COGNITIVE IMPAIRMENT IN PATIENTS WITH BREAST CANCER

by

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Chemotherapy, radiation therapy, and targeted biological therapies are cancer treatments that can increase survivorship in patients with breast cancer, yet the associated cognitive side effects of therapy can significantly reduce quality of life (QOL). Cognitive Impairment has been identified by oncology nurses and patient's as one of the most difficult symptoms to manage. However, methods to detect cognitive impairment are inconsistent in the literature.

The purpose of this study was to examine the effect of cancer treatment on cognitive impairment in women with breast cancer using self-reported instruments. A descriptive, correlational pilot study was used to compare healthy women of similar age and those women who receive surgery, radiation, and chemotherapy for breast cancer at six months or less of endocrine therapy.

This study evaluated three-self reported tools on cognition (attention, memory, and executive function) in conjunction with self-reported tools on symptom burden, QOL, anxiety, and depression. Results showed a significant difference between groups in attention and executive function but not in memory. Women with breast cancer reported significantly more symptoms and demonstrated more anxiety and depression than the healthy women. The findings

of this study corresponded with findings from previous studies. However, a larger scale study

with a larger sample size needs to be completed to validate these findings.

COGNITIVE IMPAIRMENT IN PATIENTS WITH BREAST CANCER

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CHAPTER 1: COGNITIVE IMPAIRMENT IN PATIENTS WITH BREAST CANCER

Advancement in treatments and early detection of breast cancer have contributed to the increase in breast cancer survivors. Chemotherapy, radiation therapy, and targeted biological therapies are cancer treatments that can increase survivorship in patients with breast cancer, yet the associated cognitive side effects of therapy can significantly reduce quality of life (QOL) (Allen, D.H., Myers, J.S., Jansen, C.E., Merriam, J.D., & Von Ah, D, 2018; Ahles, Root & Ryan, 2012; Janelsins, Kesler, Ahles, & Morrow, 2014). Breast cancer survivors experience long-term cognitive effects that hinder their ability to return to work, function in social settings and perform everyday tasks post-chemotherapy treatment (Dwek et al., 2015; Wefel et al., 2004). The symptoms of cognitive impairment can range from forgetfulness to the inability to focus when performing everyday tasks (Hess & Insel, 2007). Therefore, the need to understand the long-term cognitive side effects associated with cancer treatments and how they affect the QOL in patients with breast cancer is warranted.

The National Cancer Institute predicts that the total number of cancer survivors will rise to more than 18 million by 2020, strengthening the need to address the long-term effects of chemotherapy treatment to improve the QOL of cancer survivors. The 5-year survival rate of breast cancer patients with Stage I-III has an estimated rate from 72-100%, while Stage 4 is significantly lower at 22% (American Cancer Society, 2020c). With the increasing number of breast cancer survivors, it is important to determine how cognitive impairment impacts survivors' everyday lives (Allen et al., 2018; Ahles, 2013; Merriman, J. D., Aouizerat, B. E., Langford, D. J., Cooper, B. A., Baggott, C. R., et al., 2014; Vitali et al., 2017).

Cancer survivors' reports of cognitive impairment during and following chemotherapy treatment have led to increased awareness of chemotherapy-related cognitive impairment

(CRCI) by health care professionals. Cognitive impairment has been identified by oncology

nurses and patients as one of the most difficult symptoms to manage (Cox, A., Arber, A.,

Gallagher, A., MacKenzie, M., & Ream, E., 2017). Although the occurrence of cognitive

impairment has been documented with patients who undergo chemotherapy treatment (National

Cancer Institute, 2016), little is known about the potential mechanisms that cause CRCI. In a

systematic literature review, Hess and Insel (2007) found that all subjects in these breast cancer

studies showed declines in various cognitive domains, whereas subjects in ovarian cancer

studies did not show cognitive declines. The inconsistencies in these findings could be related

to variety of cognitive measures (e.g., self-report instruments versus objective instruments)

used, lack of demonstrated instrument validity and reliability and differences in chemotherapy

treatment regimens.

A challenge for researchers studying chemotherapy related cognitive functional is lack

of a consistent definition the phenomenon. Definitions of cognitive function in the literature are

nonspecific and generally refer to brain function (Allen, D.H., Myers, J.S., Jansen, C.E.,

Merriam, J.D., & Von Ah, D, 2018; Halligan, Kischka & Marshall, 2003; Jansen, 2005;

Meyers, 2009; Myers, Wick, & Kelpm, 2015). Hess and Insel (2007) developed their

conceptual model of CRCI by looking at changes in cognition due to the administration of

chemotherapy. Hess and Insel (2007) defined cognitive function as "an individual's higher-

order mental processes, may be altered among individuals diagnosed with cancer among two

distinct and interacting pathways: (a) cancer diagnosis (meaning of cancer), leading to anxiety,

stress, distress, and depression; and (b) direct physiological effects of cancer treatments, both of

which may affect cognitive function" (p. 990). These mental processes include attention and

concentration; visuospatial and constructional skills; sensory perceptual function; language,

memory, executive function; intellectual function; mood, thought content, personality, and behavior. Any mental process or processes could be affected, but most patients who receive chemotherapy report changes in attention, memory, and executive function (Jansen, 2005). Once one area of cognition is affected, eventually other domains could be affected (Halligan, Kischka & Marshall, 2003; Jansen, 2005).

Another challenge for researchers is the wide variety of terms used within the literature to describe changes in cognitive function experienced by cancer patients. These include: "chemo fog", "chemobrain", "chemotherapy-induced cognitive decline", "chemotherapy-induced cognitive changes", "chemotherapy-associated cognitive changes", "cancer-related cognitive impairment", "chemotherapy-induced cognitive disruption", "cancer-related treatment symptoms," "cancer chemotherapy-related symptoms", and "chemotherapy-related cognitive impairment" (Ahles et al., 2002; Bender et al., 2006; Hurria et al., 2006; Johns et al., 2016; Meyers, 2009; Myers, Wick, & Kelpm, 2015; van Dam et al., 1998; Vitali et al., 2017). All these terms describe changes in cognition attributed to chemotherapy. It remains unclear which cognitive domains are most effected by the administration of chemotherapy.

While, cognitive impairment is attributed to chemotherapy, Myers, Wick, & Kelpm (2015) reported that cognitive complaints are present in some patients with breast cancer before receiving chemotherapy treatment and those cognitive complaints increased during treatment. The cognitive impairment experienced by cancer patient is a complex phenomenon with multiple contributing factors. These contributing factors include predisposing factors (such as advanced age and genetics, physiological (such as types of treatment, combination of treatments) and psychological (such as depression and anxiety) (Hess and Insel, 2007). The revised conceptual model of Chemotherapy-Related Changes in Cognitive Function (Meyers,

2009) to explain influencing factors that contribute to cognitive impairment in patients with breast cancer in conjunction with six self-report measures for cognition, symptoms burden, QOL, anxiety, and depression.

Background/Significance

Chemotherapy related cognitive impairment (CRCI) has been associated specifically with the areas of attention, memory, and executive function. If left untreated, CRCI may negatively affect QOL (Ahles, 2012; Hess & Insel, 2007; Myers, Wick, & Kelpm, 2015; Von Ah D et al., 2013; Vitali et al., 2017). Studies have suggested that 15-75% of women with breast cancer experience CRCI (Ahles et al., 2002; Bender et al., 2006; Hurria et al., 2006; Johns et al., 2016; van Dam et al., 1998), with some women experiencing symptoms up to 20 years' post-treatment (Koppelmans, V., Breteler, M. M. B., Boogerd, W., Seynaeve, C., Gundy, C., & Schagen, S. B.,2012). However, it is unclear which assessment tools are most effective in assessing for cognitive impairment. Once cognitive impairment is diagnosed, then providers can develop and provide interventions to minimize cognitive impairment's impact on QOL.

This study focused on women with breast cancer for several reasons. Breast cancer long-term survival rates have increased significantly in recent years with survival rates of 78% after 15 years (American Cancer Society, 2020a). Second, reporting of cognitive impairment is common among breast cancer survivors (Ahles et al., 2002; Bender et al., 2006; Hurria et al., 2006; Johns et al., 2016). Third, researcher had access to a population of patients with breast cancer. In the next section, the researcher describes breast cancer and its treatment and the conceptual framework for the study.

Breast Cancer

Cancer is caused by mutations that alter the expression or products of individual genes, and these mutations arise in many different cell and tissue types. Breast cancer forms in the tissue of the breast. It can occur in the lining of the milk ducts, ductal carcinoma, or in the lobes of the breast, lobular carcinoma. If any of these two types of cancer spread to surrounding tissue, it is then called invasive breast cancer (American Cancer Society, 2020a).

Staging of Breast Cancer

The stages of breast cancer identify the extent to which cancer cells have spread from the original tumor. The staging of breast cancer is determined by the American Joint Committee on Cancer (AJCC) TNM system, further explained in Appendix B. T identifies the size of the breast tumor and if it has grown into nearby areas, N identifies if the cancer has reached nearby lymph nodes and M identifies whether the cancer has metastasized. Once the TMN has been determined, the oncologist will determine the stage of cancer. After the diagnosis and staging have been completed, the patient will then be informed of the recommended treatment regimen

Tumor Types of Breast Cancer

The tumor types of cancer are classified by three receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER). When classifying tumors, these receptors can either be positive (+) or negative (-). ER+ and PR+ tumors have an increased risk of cancer cells growing because these tumors have receptors for estrogen and progesterone, which can fuel the growth of cancer. In addition to these combinations, there are triple negative and triple positive breast cancer cells where all three

receptors are negative or positive. Based on the classification of the tumor cell, a treatment regimen will be identified.

Treatment Types of Breast Cancer

After surgery to remove the breast cancer cells, chemotherapy may be recommended if the cancer is 1) invasive and the patient is premenopausal 2) in the lymph nodes or distant metastases are present (regardless of menopausal status) 3) HER+ or 4) cancer is triple negative (ER-, PR-, HER-). Chemotherapy is not recommended in noninvasive cancers that have little risk of spreading to other parts of the body. Once these two types of treatment are complete, endocrine therapy (ET) is initiated for ER+ and PR+ cancer cells.

ET can include tamoxifen and aromatase inhibitors (AIs) (letrozole, anastrozole, and exemestane). Most premenopausal patients receiving AIs for a minimum of 5 years. Due to the broad range of cancer types and the range of treatments, predicting the influencing factors affecting cognition can be difficult.

Hormone therapy in patients with breast cancer has been shown to induce menopause in premenopausal patients and worsen symptoms for women who are menopausal (Kilickap et al., 2013). Menopausal-like symptoms include hot flashes, night sweats, vaginal dryness, and gradual changes in cognition. Patients treated with tamoxifen often report issues with hot flashes, vaginal discharge, and fatigue, whereas patients treated with AI report problems with arthritis, osteopenia, osteoporosis, and hyperlipidemia (Kilickap et al., 2013). Whether or not hormone therapy affects cognitive function is still to be determined. Gallicchio, Calhoun, & Helzlsouer (2017) conducted a prospective cohort study comparing cognitive function of 146 women with breast cancer to 200 postmenopausal women without a history of cancer. This study showed women with breast cancer who received AI therapy were more likely to report

symptoms of numbness or tingling in extremities, fatigue, hair loss, forgetfulness, and difficulty concentrating than healthy controls. Given the different symptoms associated with each type of hormone therapy, further evaluation is needed to determine which symptoms cause the most burden in breast cancer survivors.

CRCI in patients with breast cancer can cause impairments in attention, memory, and executive function but we do not know if chemotherapy is the defining factor or if it is the combination of breast cancer treatment (radiation, ET, chemotherapy). To address this gap, this study will compare changes in self-reported cognitive impairment by evaluating two groups (heathy controls versus breast cancer patients who have had surgery, radiation, and chemotherapy) at six months or less of endocrine therapy. By assessing these two groups, we can evaluate the effects chemotherapy has on a patient's cognitive status. This study will explore the differences in cognition between patients with breast cancer who receive chemotherapy in conjunction with radiation and ET and healthy controls. This study will also explore how self-report of cognitive impairment affects QOL.

