the connection between estrogen levels and cognitive function over time. Linking assessment to return clinic visits could possibly help with retention in the AI group and non-AI groups. Careful attention to include adequate numbers of women receiving each type of AI therapy would allow for assessment of possible relationships between type of AI and changes in cognitive function.

Although preliminary, the results of this study suggest that women receiving AI therapy perceive changes in attentional function, especially increase in attentional lapses. Future analysis of data collected but not reported in this dissertation report should include the effects of potential covariates of fatigue, sleep quality, mood disturbance, and symptoms on perception of decline in attentional function. A greater understanding of these relationships should provide important information and may suggest that interventions in one of these areas could influence perception of attentional function.

Finally, if future studies confirm these findings, it would be important to test interventions that could mitigate perceived cognitive function changes. Understanding the source

of this perception, especially if related to fatigue, depressed mood, or symptoms related to cancer and its treatment, would provide potential targets for intervention (Berman, et al, 2012). Encouraging women to take a break when they perceive trouble with attention or working memory, possibly spending time in nature to restore their attentional function, could be of great aid. While studies have suggested that nature-based therapy improves cognitive functioning in women with breast cancer and other ill populations, (Cimprich, 1992; Cimprich & Ronis, 2003), this has not yet been evaluated for efficacy in this population. Assisting women in changing their habits would be another potential intervention. This would include avoiding multi-tasking, the use of lists and other prompts to assist them in staying focused on tasks in their day.

Implications for Nursing Practice

Nurses are familiar with the global disruption experienced by women newly diagnosed with cancer. Recognizing that a woman may experience a change in self-schema with the diagnosis of breast cancer, nurses are in a prime position to provide assistance, through education and psychosocial support, as women integrate the breast cancer experience into their lives. Nurses are expert at assessing fatigue, sleep disturbance, depressed mood and other factors that are potentially related to perception of decline in attentional function; these symptoms are amenable to nursing intervention. Successful intervention for these symptoms could positively affect perception of cognitive function. Nurses are in a pivotal position to assess changes in cognitive function in women with breast cancer due to their role in direct care during hospitalization and outpatient clinic visits as well as their role in between-visit support of women with breast cancer. A full battery of objective measures of cognitive function is not practical in the setting in which most women with breast cancer receive their care, that is the outpatient clinic. However, this study suggests that the Attentional Function Index or even select subscales

may be useful in clinical assessment. It is brief and could be easily administered in the clinic. There is evidence that it is sensitive to detection of cognitive changes (Cimprich, et al., 2010) which makes it appropriate for repeated measures testing in this population receiving long term adjuvant therapy. Most importantly, it assesses patient reported effectiveness in everyday activities that rely on basic cognitive processes. These are the basic processes that women use in daily life to plan, set goals, carry out instructions and tasks, and in monitoring their behavior. Using this measure in the clinic, nurses could identify cognitive problems in women with breast cancer prior to therapy and over time and enable them to implement interventions to improve the quality of life of breast cancer survivors.

Conclusions

The findings of this study suggest that women with early stage breast cancer experienced an improvement on selected objective measures of attention and working memory and verbal memory in the first three months of AI therapy. In contrast, they perceived that their cognitive function worsened over this same time period, perceiving an increase in attentional lapses. Comparison of the AI and non-AI patient groups revealed no significant differences in objective or subjective measures of cognitive function. The AI group perceived worse cognitive function than the healthy control group over time. These findings suggest that despite an objective improvement in cognitive function over time, women receiving AI therapy for breast cancer perceive subtle worsening in attention, specifically more attentional lapses, after 3 months of AI therapy.

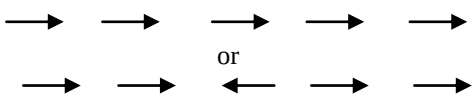
Appendix A1.

Mini Mental State Exam	
Maximum Score 5 Score ( )	**Orientation** What is the date today? _____ The day of the week? _____ The month? _____ What season is it? _____ What is the year? _____
Maximum Score 5 Score ( )	Where are we (place)? _____ What country? _____ What city? _____ What county? _____ What floor are we on? _____
Maximum Score 3 Score ( )	**Registration** I'm going to name 3 objects: HOUSE, TREE, CAR (1 second to say each). Now I want you to repeat them for me.
Maximum Score 5 Score ( ) Both items should be given if they do not achieve a score of 5 on the first and only the higher score of the two should be used.	**Attention and Calculation** Serial 7's. I'd like you to start at 100 and count backwards by 7's. (100, 93, 86, 79, 72, 65) Spell WORLD forward Spell WORLD backward
Maximum Score 3 Score ( ) 1 point for each word correctly recalled.	**Recall** I want you to recall the 3 objects I said earlier.
Maximum Score 9 Score ( ) 1 point 1 point 1 point 3 points (don't give them paper until after instruction is finished) 1 point 1 point 1 point	**Language** What is this? (Hold up pencil) What is this? (Point to watch) Repeat this sentence: "No Ifs, Ands, or Buts. Now I'd like you to take the paper in your right hand, fold it in half and put it on the floor. Please read and obey the following: CLOSE YOUR EYES Please write a sentence. Now I'd like you to copy this design. Take your time and draw it as accurately as you can.
MMSE TOTAL SCORE: /30	

