

CHEMOTHERAPY-RELATED COGNITIVE IMPAIRMENT:

THE BREAST CANCER EXPERIENCE

BY

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Abstract

The aims of this qualitative descriptive study were to describe the experience of chemotherapy-related cognitive impairment (CRCI) for women with breast cancer who received chemotherapy; and identify information about CRCI that women would find useful prior to chemotherapy and the onset of CRCI. In-depth interviews were conducted with 18 women who reported changes in cognitive function and were within 6-12 months of completing chemotherapy. Participants described issues with short term memory, trouble focusing, and difficulty with word finding, reading, and driving. Support and validation of the experience was acknowledged as important. Coping strategies included writing things down, depending on others, focusing on one task at a time, and giving oneself permission to make mistakes. Participants wanted to receive information about CRCI prior to initiating chemotherapy and desired an individualized approach to education and made specific recommendations for educational content. On-going assessment for CRCI and reinforcement of education were recommended.

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Chapter I: Introduction

Problem Statement and Study Purpose

Women with breast cancer complain of a lack of acknowledgement and education about the potential for cognitive changes related to chemotherapy. Cognitive changes can have a significant impact on cancer survivors' quality of life (QOL) and lack of information regarding the potential risk for chemotherapy-related cognitive impairment (CRCI) prevents obtaining full informed consent prior to initiation of therapy. Lack of acknowledgement of CRCI by health care providers (HCPs) is a source of frustration and dissatisfaction to patients experiencing cognitive changes. The purpose of this qualitative descriptive study was to provide an in-depth description of the patient experience of CRCI for women with breast cancer.

Background & Significance

CRCI is recognized as a serious potential sequela to treatment for cancer. Estimates of frequency range as high as 75% for patients receiving chemotherapy (Ahles, et al., 2002) and from 17-34% two or more years after completion of therapy (Ahles & Saykin, 2007). Cognitive impairment attributed to standard doses of chemotherapy (as opposed to high-dose or intrathecal regimens) has only recently been addressed consistently in the literature, although some researchers recognized this phenomenon in the late 1970s and early 1980s (Ahles & Saykin, 2001; Silberfarb, 1983; Silberfarb, Philibert, & Levine, 1980; Weiss, Walker, & Wieneke, 1974).

CRCI can have a dramatic effect on survivors' quality of life (Ahles & Saykin, 2001; Tannock, Ahles, Ganz, & van Dam, 2004). The impact has been recognized by the President's Cancer Panel, the National Coalition for Cancer Survivorship (Reuben, 2004),

and the Oncology Nursing Society as a national research priority (Berger, 2009).

Participants on the President's Cancer Panel noted that insufficient care may result from HCPs failure to acknowledge the problem and may be due in part from a lack of information about this treatment-related effect.

To date, much of the research for CRCI has been conducted in patients with breast cancer due to prolonged survival time and patients' assertiveness in communicating concern about cognitive changes (Castellon et al., 2004; Kreukels et al., 2006; O'Shaughnessy, 2003; Schagen, Muller, Boogerd, & van Dam, 2002). Up to 83% of breast cancer survivors who received chemotherapy report some degree of cognitive dysfunction (Jenkins, 2006; O'Shaughnessy), which is consistent with the overall estimated frequency for patients receiving chemotherapy cited above. Survivors of breast cancer comprise a significant portion of the cancer survivor population as breast cancer is the most common malignancy in females. Current estimates of new cases of breast cancer incidence in the United States for 2010 are 207,090 (American Cancer Society 2010) and five year survival rates for all stages of the disease are 90%. In 2010, 2.9 million breast cancer survivors are predicted in the United States (De Angelis, et al., 2009).

Very little literature exists to describe the patient experience with CRCI, including the experience related to the treatment of breast cancer (Boykoff, Moieni, & Subramanian, 2009; Mulrooney, 2007; Thielen, 2009; Wagner, Sweet, Butt, Lai, & Cella, 2009). Few educational tools are available and oncology nurses have acknowledged lack of access to appropriate patient/family educational materials (Myers & Teel, 2008). One key aspect of the oncology nursing role is patient/family education regarding expected or potential side effects of therapy. A recent pilot study was conducted to evaluate oncology nurses'

awareness of CRCI and to ascertain whether oncology nurses assessed patients for this side effect and provided education to patients prior to therapy. Results from the pilot study indicated that 38% of participants assessed patients for CRCI and 71% of participants did not have access to related educational materials for CRCI (Myers & Teel).

Recognition of CRCI as a national research priority and the potential for impact of CRCI on quality of life provides the rationale for continued research. Despite the fact that much research has been conducted with breast cancer survivors, significant gaps in the literature remain related to the description and meaning of the patient experience and practical suggestions for patient education. Lack of pre-treatment patient education contributes to less than comprehensive informed consent. As the experience of CRCI in patients with breast cancer becomes well defined, results may be used to begin to explore the experience of CRCI in patients with other types of malignancies treated with chemotherapy.