Conceptual Framework

Myers (2009) developed a revised conceptual model of Chemotherapy-Related Changes in Cognitive Function by synthesizing the conceptual model of Chemotherapy-Related Change in Cognitive Function (Hess & Insel, 2007) and the revised Theory of Unpleasant Symptoms (TUS) (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The original TUS was created by Lenz et al. (1995) using three-factor categories (physiological, psychosocial and situational) that can vary in duration, intensity, quality, and distress that showed the relationships and experience of symptoms. This original TUS model was unidirectional and hypothesized that influencing factors resulted in one symptom. As research evolved with the study of multiple symptoms

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(i.e., symptom clusters) the need for improving this model became apparent. In 1997, Lenz and colleagues revised the TUS to show a bi-directional flow. This revised model proposes that symptoms not only affect performance but in turn influence some physiological, psychological, and situational factors. This model hypothesized that symptoms also contribute to changes in the physiological, psychological, and situation factors, and thus may increase or decrease symptom intensity.

The conceptual model of Chemotherapy-Related Changes in Cognitive function was developed in 2007 by Hess and Insel through a systematic literature review focused on the experience of cognitive decline experienced by patients with cancer who received chemotherapy treatment. This model showed that cognitive function might be altered through two distinct and interactive pathways: the cancer diagnosis or the cancer treatment. The cancer diagnosis path leads to the development of anxiety, stress, distress, and depression. The second pathway illustrates a direct connection between the cancer treatment and the physiological effects. Both of these pathways interact with each other to explain which mediators and moderators may lead to changes in self-report cognitive function. These changes may affect QOL and functional ability for patients with cancer.

Revised Conceptual Model of Chemotherapy-Related Changes in Cognitive Function

The revised conceptual model of Chemotherapy-Related Changes in Cognitive Function provides "a more elaborate description and representation of the symptoms experience of cognitive impairment" (Myers, 2009, pg. E8) by combining the multiple symptom evaluations of the TUS with the antecedent components (cancer treatment and diagnosis) of the Conceptual Model of Chemotherapy-Related Changes. This allows the researcher to examine the

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antecedents in conjunction with multiple treatment symptoms that may be involved with increased cognitive impairment. By measuring these influencing factors, we can explore the relationships between symptoms, CRCI, and self-report of cognitive function in patients with breast cancer.

The model describes two pathways for changes in cognitive function. The first pathway is through the cancer treatment which has different physiological factors (chemotherapy agents, radiation therapy, treatment dose and duration, concomitant medications, comorbidities, and low levels of vitamin D) that can contribute to associated toxicities (neurotoxicity, anemia, cytokines, low serum hormone levels, vascular injury) that in turn contribute to changes in cognitive function which can affect QOL and functional ability of patients with cancer. This pathway includes the timing, intensity, distress, and quality of concurrent symptoms (fatigue, pain, depression, and anxiety). These symptoms associated with physiological factors or toxicities of cancer treatment affect the QOL of patients with cancer.

The second pathway proposes that when a person is diagnosed with a cancer diagnosis, their psychosocial state (stress, depression, anxiety, and distress) and situational state (lifestyle and personal experience) influences cognitive function. The two pathways interact to influence cognitive function and in turn affect the QOL and functional ability in patients with cancer.

Another aspect of this revised conceptual model proposes that individual moderators (age, education, intelligence, genetic factors, and coexisting neurocognitive disorders) contribute to changes in cognitive function. The moderators can be applied to both pathways. The model, as a whole, provides researchers a framework to explain how chemotherapy can contribute to cognitive impairment experienced by patients with cancer through one or both suggested pathways.

Figure 1 The Revised Conceptual Model of Chemotherapy- Related Changes in Cognitive Function.
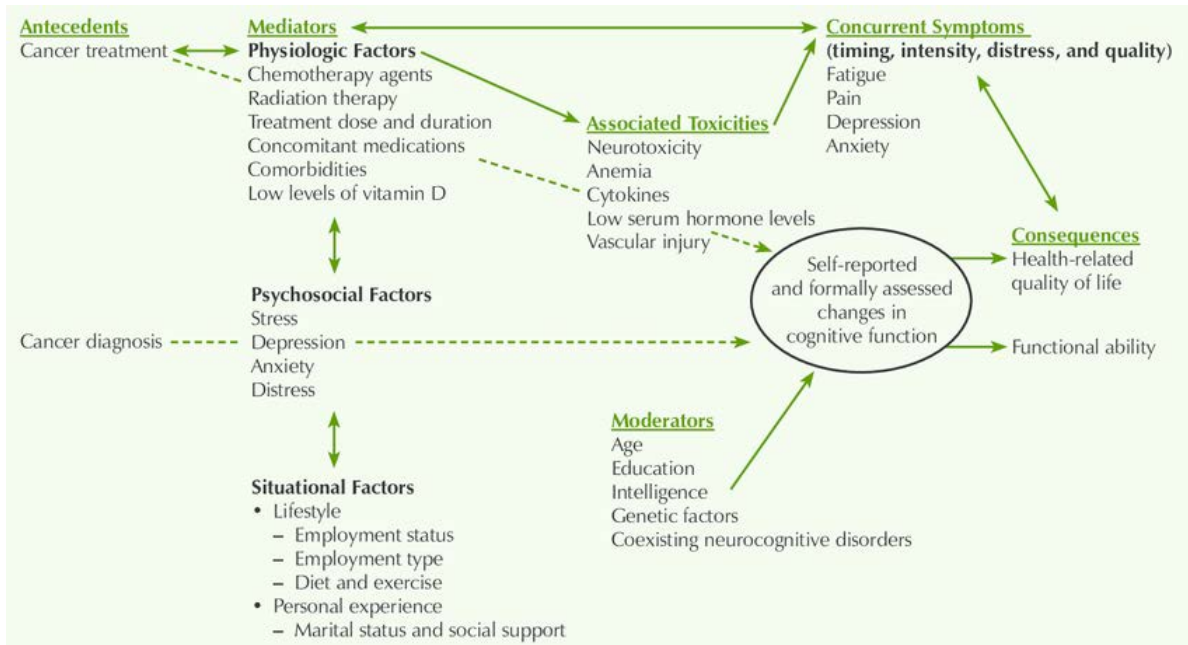
The purpose of this study was to examine the effect of cancer treatment on cognitive impairment. This study examined the effects of cancer treatments on cognitive function in women following surgery, chemotherapy, and radiation and less than six months of endocrine therapy and compared their results to a sample of women without breast cancer. By assessing these two groups we examined the contribution chemotherapy may have on the development of cognitive impairment. Based on the model above, we have adjusted the model to focus on the purpose of this study, seen in Figure 2 below.

Figure 2 Adapted Revised Conceptual Model of Chemotherapy in Cognitive Function
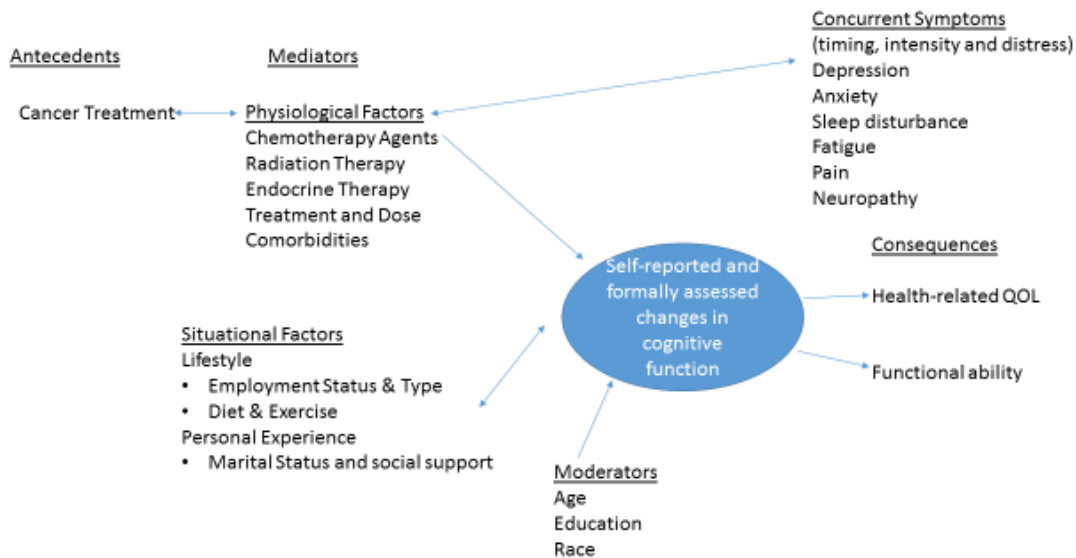
This study explored possible relationships breast cancer treatment and cognitive function. Concurrent symptoms, specifically depression, anxiety, pain, fatigue, and sleep disturbance were examined as potential influences or modifiers of cognitive function. The impact of cognitive function on QOL and functional ability were examined. Other potential moderators (age, education level and race) and situational factors (marital status, social support, diet and exercise, employment status) and physiological factors (comorbidities and menopause status) were examined in relationship to cognitive function.

Study Purpose and Aims

The purpose of this dissertation project was to: 1) Describe the differences between two groups (Group 1: Healthy controls vs. Group 2: Radiation, Chemotherapy, and ET (6 months or less) in self-reported attention, memory, and executive function 2) Explore the association between symptom burden and QOL in breast cancer survivors 3) Examine relationship between moderators (physiological factors (chemotherapy agents, radiation therapy, endocrine therapy,

treatment and dose, and comorbidities) situational factors (lifestyle and personal appearance) and cognitive function.

In Chapter 2, relevant literature is described. In Chapter 3 the methodology, research design, and analysis plan is reported. In Chapter 4 the research results are reported. Chapter 5 concludes the dissertation with a discussion and implications of the findings.

Definitions

Chemotherapy-related cognitive impairment (CRCI) is defined as a change in cognition due to the administration of chemotherapy. Typical changes associated with CRCI are executive functioning, working memory, and inability to maintain attention. CRCI will be measured by the self-reported scores from the AFI, EMQ, and Neuro-QOL Cognitive Function Short Form.

Attention is defined as "the taking possession by the mind, in clear and vivid form, of one of what seems simultaneous possible objects or trains of thought" (Macleod, 2006). It will be measured by the Attentional Functional Index.

Memory is defined as the power or process of reproducing or recalling what has been learned and retained especially through associative mechanisms (Merriam Webster, 2020). Memory will be measured by the revised Everyday Memory Questionnaire.

Executive function is defined as a "higher-order cognitive processes, which include initiation, planning, hypothesis generation, cognitive flexibility, decision-making, regulation, judgment, feedback utilization, and self-perception" (Jansen et al., 2005, pg. 330). It will be measured by Neuro-QOL Cognitive Function Short Form.

Symptom burden is defined as the collection of symptoms that may occur over the course of a patient's treatment. Symptom burden will be measured by the Memorial Symptom Assessment Scale Short Form (MSAS-SF).

Quality of Life is defined as the overall well-being of an individual that may be affected by a person's health (Hess and Insel, 2007). The QOL of patients with breast cancer will be assessed using the LASA.

Anxiety and Depression will be assessed by the PROMIS Anxiety 6a and Depression 6a. Anxiety is defined as an emotion of feeling worried and Depression is defined as an emotion of feeling sad.

CHAPTER 2: LITERATURE REVIEW

Cognitive impairment associated with cancer treatments, specifically chemotherapy is defined in the literature in multiple ways and referred to by numerous terms. With these varied definitions, multiple measures of cognitive impairment are used in the literature. Thus, it is difficult for researchers to compare results and to determine the most appropriate cognitive impairment measurement tools for patients with cancer. Over the past decade as the number of cancer survivors has increased, the potential long-term effects of chemotherapy treatment, specifically on the brain and cognitive function became an area of interest for oncology researchers. Women with breast cancer, who have been treated with chemotherapy, experience multiple symptoms that may or may not be associated with the development of cognitive impairment (Cheng, Wong, and Koh, 2016; Cutshall et al., 2015; Wagland et al., 2015). Tumor type, treatment type and patient characteristics such as age, race, ethnicity, and education influence symptom burden and development of cognitive impairment. This study included patients who have received chemotherapy in conjunction with radiation and ET. This sample allowed the exploration of symptoms experienced, other physiological conditions, and situational factors in relationship to cognitive function.