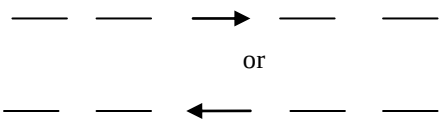
Appendix A2.
Attention Network Test

Test Instructions:

This is a test of attention. Your task is to respond to the direction of the center arrow in a group of arrows. Sometimes the arrow will be flanked by two arrows to the left and two arrows to the right, for example:



Sometimes the arrow will be flanked by straight lines, for example:



Again, your task is to respond to the direction of the CENTER arrow. You should press the left mouse button with your index finger if the center arrow points to the left or press the right mouse button with your middle finger if the center arrow points to the right Please make your response as quickly and accurately as possible. Your response time and accuracy will be recorded.

There will be a plus sign ("+") in the center of the screen. You should try to focus on the plus sign throughout the experiment.

Sometimes there will be an asterisk (*) showing when or where the arrow will occur.

For example, to show WHEN the arrows will occur, you might see:

*

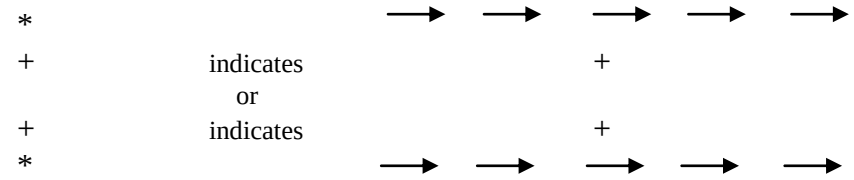
or

*

+

*

For example, to show WHERE the arrows will occur you might see:



The experiment has 4 parts:
1) Practice: 1 part, 2 minutes
2) Experiment: 3 parts, 5 minutes each

After each experiment part, there will be a message "take a break" and you may take a short rest. After your short rest, you can press the space bar to begin the next experiment part. The whole test takes about 15 minutes.

Are you ready?
Put your right hand on the mouse and use your left hand to press the SPACE bar to start the practice session.

Appendix A3.

Digit Span Forward and Backward

Digits Forward

I am going to say some numbers. Listen carefully, and when I'm through, say them right after me. For example, if I say 4 - 3, then you say 4 - 3. Ready? (Recite 1 digit / second).

Series

3	7-4-9	1-7-4	_____(3)
4	8-5-2-1	5-2-9-7	_____(4)
5	2-9-6-8-3	6-3-8-5-1	_____(5)
6	5-7-1-9-4-6	2-9-4-7-3-8	_____(6)
7	8-1-5-9-3-6-2	4-1-9-2-7-5-1	_____(7)
8	3-9-8-2-5-1-4-7	8-5-3-9-1-6-2-7	_____(8)
9	7-2-8-5-4-6-7-3-9	2-1-9-7-3-5-8-4-6	_____(9)

Digits Backward

Now I'm going to say some more numbers, but this time when I stop, I want you to say the numbers backwards - exactly reversed - from the last to the first. For example, if I say, 4 - 3, then you would say, 3 - 4. Ready?

Series

3	6-2 9	4-1-5	_____(3)
4	3-2-7-9	4-9-6-8	_____(4)
5	1-5-2-8-6	6-1-8-4-3	_____(5)
6	5-3-9-4-1-8-	7-2-4-8-5-6	_____(6)
7	8-1-2-9-3-6-5	4-7-3-9-1-2-8	_____(7)
8	9-4-3-7-6-2-5-8	7-2-8-1-9-6-5-3	_____(8)
9	1-4-2-9-5-3-7-8-6	7-2-1-8-5-9-4-3-6	_____(9)

Appendix A4.

Controlled Oral Word Association Test

I will say a letter of the alphabet. Then you give me as many words that begin with that letter of the alphabet as quickly as you can. You will have one minute.

For example if I say, "G", you might say: gate, goat, or garage

Please do not say any words that are proper nouns like: "Boston", "Bob" or "Bloomingdale's"

Please do not use the same word with a different ending like: sing, sang, singing.

Any questions?

Begin when I say the letter.

The first letter is "F". Go ahead.

Allow one minute for each letter "F", "A", "S"

Appendix A5.

Attentional Function Index

I. At this time, how well do you feel you are functioning in each of the areas below?

Circle the number that best describes how you are doing in each area at present.