The purpose of this literature review is to describe cognitive impairment and how chemotherapy treatment may affect a patient's CI. Further, this literature review describes measures of cognitive impairment used in previous studies. Included in the chapter are descriptions and research evidence that support the selected study instruments: self-report screening tools, symptom burden, cognitive function measures and QOL used in this study.

This chapter begins with a review of cognitive impairment and CRCI. This review explores the relationship between CI and CRCI for patients with cancer. Followed by the

examination of self-report measures for CRCI, specifically addressing attention, memory, and executive function. Symptoms and symptom burden associated with breast cancer treatment (radiation, chemotherapy and ET) are discussed. Lastly, findings regarding the relationship between QOL and cognitive impairment are explored.

Cognitive impairment Secondary to Chemotherapy

Cognitive impairment in patients with cancer is a complex phenomenon that remains undertreated and under recognized. Cancer survivor's complaints of problems with cognition during and following chemotherapy has led to increased recognition by medical professionals (Ahles, 2013; Merriman et al., 2013). The majority of studies conducted on CRCI report small sample sizes and limited power to detect subtle changes in cognitive function. Estimations of the incidence of cognitive impairment vary widely across studies ranging between 17% and 35%. Ahles (2013) and Jansen et al., (2011) reported that 20-30% of patients experienced cognitive impairment prior to chemotherapy treatment while Ahles and Saykin (2001) found that 17-35% experience effects of cognitive impairment two or more years after the completion of chemotherapy treatment. It is unclear if the 65-70% of patients do not experience cognitive changes after chemotherapy treatment or if the assessment tools do not adequately capture the elements of cognitive impairment that are affected by chemotherapy.

Qualitative studies. Several researchers have conducted qualitative studies with women who have received chemotherapy and reported cognitive impairment. In a phenomenological study, Myers (2013) found that women (N=18) noticed cognitive changes prior to and after completion of chemotherapy treatment, with many subjects noticing these changes within the first one to two chemotherapy cycles. Von Ah, Habermann, Carpenter, and Schneider (2013) found that women (N=22) were concerned with six major areas of cognition:

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short and long term memory, the speed of processing, attention and concentration, language and executive function. In a study of seven women, Kanaskie & Loeb (2015) found that some women began to experience cognitive changes during chemotherapy treatment, and some experienced these changes months after the completion of chemotherapy. The main cognitive difficulties noted in these samples included finding the right word, problems with memory, paying attention, concentration difficulties, organizing and prioritizing. All these identified areas fall into the three categories of cognitive impairment: attention, memory, and executive function.

Quantitative studies of cognitive impairment associated with breast cancer.

Van Dam et al. (1998) conducted the first quantitative study of women with high-risk breast cancer who had received high dose (n=34) or standard dose (n=36) of chemotherapy plus Tamoxifen and a control group (n=34) of women with breast cancer who did not receive chemotherapy. Each of the three groups were administered 13 neuropsychological tests which included: Rey Auditory Verbal Learning Test (RAVLT), Complex Figure test; Digit Span and Symbol of the Wechsler Adult Intelligence Scale (WAIS); Trailmaking A and B; D2 Test; and Stroop Test. In addition to these neuropsychological tests each participant completed the Cognitive Problems in Daily Life Checklist which is a self-reported instrument that uses a 5-point Likert scale to assess cognitive problems in memory, attention, thinking, and language. This study found that 32% of patients who received a high dose of chemotherapy, 17% of patients who received standard dose, and 9% of those who did not receive chemotherapy were cognitively impaired. No differences related to cognitive impairment and time since chemotherapy for those subjects, who were receiving chemotherapy were found.

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Wefel et al. (2004) assessed the effects of 5-fluorouracil, doxorubicin, and cyclophosphamide chemotherapy on cognition in 18 patients with breast cancer longitudinally. This study utilized neuropsychological tests which included the Arithmetic, Digital Span and Symbol WAIS; Trailmaking Test A and B; Verbal Selective Reminding Test (VSRT) 11 & 12. This study found that 66% of participants experienced a decline in cognitive performance over a six month period and 50% of those participants experienced a decline one-year later. The main domains of cognition impacted were attention, learning, and processing speed. Hurria et al. (2006) studied women with breast cancer before and six months after chemotherapy (n=28). This study found that 39% of the participants had worsened cognition over the six months. Out of the 39%, 25% (n=7) experienced a decline in cognitive function in two or more cognitive domains. The cognitive domains affected were visual memory, spatial function, psychomotor function, and attention.

Using the Survivorship Survey neurocognitive questions about thinking, memory and attention, Buchanan et al. (2015) found that 60% of 2,296 breast cancer survivors, who were one-year post-treatment experienced issues with cognitive function. Janelsins et al. (2011) also found that 75% of cancer survivors reported problems with attention, memory, or feelings of mental slowness during treatment and 35% experienced these changes in cognition up to a year post chemotherapy treatment. These studies suggest that the incidence of cognitive impairment is higher for breast cancer survivors who received chemotherapy.

Terminology and Usage of CRCI

 One of the biggest challenges in studying cognitive impairment related to chemotherapy or cancer treatment is lack of consensus on the definition of cognitive impairment. Researchers have labeled this phenomenon in numerous ways including cognitive

impairment, changes in cognition, cognitive fatigue, or any other of the various terms that examining cognitive impairment related to chemotherapy or cancer treatment (Craig et al., 2013; Hislop, 2015; Moore, 2014). As a result, these various definitions influence measurement. Recent consensus among researchers is to use the term CRCI for patients with breast cancer who are receiving chemotherapy and experience cognitive impairment (Hess & Insel, 2007). However, there still is no consensus as to which domains of cognitive impairment should be the primary focus when evaluating CRCI.

Researchers have used six domains to describe cognitive function which includes: attention/concentration, memory, executive function, psychomotor speed, processing speed, and language. Janelsins et al. (2011) conducted a systematic review and found that these four areas, executive function, memory, psychomotor speed, and attention are studied the most in patients with cancer who receive chemotherapy. More than 80 instruments have been used in assessing cognitive impairment in patients with cancer and each instrument influenced the findings, leading to the inconsistency of how researchers measure the different cognitive processes (Hess & Insel, 2007). The changes in cognitive function (CRCI) can be subtle, making detection difficult for health care professionals. Because CRCI symptoms appear and disappear, using neuropsychological assessments only provides the researcher a snapshot in time, whereas when subjects self-report cognitive changes, the estimation if change over a period (Ganz et al., 2014).

Neurocognitive tests are less likely to detect subtle cognitive changes than some self-report measures (Schagen et al., 2002). Wefel et al. (2004) found that patients can score within reasonable limits on cognitive function even when they perceive they have a deficit in their ability to perform cognitive tasks. Another study by Castellon et al. (2004) also found that

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breast cancer survivors self-reported cognitive complaints were not related to objective

performance on neurocognitive tasks. As mentioned previously, CRCI has been associated

specifically with the areas of attention, memory, and executive function.

Self-Report Measurement Tools to Evaluate CRCI

Self-report of a symptom is when a patient makes a statement about their sensation or

perception of a disturbance in normal function that is caused by treatment or disease (Cleeland

et al., 2010). These subjective responses lead to the development of patient-reported outcomes

(PRO). In 2002, the National Institute of Health (NIH) reviewed the current state of knowledge

and identified projects on how to help patients with cancer, identifying the need to refine and

utilize symptom-report measures. However, NIH retired the program responsible for these

efforts in 2013, without coming to a consensus about which self-reported assessment tools were

best suited to research symptoms of patients with cancer (National Institute of Health, 2013).

Hess and Insel (2007) found gaps in the literature about instruments used to measure

cognitive function in the cancer population. These gaps identified that there is no current

standard of measurement or assessment of cognitive function in patients with cancer. This

review also found that self-reported and objective measurement tools were not correlated and

the majority of the tools were not validated with the same patient populations.

Inconsistencies in use of instruments to examine cognitive impairment are apparent in

the literature. A meta-analysis by Jansen et al. (2007) showed that only 6 of the 13 identified

neuropsychiatric tests were sensitive to chemotherapy-induced changes in patients with breast

cancer. The six tests were: 1) Fepsy finger tapping test 2) grooved pegboard for motor

function; 3) Rey-Osterrieth Complex Figure Test (RCFT) copy, 4) Weschler Adult Intelligence

Scale (WAIS) block design subset for visuospatial skills; 5) Language subset of the High

Sensitivity Cognitive Scale (HSCS) for language; and 6) HSCS memory subset for verbal memory. None of the tests concerning attention/concentration, executive function, the speed of information processing, and verbal memory were sensitive to chemotherapy-induced changes.

Hutchinson et al. (2012) found that 8 of 24 reviewed studies demonstrated a significant relationship between objective and patient-reported cognitive impairment. These studies assessed objective cognitive function using a variety of neuropsychological measures. Self-reported cognitive impairment was significantly associated with performance on tests of memory in six studies. Significant relationships were also found in measures of attention, visuospatial performance, processing speed, and cognitive flexibility or executive function in individual studies when compared to subjective measures. Out of all the domains of cognition, only visual and verbal memory were consistently found to be associated with subjective complaints. Due to the various types of cancer, treatment plans, psychosocial, and physiological factors experienced by patients, the inconsistencies and lack of a standard of measure will continue.

Most studies use neuropsychology battery tests to assess cognitive impairment in patients with cancer who are undergoing chemotherapy treatment. For this pilot study, self-report questionnaires were used, due to the length of time required to administrate the tests, required training for administration, high cost, and anticipated subject burden of neuropsychology battery tests (Lai et al., 2009; Loh et al., 2016). Because self-reported questionnaires are readily available and easy to administer, these tools have potential as clinical screening tools and then those with screened as likely cognitively impaired could be referred for more expensive cognitive testing.

Three Areas that Define CRCI

Attention

Attention can be defined as "the taking possession by the mind, in clear and vivid form, of one of what seems simultaneous possible objects or trains of thought" (Macleod, 2006). Attention is the primary building block for cognitive function. Any deficit in attention can decrease a person's awareness or ability to perform tasks, making it hard to carry out everyday tasks or fulfill job requirements.

Findings on how CRCI impacts attention are inconsistent. There are three neurological networks (alerting, orienting, and executive) that allow a normal attentional function (Cimprich et al., 2011). Most importantly, the executive network creates a coherent response from conflicting inputs derived from separate parts of the brain (Merriman et al., 2014). While two studies found significant deficits in attention (Bender et al., 2013; van Dam et al., 1998) post chemotherapy, another study has found no gaps in attention (Wefel et al., 2004). Interestingly, Bender et al. (2013) found deficits in attention in patients with breast cancer prior to treatment when cognitive function was tested using a psychometrically sound test battery and scored by neuropsychology trained project nurses. Visovatti et al. (2016) assessed cognitive function in patients with colorectal cancer (CRC), precisely the domains of attention, memory, and cognitive control. They found that CRC patients had lower scores on the AFI compared to healthy controls, indicating that CRC patients perceive their effectiveness on everyday tasks that require attention and cognitive control as inadequate.

In a repeated measures study with newly diagnosed breast cancer patients, Chen, Miaskowski, Liu, and Chen (2012) assessed these patients at multiple times starting from one month after surgery to 24 months after surgery. Measures included AFI, Speilberger State-Trait

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Anxiety Inventory (STAI) State Anxiety Scale, Center for Epidemiological Study-Depression (CES-D), Lee Fatigue Scale (LSF), and the General Sleep Disturbance Scale (GSDS). Chen et. al. (2012) found that patients experienced lower scores for attention every month for eight months and then at ten months after surgery (n=200). Fifty-four percent had a decline in perceived attentional function one month after surgery, with 30-41% showing a continued decline one and two years later. Initial attentional function scores were lower in the chemotherapy plus radiation group. Further results included statistically significant positive correlations of attention scores with anxiety, depression, fatigue, and sleep disturbance ($p<.001$) at each time point.

Memory

Memory is the power or process of reproducing or recalling what has been learned and retained especially through associative mechanisms (Merriam Webster, 2016). When researchers use neurocognitive tests or self-report tools, they refer to memory as either visual or verbal. Cognitive issues associated with memory can be found in patients with breast cancer.

In 2005, Jansen et al. conducted a meta-analysis (n=16) to determine the impact chemotherapy has on each domain of cognitive functioning. This study found that visual memory was the one area with a small effect size and none of the other tests for attention or concentration, executive function, information processing speed, or verbal memory produced a significant effect size. Bender et al. (2006) conducted a repeated measure study on three different groups of patients with breast cancer. Group 1 only received chemotherapy (n=19); Group 2 received chemotherapy plus tamoxifen (n=15); Group 3 did not receive chemotherapy or tamoxifen (n=12). Group 1 and 2 had declines in verbal working memory, with Group 2 exhibiting additional declines in visual memory.

Myers, Sousa, & Donovan (2010) conducted a secondary analysis which looked at patients with ovarian cancer and issues with memory. This study compared two groups: 1) received chemotherapy (n=638); 2) those who do not receive chemotherapy (n=68). Of the total sample of patients who received chemotherapy (n=638), 73% reported memory problems and had a higher mean score for self-reported memory problems than those who did not receive chemotherapy. These findings are supported by previous research that reports memory problems associated with chemotherapy (Ahles et al., 2002, Bender at al., 2006; Hurria et al., 2006). This study also found a significantly negative correlation between memory and education level in patients who received chemotherapy (r =0.14, $p<0.01$). After controlling for education level and time since chemotherapy, four symptoms (fatigue, mood swings, neuropathy, and sleep disturbance) explained 37% of the variance for memory problems. Bender et al. (2013) found poorer verbal memory ($p=0.05$) in patients with breast cancer before treatment when compared to healthy controls, while Von Ah & Tallman (2015) found verbal memory to be significantly correlated with cognitive impairment in breast cancer survivors.

Visovatti et al. (2016) assessed cognitive function in patients with colorectal cancer (CRC), precisely the domains of attention, memory, and cognitive control. They found no difference between groups (specify groups) using the self-report measure of memory, EMQ. The results from the EMQ was consistent with the Rey Auditory Verbal Learning Test (RAVLT) which is a neuropsychological test used to measure long-term, verbal memory (Van Dam et al., 1998). The study did indicate that older age, fewer years of education, and male gender had a significant association with lower long-term memory performance ($p< 0.05$) after controlling for CRC diagnosis.

Executive Function

Executive function refers to a "higher-order cognitive processes, which include initiation, planning, hypothesis generation, cognitive flexibility, decision-making, regulation, judgment, feedback utilization, and self-perception" (Jansen et al., 2005, pg. 330). In the literature review by Jansen et al. (2005), quantitative studies identified that executive function could be affected in breast cancer survivors who received chemotherapy, along with memory, language, attention, and concentration. Pickens et al. (2010) conducted a systematic review of executive function measures, specifically for Alzheimer's and Parkinson's disease, and could not identify a standard of measure. Wefel & Schagen (2012) conducted a review of studies with breast cancer patients and found that most neuropsychological studies show a decline in executive function.

Koppelmans et al. (2012) used the Stroop Color Word Test and Verbal Fluency neuropsychological tests to measure executive function. This study found that breast cancer survivors who received chemotherapy had a lower performance in executive function than women without a history of cancer. Von Ah & Tallman (2015) assessed executive function in breast cancer survivors using two neuropsychological tests: Trail Making Test B and Controlled Oral Word Association (COWA) and one self-reported questionnaire: the Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog). The self-report and neuropsychological results were significantly related ($p<0.05$). However, only the results from the FACT-Cog for executive function was significantly correlated with perceived cognitive impairment.

The PROMIS Neuro-QOL Cognitive Function Short form has been validated in patients with neurocognitive diseases, showing good reliability and validity when measuring

executive function (HealthMeasures, 2020a). This study will be one of the first to use this tool in breast cancer patients to accurately target potential issues with executive function.

Symptom Burden

Patients with breast cancer rarely experience only one symptom. Wagland et al. (2015) conducted a scoping review to determine the treatment-related problems experienced by cancer patients and found 40 different outcome measurement instruments were used (n=51). Due to the different outcome measurement instruments, various definitions (n=98) were used to identify common symptoms. For example, cognitive problems had seven terms used to identify this symptom. Illustrating the importance of identifying common terms that identify common symptoms experienced by patients. This scoping review demonstrated that cancer patients who receive chemotherapy experience both physical and psychosocial symptoms. The top five symptoms according to prevalence were: nausea, vomiting, fatigue, cognitive problems, and depression. Hines et al. (2014) also reported that chemotherapy treatment may result in peripheral neuropathy, electrolyte imbalances, stress, fatigue, nausea/vomiting, pain, and medication side effects.

Cutshall et al., (2015) surveyed cancer survivors (n=171) regarding symptom burden and found that the most bothersome symptoms included fear of re-occurrence, stress, fatigue, difficulty sleeping, weight gain, mental fogginess, pain, and neuropathy. A cross-sectional study by Cheng, Wong, and Koh (2016) evaluated symptom burden in women with breast cancer (n=222) using the Memorial Symptom Assessment Scale (MSAS) and found that 53% of respondents reported 1-5 symptoms, and 33% reporting 6-10 symptoms. The most commonly reported symptoms were lack of energy, peripheral neuropathy, pain, and difficulty sleeping. Another cross-sectional study by Webber and Davies (2011) of cancer patients using

the MSAS-SF (n=120) found that 92% felt a lack of energy and 69% had difficulty concentrating.

A systematic review by Kirkova et al. (2006) found that the MSAS-SF was the most comprehensive questionnaire for both clinical and research assessments of symptom experience in patients with cancer. By incorporating this scale, we can examine what symptoms emerge as cognition declines in patients with cancer who have been treated with chemotherapy. The MSAS-SF is designed to evaluate the physiological and physical symptom burden in patients with cancer. The MSAS-SF is a valid and reliable measure of symptoms experienced in different types of cancer (Browall et al., 2013). The MSAS-SF measures 32 symptoms that may be expressed in patients with breast cancer. The revised conceptual model of Chemotherapy-Related Change in Cognitive Function proposed that multiple symptoms (symptoms clusters) affect cognition. Also, psychological factors (anxiety and depression) are associated with of cognitive function and will be measured by the PROMIS Anxiety 6a and Depression 6a self-report instrument.

Anxiety and Depression

According to the revised conceptual model of Chemotherapy-related changes in Cognitive function, multiple factors including anxiety and depression impact the development of cognitive impairment. Patients may experience anxiety or depression before, during or following cancer treatment. However, previously studies (Ahles et al., 2012; Jenkins et al., 2006; Kanaskie, M., 2012; Myers et al., 2008; Saykin & Ahles, 2007; Schagen et al., 2014; van Dam et al., 1998) statistically controlled for pretreatment significant psychological distress and found that persistent cognitive changes post-chemotherapy occur irrespective of pretreatment anxiety and depression. Ramalho, M., Fontes, F., Ruano, L., Perira, S., & Lunet, N. (2017) also

showed a significant increase in risk of cognitive impairment among patients with no anxiety

prior to treatment. Leading researchers to question how anxiety and depression contribute to the

development of cognitive impairment.

Higher levels of anxiety ($p < 0.001$) and depression ($p < 0.001$) has been associated with

decreased cognitive function in patients with breast cancer (Chen et al., 2016; Chen,

Miakowski, Liu, and Chen, 2012; Merriman et al., 2017; Miura, Ando, & Imani, 2016).

Miakowski et al. (2006) measured depression with fatigue and found that patients with the

highest reported levels of fatigue had the highest levels of depression. In another study by

Kreukels et al. (2008) anxiety and depression were significantly correlated ($p < 0.001$) with

fatigue in patients with breast cancer who received adjuvant chemotherapy. Webber and Davies

(2011) study (n=120) found that 15% screened positive for anxiety and 25% screened positive

for depression, with 6% screening positive for both. Deschields, Potter, Olsen, and Liu (2014)

conducted a longitudinal study of patients with breast cancer (n=542) over a 12 month period

and found that "feeling sad, worrying, and feeling irritable" were 3 out of the top 10 symptoms

identified as most burdensome to patients.

To further evaluate this evidence, this study focused on psychological factors of

depression and anxiety by administering the PROMIS Anxiety 6a and Depression 6a to our

target population. In addition to these two psychological factors, we examined one groups of

cancer patients to explore the relationship between symptoms and cancer treatment plan.

Chemotherapy

A study by Koppelmans et al. (2012) found that breast cancer survivors who received

cyclophosphamide, methotrexate, and 5-fluorouracil had a lower performance in memory,

attention, and executive function than women without a history of cancer. These women on

average had a cognitive decline that correlated with a healthy control who was six years older. Jenkins et al. (2016) found that six months after chemotherapy treatment, patients with breast cancer reported fatigue, memory problems, and poorer QOL than those patients with breast cancer who did not receive chemotherapy. Wefel & Schagen (2012) found that the areas of cognition predominantly affected by chemotherapy were learning, memory, processing speed, and executive functioning. Ahles et al. (2010) also reported that patients with breast cancer treated with chemotherapy and those treated with ET both showed declines in cognitive function compared to healthy controls, suggesting that hormone therapy may also lead to CRCI. The study patients treated with both chemotherapy and ET had greater self-report of cognitive decline than those patients who just received chemotherapy.

Endocrine Therapy

Hormonal changes secondary to CRCI can affect the cognitive function of patients with breast cancer due to the depletion in estrogen. This oral anti-estrogen therapy is usually prescribed for five years for patients with breast cancer, and typical side effects include perceived changes in cognitive function, specifically in concentration and recall (Bender et al., 2013). Patients with breast cancer who received aromatase inhibitors (AI) for six months were more likely to report symptoms of peripheral neuropathy, fatigue, difficulty concentrating, forgetfulness, and hair loss compared to women with no history of cancer who were also on AI therapy (Gallicchio, Calhoun, and Helzlsouer, 2017). These patients with breast cancer also reported a higher incidence of peripheral neuropathy and forgetfulness at one year of AI therapy.

Miura, Ando, and Imai (2016) conducted a cross-sectional study with women with breast cancer who had just had surgery (n=93) found that patients with higher cognitive decline

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had more severe menopause and depressive symptoms. Kilickap et al. (2013) found that ET with either tamoxifen or AI did not affect cognitive function when compared to patients with breast cancer who did not receive ET. In addition to cognitive function, they also found similar scores in QOL. However, the majority of the patients in each group (>90%) had received chemotherapy, furthering the need for studies to look at the effects chemotherapy and ET may have on the development of cognitive impairment.

Breckenridge et al. (2012) conducted a cross-sectional study of breast cancer patients three years into anti-estrogen therapy and found associations among ET therapy, poorer cognitive function, and worse mood. Ribi et al. (2012) found no change in self-reported cognitive function one year after completion of ET, leading researchers to question the actual effects ET has on cognition and if ET alone can cause cognitive changes. This study will compare two groups: group 1 will be healthy controls and group 2 will be women with breast cancer who have received radiation, chemotherapy, and six months or less of ET therapy. In addition to contributing psychological factors and symptoms that affect self-report cognitive impairment, QOL will be addressed in patients with breast cancer.

Quality of Life

Cancer treatments, including chemotherapy, radiation, and ET have led to the increase in number of breast cancer survivors; however, side effects associated with their administration can significantly reduce QOL. Issues with cognitive function are one of the most frequently reported symptoms of patients with breast cancer who have been treated with chemotherapy. Cognitive Impairment can substantially affect the QOL in breast cancer survivors (Myers, 2013; Voh AH, Habermann, Carpenter, & Schneider, 2013)

Myers, Wick, & Kelpm (2015) reported that cognitive complaints are present in some patients with breast cancer before receiving chemotherapy treatment and those cognitive complaints increased during treatment. In this study, subjects reported a negative rating for QOL within five years of receiving chemotherapy, however, those patients with breast cancer who completed chemotherapy more than five years previously did not differ in their QOL scores from healthy controls. Miura, Ando, and Imai (2016) cross-sectional study of women with breast cancer (n=93) had 90.8% undergoing ET, and this majority had low QOL scores. The lower QOL scores were also associated with higher cognitive impairment and depression scores. Deschields, Potter, Olsen, and Liu (2014) measured QOL with the Functional Assessment of Cancer Therapy-General Scale (FACT-G) and found that overall QOL scores were stable over the 12-months. This study also found that patients QOL scores were decreased as symptom burden increased, with 89-93% of patients (n=542) reporting at least one symptom. This study also showed the QOL correlated negatively with the total MSAS scores for each time point. These results were all significant ($p<0.001$) and found that patients with low QOL scores had higher reported symptom burden.