1. Getting started on activities (tasks, jobs) you intend to do

Not at all — Extremely well

0 1 2 3 4 5 6 7 8 9 10

2. Planning your daily activities.

Not at all — Extremely well

0 1 2 3 4 5 6 7 8 9 10

3. Following through on your plans.

Not at all — Extremely well

0 1 2 3 4 5 6 7 8 9 10

4. Doing things that take time and effort.

Not at all — Extremely well

0 1 2 3 4 5 6 7 8 9 10

5. Making your mind up about things.

Not at all — Extremely well

0 1 2 3 4 5 6 7 8 9 10

6. Finishing things you have started.

Not at all — Extremely well

0 1 2 3 4 5 6 7 8 9 10

7. Keeping your mind on what you are doing.

Not at all — Extremely well

0 1 2 3 4 5 6 7 8 9 10

8. Remembering to do all thing things you started out to do.

Not at all — Extremely well

0 1 2 3 4 5 6 7 8 9 10

9. Keeping track of what you are saying or doing (keeping your train of thought).

Not at all Extremely well

0 1 2 3 4 5 6 7 8 9 10

10. Keeping your mind on what others are saying.

Not at all Extremely well

0 1 2 3 4 5 6 7 8 9 10

11. Keeping yourself from saying or doing things you did not want to say or do.

Not at all Extremely well

0 1 2 3 4 5 6 7 8 9 10

12. Being patient with others.

Not at all Extremely well

0 1 2 3 4 5 6 7 8 9 10

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

13. How hard you find it to concentrate on details.

Not at all A great deal

0 1 2 3 4 5 6 7 8 9 10

14. How often you make mistakes on what you are doing.

Not at all A great deal

0 1 2 3 4 5 6 7 8 9 10

15. Forgetting to do important things.

Not at all A great deal

0 1 2 3 4 5 6 7 8 9 10

16. Getting easily annoyed or irritated.

Not at all A great deal

0 1 2 3 4 5 6 7 8 9 10

Appendix A6.

Demographic Survey

1. Age_____

2. Present Marital Status? Are you: (Circle your answer)

   (1) Never married
   (2) Married
   (3) Divorced
   (4) Widowed
   (5) Separated
   (6) Living with a partner

3. Do you have children? (Circle your answer)

   (1) No
   (2) Yes If yes, number of children? _____ Ages of children? _____

4. Who lives in the household beside yourself? (Circle all that apply)

   (1) Husband
   (2) Children Number? _____
   (3) Other relatives Number? _____
   (4) Non-related persons Number? _____
   (5) No one else

5. Highest level of education completed: (Circle your answer)

   (1) None
   (2) Grades 1 – 7 (some grade school)
   (3) Grade 8 (completion of grade school)
   (4) Grades 9 – 11 (some high school)
   (5) Grade 12 (high school diploma, GED, or any high school equivalent)
   (6) Some college without degree
   (7) Undergraduate college degree Type _____
   (8) Graduate degree Type _____
   (9) Other schooling Type _____

6. Your occupation _____
7. Your present employment status (Circle your answer)

   (1) Employed outside the home – Number of hours per week? _____
   (2) Homemaker
   (3) Unemployed
   (4) Retired
   (5) Disabled
   (6) Other (specify)_____

8. Ethnicity: Please circle the group which you think best applies to you:

   (1) Hispanic or Latino Not Hispanic or Latino

9. Race: Please circle the group or groups which you think best applies to you:
   (1) White
   (2) Black/African American
   (3) Asian
   (4) American Indian/Alaskan Native
   (5) Native Hawaiian or other Pacific Islander

10. Your approximate household income:
   (1) Less than $15,000/year
   (2) Between $16,000 - $30,000/year
   (3) Between $31,000 - $45,000/year
   (4) Between $46,000 - $60,000/year
   (5) Between $61,000 - $75,000/year
   (6) Over $76,000/year

Appendix A7.

Medical Information Form - Breast Cancer

1. Date of diagnostic biopsy: ___/___/___

2. Menopausal state at diagnosis: (check one)

(1) _____Pre (2)_____Peri (3)_____Post

3. Hormone replacement therapy?

(1) _____Yes (2)_____No

If yes, last dose date: _____/_____/_____

4. Surgery: (Check all surgeries)

(1) Lumpectomy _____No _____Yes date___/___/___

(2) Re-excision lumpectomy _____No _____Yes date___/___/___

(3) Segmental mastectomy _____No _____Yes date___/___/___

(4) Modified radical mastectomy _____No _____Yes date___/___/___

5A. Axillary lymph nodes

(1) Dissection _____No _____Yes date___/___/___

(2) Sentinel node mapping _____No _____Yes date___/___/___

(3) # nodes positive _____

5B. Breast reconstruction

(1) Reconstructive implant _____No _____Yes date___/___/___

(2) Reconstructive tram flap _____No _____Yes date___/___/___

6. Radiation Therapy _____No _____Yes

(a) Start of treatment date___/___/___

(b) End of treatment date___/___/___

(c) Total dose: (write in) _____

(d) Was radiation delayed or discontinued for any reason? (check one)
_____Yes _____No

(e) Radiation sites

(1) Breast _____No _____Yes

(2) Chest wall _____No _____Yes

(3) Axilla _____No _____Yes

(4) Internal mammary/ supraclavicular nodes _____No _____Yes

7. Hormonal therapy 1) _____Yes 2)_____No

If yes, date begun ___/___/___

Length of expected treatment _____

8. Type of breast cancer _____

(from pathology report)

9. Staging of breast cancer (pathological staging)

(1) Stage I _____
(2) Stage IIA _____
(3) Stage IIB _____

10. Her 2 status _____Positive _____Negative

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