Chen et al. (2016) conducted a secondary analysis of data from the previous study (Chen, Miaskowski, Liu, and Chen (2012) to examine QOL in breast cancer survivors two years after surgery (N=97). There were four groups in the study: Group A= low mean scores on all five symptoms; Group B= low scores on cognitive impairment and physical fatigue but moderate for sleep disturbance, anxiety, and depression; Group C= moderate levels on all five symptoms; Group D= highest mean scores on all five symptoms. Group A had the highest QOL scores and had a significantly better overall QOL than those in Group D ($p=0.08$). Illustrating that QOL can be impacted by symptoms experienced by the patients.

This study measured QOL using the LASA since chemotherapy may increase symptom burden on patients with breast cancer, contributing to a change in self-report of cognitive function and QOL.

Summary

Further research is needed to identify patients which breast cancer are at an increased risk for declines in cognitive function due to the administration of chemotherapy. Subsequent studies are needed to identify intervention(s) to mitigate the impact of chemotherapy on cognitive function. First, we need to determine the best tools possible to detect these subtle changes in cognition and determine if chemotherapy is the determining factor for declines in self-reported cognitive function. In Chapter 3, the methodology of the study is discussed with a description of the psychometric properties of the seven self-report questionnaires used to measure cognitive impairment, symptom burden, QOL, anxiety, and depression.

CHAPTER 3: RESEARCH DESIGN

Cognitive impairment in breast cancer patients who receive chemotherapy has been shown to affect the cognitive domains of attention, memory, and executive function, so this study focused on these specific areas (Hess & Insel, 2007; Von Ah D et al., 2013; Myers, Wick, & Klemp, 2015). Symptom burden (number of symptoms and distress level), QOL, and cognitive impairment (attention, memory, and executive function) have been found to be correlated, so this study explored which symptoms were experienced by this patient sample. These symptoms may or may not be associated with the type of cancer treatment (chemotherapy, radiation, and ET). This study included two groups: one breast cancer patient group who received surgery chemotherapy, radiation, and ET and a healthy control group.

The purpose of this study was to examine the effect of cancer treatment on cognitive impairment. This pilot study compared cognitive function in 2 groups: 1) healthy control similar in age to group with breast cancer and 2) a breast cancer group following surgery, radiation, and chemotherapy and currently receiving ET for six months or less. By comparing these two groups, it was possible to evaluation the relative influence of chemotherapy on the cognitive function.

This descriptive, correlational pilot study that compared healthy women of similar age and those women who receive surgery, radiation, and chemotherapy for breast cancer at six months or less of endocrine therapy. The measured variables included cognitive function (attention, memory, and executive function), symptom burden (anxiety, depression), symptoms measured by MSAS-SF, and QOL. Each participant was administered a demographic form, three cognitive impairment tools (AFI, EMQ, Neuro-QOL), LASA, MSAS-SF, PROMIS Anxiety 6a and Depression 6a at one clinic appointment.

Research Questions

1. What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer in executive function, memory, and attention?

2. What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer and QOL?

3. What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer and self-report of symptom burden, anxiety, and depression?

4. Is there an association between QOL, anxiety, depression and symptom burden among women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer?

Sampling methods/subjects

This pilot study was a descriptive, correlational study that used a consecutive convenience sample to examine cognitive impairment with QOL and symptom burden at one time-point in the patient's treatment plan (6 months or less on ET therapy). This pilot study was conducted at the Leo Jenkins Cancer Center, a cancer center associated with a tertiary medical center and university.

In determining the sample size for this pilot study, Hetzog (2008) was used, providing evidence that 20 patients per group (n=40) would sufficiently assess the feasibility and acceptability of this study. Hertzog (2008) also states that finding an effect size for this sample is not appropriate or precise. Since we are conducting a pilot study, attempting to estimate

effect size or provide a preliminary test of a research hypothesis is not appropriate (NCCIH, 2017).

The inclusion criteria for patients with breast cancer will include current patients with breast cancer, who have had surgery, chemotherapy and radiation, are on ET for 6 months or less, English speaking, female, all ethnic/racial groups, and < 18 years of age. Exclusion criteria 1) any prior cancer diagnosis 2) Non-English-speaking patients. Inclusion criteria for healthy controls will be English speaking, female, all ethnic/racial groups, < 18 years of age. Exclusion criteria will be 1) any prior diagnosis of cancer 2) Non-English speaking.

An employee of the Leo Jenkins Cancer Center identified potential participants for the study based on the inclusion and exclusion criteria. The PI approached all potential participants at the Leo Jenkins Cancer Center during their regularly scheduled clinic visit. The PI explained the study to the potential participant, using the informed consent IRB Human subjects approved. If the potential participants agree to participate, the PI enrolled the patient into the study by having the patient sign the informed consent and HIPPA form. The healthy controls were obtained by utilizing East Carolinas University email blast that utilized information about the study. All willing participants responded to the PI through email and a link to the survey in REDCAP was sent to the participant to complete. All participants were asked to complete the seven questionnaires and demographic form AFI, EMQ, Neuro-QOL, MSAS-SF, LASA, PROMIS Anxiety 6a and Depression 6a).

Methods/Data collection procedures

The demographic form, AFI, EMQ, Neuro-QOL, MSAS-SF, LASA, PROMIS Anxiety 6a and Depression 6a were administered at the one-time point and took about 30 minutes to

complete. Demographic information collected included age, gender, race, ethnicity, education level, income, marital status, and smoking status. The PI abstracted from the patient's chart all remaining information not collected in the demographic form. The demographic and data abstracted from the chart will be stored on an ECU pirate drive under a secured and locked folder.

Electronic Medical Record (EMR) Abstraction

The electronic medical records (EMR) of 20 participants were accessed through the Vidant Medical Center (VMC) intranet. Utilizing the EMR, the PI abstracted demographic data and key contributing factors to the development of CRCI. An SPSS spreadsheet created by the PI served as the data collection tool and was stored on ECU pirate drive, a secure site. Only the PI had access to the data collection sheet once all data has been abstracted. Once a patient was recruited into the study, they were given a unique identification number, and only the PI had access to that list.

All information was entered using the unique identification number. Information that was collected from the EMR after patient's permission is (a) height and weight; (b) type and stage of cancer; (c) laboratory values for hemoglobin, hematocrit, and c-reactive protein (CRP); (d) medication regimens that include type of medication and dose (chemotherapy medications, ET medications, anti-anxiety, anti-depression, pain, steroids, anti-inflammatory, sleep medications); (e) current/previous medical diagnosis; (f) location of radiation. All data was de-identified for statistical analysis. An SPSS spreadsheet was used for the data where the PI stored the participant's information.

Self-Report Instruments

Attentional Functional Index

The Attentional Functional Index (AFI, Cimprich, 1992) is a 16-item instrument that measures directed attention and accesses cognitive distress. The design of the instrument allows measurement of perceived effectiveness in everyday activities that are identified through attention and working memory. The first 12 questions measure attentional function in the higher level of cognitive activities and the remaining four measure subjective experience of attentional difficulties; the last four are reversed scored. The scores on the AFI range from 0-10 with lower scores indicating poorer levels of attentional function. The AFI has been validated with register nurse students (Sanders, C. M., Yankou, D., & Andrusyszyn, M., 2005) and various cancer patients, specifically breast, lung, and colorectal (Cimprich, Visovatti, & Ronis, 2011; Chen et al., 2016 (Cronbach alpha= 0.95); Chen, Miaskowski, Liu, & Chen, 2012 (Cronbach's alpha= 0.95); Johns et al., 2016 (Cronbach's alpha= 0.87); Myers, Wick, and Klemp, 2015 (Cronbach's alpha=.89); Visovatti et al., 2016 (internal consistency coefficient= 0.91).

Everyday Memory Questionnaire

The revised Everyday Memory Questionnaire (EMQ) measures the various everyday memory problems and consists of subjective, meta-memory reports that examine the objective level of performance (Sunderland et al., 1983). The revised EMQ is a 13-item scale that can range from 0 to 52. Higher scores indicate more reported difficulties; each item is scored on a 5-point rating scale (0 to 4), based on the frequency of the reported problem. This revised 13 item EMQ is easy to use and screen objective memory impairment in patients in the clinical setting. The EMQ has been used and validated in adult populations (Efklides et al., 2002 (Cronbach's alpha= 0.89); Royle & Lincoln, 2008 (Cronbach's alpha= 0.91)) and colorectal cancer (Visovatti et al., 2016 (internal consistency coefficient= 0.9).

Neuro-QOL Cognitive Function Short Form

The Neuro-QOL Measurement System has self-report instruments of health-related

QOL for adults and children which are available as adaptive computer tests (CAT) or fixed

length short form tests. Neuro-QOL psychometricians calibrated each item bank using item

response theory (IRT). Per the standardized Neuro-QOL manual, the T-score (mean of 50, SD

of 10) for this form is 36.4 with a standard error of 5.2. The 95% CI is 26.2 to 46.6. To evaluate

executive function, we will use the Neuro-QOL Cognitive Function Short Form. The Neuro-

QOL Cognitive Function short form is an 8-item Likert scale that ranges from 1-5 (1=very

often to 5= never). The scores can range from 8-40 with higher scores indicating a decrease in

executive functioning. The Neuro-QOL Cognitive Function short form was chosen based on the

recommendations from NIH to have researchers use the same measurement tools when

assessing specific patient-reported outcomes.

Memorial Symptom Assessment Scale-Short Form (MSAS-SF)

The Memorial Symptom Assessment Scale-Short Form (MSAS-SF) is used to evaluate

the physical and psychological symptom burden in patients with cancer. The MSAS-SF is a

self-report instrument that allows patients to rate symptom distress associated with 28 physical

and four psychological symptoms. MSAS-SF subscales include the global distress index (GDI)

(4 psychological symptoms: feeling sad, worrying, feeling irritable, and feeling nervous, and

six physical symptoms: lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry

mouth, numbness or tingling). The physical symptom distress score (PHYS) comprises 12

prevalent physical symptoms (pain, lack of energy, lack of appetite, feeling drowsy,

constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and

dizziness) The six prevalent psychological symptoms (worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating).

The frequency of all symptoms is over a seven-day period or within the past week. Each physical symptom is scored on a 5-point Likert scale (0.8=not at all; 1.6=a little bit; 2.4= somewhat; 3.2= quite a bit; 4= very much). Each psychological symptom is scored from 1-4 (1= rarely; 2= occasionally; 3=frequently; 4= almost constantly). Scores range from 0-104, with higher scores indicating a higher symptom burden. The Cronbach alpha coefficient for the MSAS ranges from 0.76-0.87 (Protenoy et al., 1994). The MSAS-SF has been validated in patients with cancer in numerous studies (Browall et al., 2013; Cheng, Wong, and Koh, 2016 (Cronbach's alpha from 0.72 to 0.78); Deschields, Potter, Olsen, and Liu, 2014 (alpha reliability score= 0.90); Kirkova et al., 2006; Webber & Davies, 2011)

Linear Analogue System Assessment (LASA)

The LASA scale is used to measure quality of life by using single-item assessments. This instrument asked to describe a person's overall quality of life during the past week. It is a 10 point Likert scale that can range from 0-10 (0= as bad as it can be to 10= as good as it can be), with higher scores indicating a higher quality of life. The purpose of the LASA is to have each item standalone so there is no total score. Without a total score, no statistical verification for internal consistency or Cronbach's alpha is obtained.

PROMIS Anxiety 6a and Depression 6a

Both PROMIS tools for anxiety and depression are a 6-item scale rated on a 5 point Likert scale (ranging from 1=never to 5=always). They both are self-report instruments that ask the patient to recall how they felt in the past 7 days. Both can range from 6-30, with higher scores indicating worse anxiety or depression. These two measures were selected due to the

recommendations from NIH to standardize the use of specific measurement instruments that will be used in all research studies.

Data Analysis

All statistical analysis was analyzed through Statistical Package for the Social Sciences (SPSS), version 26. Preliminary analysis was conducted to confirm there was no violation of the normality, linearity and homoscedasticity assumptions for the correlation analysis.

Research Question 1: What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer in executive function, memory, and attention?

T-Tests were used to compare cognitive impairment for each test (AFI, EMQ, and Neuro-QOL) by comparing Group 1 and Group 2. Pearson product-moment correlation coefficients were used to examine the relationship between cognitive impairment and cancer treatment.

Research Question 2: What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer and QOL?

T-Tests were used to compare QOL scores of the two groups. Pearson product-moment correlation coefficients were used to examine the relationship between QOL and cancer treatment.

Research Question 3: What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer and self-report of symptom burden, anxiety, and depression?

T-Tests were used to compare symptom burden scores of the two groups. Pearson product-moment correlation coefficients were used to examine the relationship between symptom burden and cancer treatment.

Research Question 4: Is there an association between QOL, anxiety, depression and symptom burden among women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer?

Pearson product-moment correlation coefficients were used to examine the relationship between QOL (LASA) and symptom burden (MSAS-SF, PROMIS Anxiety 6a, and Depression 6a) in the two groups.

CHAPTER 4: RESULTS

This chapter reports the findings from a descriptive, correlational pilot study of cognitive function of 20 women with breast cancer who received chemotherapy treatment and a comparison group of 20 healthy women. The healthy women answered an electronic survey through REDCAP while the women with breast cancer completed the survey instruments during a clinical visit to the Leo Jenkins Cancer Center. The purpose of this study was to examine the effect of cancer treatment on cognitive impairment, while investigating other potential symptoms through the different survey instruments. The following research questions were asked:

1. What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer in executive function, memory, and attention?

2. What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer and QOL?

3. What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer and self-report of symptom burden, anxiety, and depression?

4. Is there an association between QOL, anxiety, depression and symptom burden among women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer?

All statistical analysis was analyzed through Statistical Package for the Social Sciences (SPSS), version 26. Preliminary analysis was conducted to confirm there was no violation of the normality, linearity and homoscedasticity assumptions for the correlation analysis.

This chapter describes the characteristics of the sample, followed by the findings for each of the four research questions.

Sample Characteristics

A total of 40 participants were enrolled in this study, 20 healthy controls and 20 breast cancer patients. Demographic characteristics are shown in Table 1. Seventy percent of the healthy control group were between the ages of 50 and 69 while 75% of breast cancer group were between ages of 50 and 69. Fifty percent of participants were married in both groups, however 25% of the breast cancer group were single while only 10% of healthy controls were single. The main differences between the groups were in education and ethnicity; 75% of breast cancer survivors were black and only 30% of healthy controls were black. The healthy controls were more likely to have earned a college degree or higher (65%) compared to 30% of the breast cancer group, who had a college degree or higher. The majority of both groups did not smoke.

Table 1

Demographic Characteristics of Sample (N=40)

Characteristics	Healthy Controls n (%)	Breast Cancer Patients n (%)
Age at Time of Study		
40-49	3(15)	3(15)
50-59	5(25)	8(40)
60-69	9(45)	7(35)
>70	3(15)	2(10)
Marital Status		
Single	2(10)	5(25)
Married	10(50)	10(50)
Divorced	6(30)	4(20)
Widowed	2(10)	1(5)
Ethnicity		
White, non-Hispanic	13(65)	5(25)
Black, non-Hispanic	6(30)	15(75)
Asian	1(5)	0
Highest Level of Education		
Kindergarten thru 8th grade	0	1(5)
High School or GED	4(20)	8(40)
Some College	3(15)	5(25)
College	6(30)	3(15)
Graduate School	7(35)	3(15)
Smoker		
Yes	0	2(10)
No	20(100)	18(90)

Research Question 1. Comparison of Control and Breast Cancer Survivors' Cognitive Function: Attention (AFI), Executive Control (Neuro-QOL) and Memory (EMQ).

An independent samples t-test was conducted to compare the attention, executive function, and memory scores between the healthy control and breast cancer patients' groups. There were significant differences between control and patient groups in attention (AFI) with moderate effect size ($\eta^2 = .104$). In addition, there were significant differences between control and patient groups in executive function (Neuro-QOL) with a large effect size ($\eta^2 = .142$). There were no

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significant differences (p >.05) between control and patient groups in memory (EMQ) as seen

in Table 2.

Table 2

Group Differences for Cognitive Impairment, Symptom Burden, and Quality of Life Between
Healthy Controls and Women with Breast Cancer on Endocrine therapy

| | Control | | Breast cancer | | | | |
Variable	M	SD	M	SD	t(38)	p	η^2
Attention	7.90	1.10	6.61	2.51	2.10	.043	.104
Memory							
Retrieval	0.74	0.65	1.24	1.17	1.65	.107	.067
Attentional tracking	0.48	0.58	0.93	1.11	1.61	.115	.064
Total score	0.59	0.54	1.09	1.06	1.88	.067	.085
Executive Function	4.31	0.49	3.68	0.78	2.51	.016	.142
Symptom Burden							
Physical symptoms	0.27	0.20	0.89	0.78	3.42	.002	.235
Psychological symptoms	0.69	0.89	1.73	1.02	3.42	.001	.235
Global distress index	0.58	0.48	1.47	0.94	3.77	<.001	.273
Total score	0.30	0.29	1.02	0.75	4.00	<.001	.296
Anxiety	1.34	0.52	2.16	0.96	3.35	.002	.228
Depression	1.28	0.32	1.77	0.77	2.70	.01	.161
Overall quality of life	8.25	1.29	7.40	2.46	1.37	.179	.047

Question 2: Comparison of Control and Breast Cancer Survivors' Quality of Life (QOL)

An independent samples t-test was conducted to compare the QOL scores between the healthy

control (M=8.25, SD=1.29) and breast cancer patients (M=7.40, SD=2.46) groups. While breast

cancer patients reported a lower QOL (global quality of life), this difference between groups

was not significant (p=.179) in perception of QOL and showed a small effect size (η^2=.047).

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Question 3: Comparison between groups on symptom burden, anxiety and depression

Symptom burden: An independent samples t-test was conducted to compare the total symptom burden scores between the healthy control group (M=.30, SD=.29) and breast cancer patients (M=1.02, SD=.75) groups. Breast cancer patients reported significantly more symptoms as shown in Table 3. The most prevalent symptoms reported by the breast cancer patients were lack of energy (40%) and difficulty sleeping (35%). For the healthy controls, the most prevalent symptoms were difficulty sleeping (15%) and worrying (15%) and there were few other symptoms reported. Also noted in Table 2 is the difference between the physical symptoms, psychological symptoms, and global distress between the two groups. The breast cancer patients had a mean score that was either double or triple in comparison to the healthy control group.

Table 3

Symptoms reported in 10% or more in breast cancer patients compared to symptoms in healthy controls (N=40)

Symptom	Healthy Controls n (%)	Breast Cancer Patients n (%)
Difficulty Sleeping	3(15)	7(35)
Worrying	3(15)	6(30)
Pain	2(10)	7(35)
Lack of Energy	0	8(40)
Hair Loss	1(5)	6(30)
Difficulty Concentrating	1(5)	6(30)
Numbness and tingling	0	5(25)
Dry Mouth	0	5(25)
Changes in Skin	0	4(20)
Don't look Like Myself	0	4(20)
Feeling Irritable	1(5)	4(20)
Feeling Sad	0	4(20)
Feeling Drowsy	0	4(20)
Sweats	0	3(15)
Feeling Nervous	0	3(15)
Swelling of Arms and Legs	0	2(10)
Sexual Problems	0	2(10)
Shortness of Breath	0	2(10)
Difficulty Swallowing	0	2(10)
Itching	1(5)	2(10)
Feeling bloated	0	2(10)
Constipation	0	2(10)

Anxiety and Depression

An independent samples t-test was conducted to compare the anxiety scores between the healthy control (M=1.34, SD=.52) and breast cancer patients (M=2.16, SD=.96) groups. Breast cancer patients demonstrated significantly more anxiety than healthy controls (p=.002) and the effect was large (η^2=.228). An independent samples t-test was conducted to compare the depression scores between the healthy control (M=.1.28, SD=.32) and breast cancer patients

(M=1.77, SD=.77) groups. Breast cancer patients in this sample were significantly more depressed than healthy controls (p=.01) and the effect size was large (η^2=.161).

Question 4: Association between QOL, anxiety, depression, and Symptom burden:

Pearson product-moment correlation coefficients were used to examine the relationship between QOL (LASA) and symptom burden (MSAS-SF, PROMIS Anxiety 6a, and Depression 6a) in the two groups shown in Table 4 and Table 5. For the healthy controls there was a strong negative relationship between QOL and depression (r =-.62), with higher quality of life associated with lower levels of depression. For the breast cancer patients there was a strong negative relationship between QOL and anxiety (r = -.59), depression (r = -.62), physical symptom subscale (r = -.50), psychological subscale (r = -.56), global distress index (r = -.56), and total symptom burden (r = -.61). These correlations demonstrate that higher quality of life scores are associated with lower levels of anxiety, depression, and symptom burden.

Table 4

Pearson Product-moment Correlations Between Measure of Quality of Life and Symptom Burden for Healthy Controls

Measure	1	2	3	4	5	6	7
1. Overall Quality of Life	-						
2. Anxiety	-.45	-					
3. Depression	-.62**	.72***	-				
4. Physical Symptom Subscale	-.48	.11	.37	-			
5. Psychological Subscale	-.30	.56*	.68***	.51	-		
6. Global distress Index	-.38	.43	.65**	.75***	.92***	-	
7. Total Symptom Burden	-.33	.41	.59**	.79***	.87***	.95 ***	-

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

Table 5

Pearson Product-moment Correlations Between Measure of Quality of Life and Symptom Burden for Breast Cancer Patients

Measure	1	2	3	4	5	6	7
1. Overall Quality of Life	-						
2. Anxiety	-.59*	-					
3. Depression	-.62**	.57*	-				
4. Physical Symptom Subscale	-.50*	.74***	.59*	-			
5. Psychological Subscale	-.56*	.77***	.64**	.77***	-		
6. Global distress Index	-.56*	.81***	.60**	.99***	.90***	-	
7. Total Symptom Burden	-.61**	.78***	.64**	.95***	.86***	.95***	-

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

Summary

The results from the statistical analysis showed that attention (AFI) and executive function (Neuro-QOL) were significantly different between the two groups. However, the two groups were not significantly different in memory (EMQ). The women with breast cancer group also reported more symptoms than the healthy control group, with both reporting difficulty sleeping as one of the top symptoms they experienced during the past week. One of the main symptoms expressed by the women with breast cancer, lack of energy, was not reported by any in the healthy control group. For both groups a higher QOL (LASA) was associated with a lower level of depression. However, women with breast cancer reported higher depression and anxiety scores. The results from this sample found that women with breast cancer differ from women without breast cancer of a similar age different in two dimensions of cognitive function (attention and executive function) and symptom burden. The groups did not differ in overall QOL.

CHAPTER 5: CONCLUSION

This chapter will discuss the descriptive, correlational pilot study conducted with 20 women with breast cancer and 20 healthy women to evaluate cognitive function, quality of life (QOL), and symptom burden. The purpose of this study was to examine the effect of cancer treatment on cognitive impairment. This pilot study compared cognitive function in 2 groups: 1) healthy control similar in age to group with breast cancer and 2) a breast cancer group following surgery, radiation, and chemotherapy and currently receiving endocrine therapy (ET) for six months or less. By comparing these two groups, it was possible to evaluate the relative influence of chemotherapy on the cognitive function.

This descriptive, correlational pilot study compared healthy women of similar age and those women who receive surgery, radiation, and chemotherapy for breast cancer at six months or less of endocrine therapy. The measured variables included cognitive function (attention, memory, and executive function), symptom burden (anxiety, depression), symptoms measured by MSAS-SF, and QOL. For the women with breast cancer, a demographic form, three cognitive impairment tools (AFI, EMQ, Neuro-QOL), PROMIS Anxiety 6a and Depression 6a, MSAS-SF, and LASA were administered at one clinic appointment at the cancer center. The healthy control group was sent an electronic survey with the seven instrument tools and demographic form through REDCAP. All information for both groups was imported into SPSS for statistical analysis to answer the following research questions:

1. What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer in executive function, memory, and attention?

2. What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer and QOL?

3. What is the difference between women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer and self-report of symptom burden, anxiety, and depression?

4. Is there an association between QOL, anxiety, depression and symptom burden among women with breast cancer who have been on endocrine therapy for 6 months or less and women without breast cancer?

Discussion of Findings

This study utilized the Revised Conceptual Model of Chemotherapy-Related Changes in Cognitive Function by Hess and Insel (2007) to evaluate the effects of chemotherapy treatments on cognitive function as well as other factors such as demographic characteristics, QOL, anxiety, depression, and symptom burden. The two groups were similar in age but had major differences in ethnicity and education status. Most previous studies have included primarily white women with breast cancer. This study differed in that the sample of breast cancer patients was predominantly black, however, the sample size was small and as a result insufficient for comparison by ethnicity and education level.

The healthy control group had 65% with a college degree or higher while the women with breast cancer only had 30%. The healthy control group was acquired through the ECU list server email. This email went to faculty and staff of ECU, with majority of the participants having a bachelor's degree or higher, which is required for their job. According to the United States Census, 30.5% of the population in North Carolina has a college degree or higher while residence in Pitt County have a higher educational level at 31.8% (United States Census

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Bureau, 2019). This study's healthy control group had a significantly higher educational level compared to North Carolina and Pitt County statistics. The women with breast cancer had a lower educational level compared to the healthy control but was comparable to North Carolina and Pitt County statistics. Issues with lower educational status can have an impact on CI according to previous studies (Myers, Sousa, & Donovan, 2010; Visovatti et al., 2016) and thus may be a consideration in interpretation of the results. It is possible the differences in cognitive function between the healthy control group and the women with breast cancer can be partially explained by the difference in education levels between groups.

The women with breast cancer all had chemotherapy, radiation and six months or less of endocrine therapy. Women in this study received a variety of chemotherapy agents, thus with this limited sample size, no statistical analysis could be conducted for the variations in chemotherapy drugs, dosage, or duration of treatment and chemotherapy regimens' possible effects on cognitive function. The women with breast cancer did show significant differences in attention (AFI) and executive function (Neuro-QOL) when compared to healthy control group. Memory (EMQ) was not significantly different between groups, which contradicts with previous findings of similar studies that used neuropsychological battery tests (Bender at al., 2006; Hurria et al., 2006).

Reasons for the differences in results from previous studies that contradict our findings could be contributed by the difference in tools administered, subject demographics and study design. Bender et al. (2006) used the following neuropsychological tests: the Digital Vigilance Test, Trail-Making test-B, Rey Auditory Verbal Learning Test (RAVLT) and Rey Complex Figure Test (RCF). Then compared these tests to the participants self-reported cognitive function results from the Patient's Assessment of Own Functioning. The scores for memory

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deteriorated over time on both the neuropsychological tests and self-reported questionnaire. Hurria et al. (2006) assessed attention, memory, and executive function through several neuropsychological tests. The results of the test showed a decline in cognitive function from before to 6 months after chemotherapy, with the most affected areas being memory and attention.

In another study, Johns et al. (2016) compared neuropsychological tests (Stroop Test) and self-reported questionnaires (AFI) on attention to evaluate the effectiveness of a mindfulness-based stress reduction class on breast and colorectal cancer patients. The results showed an improvement in the scores using the AFI questionnaire, but no differences were show with the Stroop Test. Visovatti et al. (2016) assessed cognitive function in patients with colorectal cancer (CRC), precisely the domains of attention, memory, and cognitive control. This study compared neuropsychological tests (Attention Network Test (ANT), digital span (DS) test, Rey Auditory Verbal Learning Test (RAVLT)) and self-reported questionnaires (AFI and EMQ) for attention and memory. The results for the neuropsychological tests showed that for attention, the CRC group had slower response times and reported lower scores on the AFI. The EMQ and RAVLT results showed no significance differences between groups.

Jansen et al. (2007) conducted a meta-analysis of the sensitivity of various neuropsychological tests used to detect CRCI. There review of 13 studies showed 29 different neuropsychological tests, but no clear indication on why these tests were chosen. All tests for executive function, attention, and concentration did not show a significant effect size. While only one test showed a significant effect size for memory. Hess and Insel (2007) review of the literature also noted that there were no correlations between self-reported cognitive changes and formal assessments (i.e. neuropsychological battery tests). This review also listed various

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tools that were utilized when assessing attention, memory, and executive function. Majority of the tools used to assess these areas of cognition were neuropsychological tests and these tests can be expensive for the patients. Hence the need for further research on self-reported cognitive impairment tools that can be utilized to assess patients prior to utilizing the neuropsychological tests.

In this pilot study QOL was also examined. This study showed that women with breast cancer reported a lower QOL (global quality of life), which is congruent with previous studies (Ahles, 2012; Hess & Insel, 2007; Miura, Ando, and Imani, 2016; Myers, Wick, & Kelpm, 2015; Von Ah D et al., 2013; Vitali et al., 2017). However, with this single-item measure for QOL (LASA) there was no significant difference between the groups. Upon further analysis between QOL and symptom burden (MSAS-SF, PROMIS Anxiety 6a, and Depression 6a) higher QOL was associated with low levels of anxiety, depression, and symptom burden in both healthy controls and women with breast cancer. However, the women with breast cancer demonstrated significantly more anxiety than healthy controls and were significantly more depressed. Women with breast cancer also reported more symptoms than the healthy controls. The healthy controls reported seven symptoms, while the women with breast cancer reported 22 symptoms.

MSAS-SF was used to assess symptom burden. The results were consistent with previous studies (Cheng, Wong, and Koh, 2016; Weber and Davies, 2011) showing that lack of energy, difficulty sleeping, worrying, pain, hair loss, and difficulty concentrating were the most commonly reported by cancer patients. The women with breast cancer group also reported several more symptoms as bothersome over the past week compared to the healthy control group. Healthy controls did not report any issues with lack of energy but most this symptom

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was frequently reported in women with breast cancer. Also, difficulty sleeping, pain and worrying were the highest reported symptoms for both groups but more common for women with breast cancer. These symptoms could be higher in the women with breast cancer due to the treatment, but further studies are needed to confirm this relationship. These findings correspond to previous studies that suggested that women with breast cancer may experience multiple symptoms that may or may not be associated with the development of cognitive impairment (Cheng, Wong, and Koh, 2016; Cutshall et al., 2015; Wagland et al., 2015).

Limitations

The first limitation was the small sample size (N=40). In addition, the sample population had variability regarding endocrine therapy and chemotherapy agents used in their treatment regimens. The second limitation was the feasibility of recruiting subjects. This researcher encountered difficulties in recruitment for the following reasons: medical oncologists decreased clinic hours, nurse navigator who identified potential participants went out on leave of absence, and patients missing or cancelling clinical visits. In future studies, the researcher should incorporate the office scheduling personnel to ask the patient when confirming the appointment if the potential participant could come 30 minutes earlier to participate in this study. The third limitation was the differences in race and education between the groups: women with breast cancer and healthy controls. Most healthy controls were white (65%) more highly educated while the women with breast cancer who were predominately black (75%) and less educated. Previous mentioned studies found that race, age, and fewer years of education (Visovatti et al., 2016) had significant associations with cognitive impairment. The fourth limitation of the study was due to the time subjects spent completing the forms. Some of the participants were able to finish the questionnaires within 30 minutes,

while others took 40 minutes or longer to complete. When the tools were administered to the women with breast cancer, the majority found that completing the Symptom burden scale (MSAS-SF) was difficult due to the large number of symptoms on the instrument. The final limitations was that this study used a convenience sample, was not longitudinal, had many variations of chemotherapy regimens received, and the inconsistency of length of time on ET therapy. Further, there were no baseline assessments for the women with breast cancer to determine if there was a change in cognitive function before breast cancer treatment.

Future research

This study utilized two different methods when recruiting participants which included the ECU email list server and utilization of a nurse navigator that screened breast cancer potential participants. The ECU email list server was excellent means of obtaining participants. However, by using the ECU email list server, the resulting healthy control group had a higher educational level then the women with breast cancer group. In the future, a different list serve that was more reflective of the general community might result in a greater congruence with the typical breast cancer patient treated in this university clinic. Attempts to find subjects more closely matched regarding education status, ethnicity, and age would need to be taken. In future studies, enlisting women with breast cancer group prior to obtaining healthy controls might result in a sample that is more reflective of the breast cancer patients.

In addition to the demographics, treatment protocols for the women with breast cancer need to be evaluated. Due to the small sample size, comparison of treatment protocols could not be assessed. During recruitment it was difficult to obtain participants who did not receive chemotherapy, so future studies should utilize multiple clinics for recruitment. This study was limited by use of a single facility and thus the sample size was limited. One way to evaluate the

treatment protocols prior to conducting the next study would be to have a chart review pulled

from all women with breast cancer who received treatment. This would give a firm

understanding of the types of treatment protocols used, in addition to the age and ethnicity of

the potential participants.

The tools for CI were easy to administer but a larger sample is needed to determine if

these are useful as a screening tool for cognitive impairment. It took the participants on

average 30-40 minutes to complete all of the survey instruments. Utilizing shorter instrument

tools to reduce the time it took to complete would need to be considered for future studies. The

PROMIS Anxiety and Depression tools can be streamlined from a six item tool down to three

items. The MSAS-SF, when administered was complicated and time consuming with the

number of symptoms evaluated, future studies should focus on previous symptoms noted to be

involved with women with breast cancer, which could help to eliminate several symptoms. This

study could be used as a reference to assess which symptoms were not bothersome to the

women with breast cancer. Both groups also expressed confusion when filling out the EMQ,

they expressed concerns with how to code responses, which could have led to the mixed results.

Future studies would need to evaluate and look at alternative tools that assess memory.

This study found that for two of the three cognitive function self-reported tools, there

were significant differences between groups. Illustrating the need to reproduce this study with a

larger to determine if these measures continue to demonstrate differences between healthy

controls and breast cancer patients. Additionally, another study could be conducted to test the

utility of these measures as screening instruments. Subjects in the proposed study would all be

screened and then receive a battery of psychologist administered tests for CI to determine if

scores on screening instruments are correlated with psychologist administrated tests. This type

of study could be utilized to determine if there is a cut-off scores that indicate a need for further neurological testing.

This study also suggests that greater number of symptoms are associated with increased CI impairment, so a larger sample of subjects would be needed to confirm the relationship between symptom burden and CI. Also, the next study should be proposed as a longitudinal study instead of a cross-sectional study so we can measure these CI impairment tools over a course of time and compare the results throughout the patient's treatment.

Conclusion

This study evaluated three-self reported tools on cognition (attention, memory, and executive function) in conjunction with self-reported tools on symptom burden, QOL, anxiety, and depression. The findings of this study corresponded with findings from previous studies. However, a larger scale study with a larger sample size needs to be completed to validate these findings. In addition, scheduling time with potential participants so they are not rushed and come prepared to complete the survey. Many women found that due to the large number of surveys, it seemed overwhelming at times, since it took most of the participants 30 minutes or longer to complete. Women with breast cancer did report more symptoms than the controls group further warranting additional studies on a larger scale. This study did show that women with breast cancer are experiencing more symptoms and at more severe rating, but with this small sample and the cross-sectional design, it is impossible to attribute these symptoms to the cancer treatment.

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APPENDIX A: NOTIFICATION OF UMCIRB APPROVAL

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** ·
www.ecu.edu/ORIC/irb

Notification of Continuing Review Approval: Expedited

From:	Biomedical IRB
To:	Amanda Lucas
CC:	Ann Schreier
	Amanda Lucas
Date:	4/25/2019
Re:	CR00007725
	UMCIRB 17-000004
	Cognitive Function in Patients with Breast Cancer

The continuing review of your expedited study was approved. Approval of the study and any consent form(s) is for the period of 4/22/2019 to 4/21/2020. This research study is eligible for review under expedited category #5,7. The Chairperson (or designee) deemed this study no more than minimal risk.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The Investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Document	Description
15-09-01_02-09-32_Neuro-QOLv2.0-CognitiveFunctionSF_09-8-2014.pdf (0.01)	Surveys and Questionnaires
AFI(0.01)	Surveys and Questionnaires
Amanda Lucas Dissertation(0.02)	Study Protocol or Grant Application
Consent Form for breast cancer participants(0.06)	Consent Forms
Consent Form for healthy controls(0.03)	Consent Forms
demographic form(0.01)	Surveys and Questionnaires
EMQR quest v3.pdf(0.01)	Surveys and Questionnaires
Flyer for Healthy Controls(0.03)	Recruitment Documents/Scripts
LASA(0.01)	Surveys and Questionnaires
Memorial Symptom Assessment Scale Short Form(0.02)	Surveys and Questionnaires
Promis Anxiety 6a(0.01)	Surveys and Questionnaires
Promis Depression 6a(0.01)	Surveys and Questionnaires

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

IRB00000705 East Carolina U IRB #1 (Biomedical) IORG0000418
IRB00003781 East Carolina U IRB #2 (Behavioral/SS) IORG0000418

APPENDIX B: STAGING OF BREAST CANCER

Stage	TMN	Explanation
Stage 0		This is ductal carcinoma in situ *(DCIS)*, the earliest form of breast cancer. In DCIS, cancer cells are still within a duct and have not invaded deeper into the surrounding fatty breast tissue. Lobular carcinoma in situ *(LCIS)* sometimes also is classified as stage 0 breast cancer, but most oncologists believe it is not a true cancer or pre-cancer. *In all cases the cancer has not spread to lymph nodes or distant sites.
Stage IA	**T1, N0, M0**	The tumor is 2 cm (about 3/4 of an inch) or less across (T1) and has not spread to lymph nodes (N0) or distant sites (M0).
Stage IB	**T0 or T1, N1mi, M0**	The tumor is 2 cm or less across (or is not found) (T0 or T1) with micrometastases in 1 to 3 axillary lymph nodes (the cancer in the underarm lymph nodes is greater than 0.2mm across and/or more than 200 cells but is not larger than 2 mm)(N1mi). *The cancer has not spread to distant sites (M0).
Stage IIA	**T0 or T1, N1 (but not N1mi), M0:**	The tumor is 2 cm or less across (or is not found) (T1 or T0) and either: It has spread to 1 to 3 axillary (underarm) lymph nodes, with the cancer in the lymph nodes larger than 2 mm across (N1a), OR Tiny amounts of cancer are found in internal mammary lymph nodes (nodes near the breast bone) on sentinel lymph node biopsy (N1b), OR It has spread to 1 to 3 axillary lymph nodes and to internal mammary lymph nodes (found on sentinel lymph node biopsy) (N1c). The cancer has not spread to distant sites (M0).
	OR	

	T2, N0, M0	The tumor is larger than 2 cm but less than 5 cm (about 2 inches) across (T2) but hasn't spread to the lymph nodes (N0). The cancer has not spread to distant sites (M0).
Stage IIB	**T2, N1, M0**	The tumor is larger than 2 cm but less than 5 cm across (T2). It has spread to 1 to 3 axillary lymph nodes and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N1). The cancer hasn't spread to distant sites (M0).
	OR	
	T3, N0, M0	The tumor is larger than 5 cm across but does not grow into the chest wall or skin (T3). The cancer has not spread to the lymph nodes (N0) or to distant sites (M0).
Stage IIIA	**T0 to T2, N2, M0**	The tumor is not more than 5 cm across (or cannot be found) (T0 to T2). It has spread to 4 to 9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes (N2). The cancer hasn't spread to distant sites (M0).
	OR	
	T3, N1 or N2, M0	The tumor is larger than 5 cm across but does not grow into the chest wall or skin (T3). It has spread to 1 to 9 axillary nodes, or to internal mammary nodes (N1 or N2). The cancer hasn't spread to distant sites (M0).
Stage IIIB	**T4, N0 to N2, M0**	The tumor has grown into the chest wall or skin (T4), and one of the following applies: • It has not spread to the lymph nodes (N0). • It has spread to 1 to 3 axillary lymph nodes and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N1).

		• It has spread to 4 to 9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes (N2). The cancer hasn't spread to distant sites (M0). **Inflammatory breast cancer** is classified as T4d and is at least stage IIIB. If it has spread to many nearby lymph nodes (N3) it could be stage IIIC, and if it has spread to distant lymph nodes or organs (M1) it would be stage IV.
Stage IIIC	**any T, N3, M0**	The tumor is any size (or can't be found), and one of the following applies: • Cancer has spread to 10 or more axillary lymph nodes (N3). • Cancer has spread to the lymph nodes under the collar bone (infraclavicular nodes) (N3). • Cancer has spread to the lymph nodes above the collar bone (supraclavicular nodes) (N3). • Cancer involves axillary lymph nodes and has enlarged the internal mammary lymph nodes (N3). • Cancer has spread to 4 or more axillary lymph nodes, and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N3). The cancer hasn't spread to distant sites (M0).
Stage IV	**any T, any N, M1**	The cancer can be any size (any T) and may or may not have spread to nearby lymph nodes (any N). It has spread to distant organs or to lymph nodes far from the breast (M1). The most common sites of spread are the bones, liver, brain, or lungs.

• American Cancer Society (2020, February 17). Stages of Breast Cancer. Retrieved from https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/stages-of-breast-cancer.html

APPENDIX C: DEMOGRAPHIC TOOL

ID Number:_____

1. Date of diagnosis with breast cancer? ____

2. Age today? ___

3. Marital status?

___single

___ married

___ divorced

___ widowed

___ in a relationship

4. Ethnicity?

___ White, non-Hispanic   ___ Native Hawaiian/Pacific Islander

___ Black, non-Hispanic   ___ Two or more races, non-Hispanic

___ American Indian   ___ Hispanic/Latino

___ Asian   ___ Other (please describe)

5. Highest level of education?

___ grade school

___ high school

___ college

___ graduate school

7. Smoker? Y or N

8. Height_____   Weight_____

9. List of current medications (leave out for health controls)

10. List of medications for chemotherapy treatment

APPENDIX D: ATTENTIONAL FUNCTIONAL INDEX

ID Number_____/Interviewer_____/Date_____

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

   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 E: EVERYDAY MEMORY QUESTIONNAIRE

Everyday Memory Questionnaire - Revised

Instructions Below are listed some examples of things that happen to people in everyday life. Some of them may happen frequently and some may happen very rarely. We would like to know how often on average you think each one has happened to you over the past month. Write the appropriate number in the box beside the item.

0. Once or less in the last month. 1. More than once a month but less than once a week. 2. About once a week. 3. More that once a week but less than once a day. 4. Once or more in a day.

1. Having to check whether you have done something that you should have done.

2. Forgetting when it was that something happened; for example, whether it was yesterday or last week.

3. Forgetting that you were told something yesterday or a few days ago, and maybe having to be reminded about it.

4. Starting to read something (a book or an article in a newspaper, or a magazine) without realizing you have already read it before.

5. Finding that a word is "on the tip of your tongue". You know what it is but cannot quite find it.

6. Completely forgetting to do things you said you would do, and things you planned to do.

7. Forgetting important details of what you did or what happened to you the day before.

8. When talking to someone, forgetting what you have just said. Maybe saying "what was I talking about?"; losing track of what it is about.

9. When reading a newspaper or magazine, being unable to follow the thread of a story

10. Forgetting to tell somebody something important, perhaps forgetting to pass on a message or remind someone of something.

11. Getting the details of what someone told you mixed up and confused.

12. Forgetting where things are normally kept; or looking for them in the wrong place.

13. Repeating to someone what you have just told them; or asking someone the same question twice.

APPENDIX F: NEURO-QOL COGNITIVE FUNCTION SHORT FORM

Please respond to each question or statement by marking one box per row. In the past 7 days…	Never	Rarely (once)	Sometimes (2-3 times)	Often (once a day)	Very often (several times a day)
NQCOG64r1 I had to read something several times to understand it………… ……………. ……...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG75r1 My thinking was slow……… …………….	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG77r1 I had to work really hard to pay attention or I would make a mistake… ……………. .	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG80r1 I had trouble concentratin g…………… …….	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	None	A little	Somewhat	A lot	Cannot do
How much DIFFICULTY do you currently have…					
NQCOG22r1 — Reading and following complex instructions (e.g., directions for a new medication)...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG24r1 — planning for and keeping appointments that are not part of your weekly routine, (e.g., a therapy or doctor appointment, or a social gathering with friends and family)?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG25r1 — Managing your time to do most of your daily activities...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
NQCOG40r1 — Learning new tasks or instructions...	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

APPENDIX G: LASA

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

How would you describe:

1. **your overall Quality of Life?**

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX H: MEMORIAL SYMPTOM ASSESSMENT SCALE-SHORT FORM

Date ___/___/___   ID # ____

MEMORIAL SYMPTOM ASSESSMENT SCALE – Short Form [MSAS-SF]

I. **INSTRUCTIONS:** Below is a list of symptoms. If you had the symptom **DURING THE PAST WEEK**, please check Yes. If you did have the symptom, please check the box that tells us how much the symptom DISTRESSED or BOTHERED you.

Check *all* the symptoms you have had during the PAST WEEK.	Yes [✓]	→ → IF YES: How much did it DISTRESS or BOTHER you?				
		Not at All [0]	A little Bit [1]	Some-what [2]	Quite a Bit [3]	Very Much [4]
Difficulty concentrating						
Pain						
Lack of energy						
Cough						
Changes in skin						
Dry mouth						
Nausea						
Feeling drowsy						
Numbness/tingling in hands and feet						
Difficulty sleeping						
Feeling bloated						
Problems with urination						
Vomiting						
Shortness of breath						
Diarrhea						
Sweats						
Mouth sores						
Problems with sexual interest or activity						
Itching						
Lack of appetite						
Dizziness						
Difficulty swallowing						
Change in the way food tastes						
Weight loss						

1

_____ Date ___/___/___ ID # ____

MEMORIAL SYMPTOM ASSESSMENT SCALE – Short Form [MSAS-SF]

I. <u>INSTRUCTIONS:</u> Below is a list of symptoms. If you had the symptom <u>DURING THE PAST WEEK</u>, please check Yes. If you did have the symptom, please check the box that tells us how much the symptom DISTRESSED or BOTHERED you.

Check *all* the symptoms you have had during the PAST WEEK.	Yes [✓]	➔➔ IF YES: How much did it DISTRESS or BOTHER you?				
		Not at All [0]	A little Bit [1]	Some-what [2]	Quite a Bit [3]	Very Much [4]
Hair loss						
Constipation						
Swelling of arms or legs						
"I don't look like myself"						
If you had <u>any other symptoms</u> during the PAST WEEK, please list them below, and indicate how much the symptom **DISTRESSED or BOTHERED you.** 1. _____						
2. _____						

II. Below are other commonly listed symptoms. Please indicate if you have had the symptom DURING THE PAST WEEK, and if so, how OFTEN it occurred.

Check *all* the symptoms you have had during the PAST WEEK	Yes [✓]	➔➔ IF YES, How OFTEN did it occur?			
		Rarely [1]	Occasionally [2]	Frequently [3]	Almost Constantly [4]
Feeling sad					
Worrying					
Feeling irritable					
Feeling nervous					

2

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APPENDIX I: PROMIS ANXIETY 6A

Please respond to each question or statement by marking one box per row. In the past 7 days…		Never	Rarely	Sometimes	Often	Always
EDANX01	I felt fearful..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety...................................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me......................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	I felt nervous...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX07	I felt like I needed help for my anxiety......	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

APPENDIX J: PROMIS DEPRESSION 6A

Please respond to each question or statement by marking one box per row. In the past 7 days...		Never	Rarely	Sometimes	Often	Always
EDDEP04	I felt worthless.................................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless.................................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed.................................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless.................................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP22	I felt like a failure.................................	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP36	I felt unhappy.................................	☐ 1	☐ 2	☐ 3	☐ 4	☐