Chemotherapy-Related Cognitive Impairment

Mild cognitive impairment following chemotherapy often is referred to as “chemo brain” by the lay public (Matsuda et al., 2005). Cull, et al. (1996) described CRCI as subjective and objective changes in cognitive function related to chemotherapy. The impact of CRCI typically is subtle and is believed to reduce over time. The specific domains of cognitive function that may be affected include executive function, information-processing speed, language, motor function, spatial skills, learning, and memory (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005). Patients describe the effects on cognitive function as forgetfulness, absentmindedness, and an inability to focus when performing daily tasks (Hess & Insel, 2007).

A variety of potentially associated factors have been identified, including age, education level, intelligence, and social support; anxiety, depression, and fatigue; disease site, stage, and comorbidities; treatment regimen, timing, duration, and concomitant therapies; hormonal levels, cytokine levels, damage to neural progenitor cells, and the presence of the apolipoprotein E 4 allele (Hess & Insel, 2007; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005). These factors are acknowledged for the potential to contribute to changes in cognitive function. Further research is needed to describe the relationships between these factors and the development and severity of CRCI. Advancing age has been associated with memory problems unrelated to cancer or cancer therapy (Barnes et al., 2003) and thus may exacerbate the risk of CRCI. Recent research indicates that younger age may be associated with an increased perception of changes in cognitive function and therefore a greater impact on quality of life (Cimprich et al., 2005). Higher levels of education and intelligence are hypothesized to be associated with high baseline function and cognitive reserve that may impact the effects of chemotherapy on cognitive performance (Jansen et al., 2007). Lack of social support, anxiety, depression, fatigue, and decreased levels of circulating estrogen and testosterone may contribute to decreased mental acuity. The timing, intensity and composition of the chemotherapy treatment regimen may contribute to the severity of changes in cognitive function (Jansen et al., 2007).

The exact etiology of CRCI is not known, but a number of etiologies have been proposed, including direct injury to cerebral gray and white matter, microvascular injury (Wefel et al., 2004), DNA damage and oxidative stress (Ahles & Saykin, 2007; Chen, Jungsuwadee, Vore, Butterfield, & St. Clair, 2007), cytokine-induced inflammatory response (Ahles & Saykin, 2007), chemotherapy-induced anemia (Mancuso, Migliorino, De Santis,

Saponiero, & De Marinis, 2006; Massa, Madeddu, Lusso, Gramignano, & Mantovani, 2006), and chemotherapy-induced menopause (Jansen, Miaskowski, Dodd, & Dowling, 2005).

Recent preclinical investigation has highlighted a potential relationship between injury to neural progenitor cells (NPCs), impaired maintenance of white matter integrity, and subsequent cognitive impairment (Dietrich, Han, Yang, Mayer-Proschel, & Noble, 2006; Dietrich, Monje, Wefel, & Meyers, 2008; Han, et al., 2008). Dietrich, Han, et al. noted that self-renewing, lineage-committed NPCs and nondividing mature oligodendrocytes (myelin-forming cells) are the most vulnerable cell populations to chemotherapeutic agents.

Repetitive exposure to chemotherapeutic agents exceeded cellular repair potential and resulted in long-term suppression of cell division and apoptosis in the subventricular zone, hippocampus, and major white matter tracts of the CNS in animal models. Animal modeling work provides the basis for further research to attribute causality to specific chemotherapy agents or combinations to areas of the brain important to cognitive performance and executive function.

Secondary inflammatory response has been related to the sickness behavior seen with proinflammatory cytokine release. Some understanding of the role of cytokines in induction of sickness behavior evolved from observing the side effects experienced by patients with cancer receiving treatment with immunomodulating agents, such as interferon alpha, tumor necrosis factor and interleukin-2. The side effect called “flu-like syndrome” is comprised of the same characteristics seen with sickness behavior (De La Garza, 2005). Patients exhibit fever, chills, lethargy, anorexia, and cognitive impairment. Rationale for the cognitive impairment seen in conjunction with the release and exogenous administration of cytokines is emerging. Chemotherapy-induced side effects are similar to those seen in the sickness

behavior attributed to proinflammatory cytokine release (Wood, Nail, Gilster, Winters, & Elesea, 2006). A variety of antineoplastic agents induce production of proinflammatory cytokines in various cell lines in vitro (Maier & Watkins, 2003; Niiya et al., 2003; Wichmann, et al., 2003; Zaks-Zilberman, Zaks, & Vogel, 2001). The taxanes (paclitaxel and docetaxel) have been associated with increased plasma levels of interleukins 6, 8, and 10 (Ahles & Saykin, 2007).

Oxidative stress occurs when the generation of reactive oxygen and nitrogen species exceed cellular adaptive and repair capacities (Chen et al., 2007). Antineoplastic agents used to treat breast cancer that have been reported to induce oxidative stress include the anthracyclines, cyclophosphamide, and fluorouracil.

Oxidative stress associated with doxorubicin therapy (an anthracycline) occurs in nontargeted tissues and leads to injury of normal tissues (Chen et al., 2007). Doxorubicin, like other chemotherapy agents administered in standard doses, was believed not to cross the blood brain barrier. However, doxorubicin has been associated with increased circulating levels of tumor necrosis factor alpha (TNF- α) in animal models. TNF- α can penetrate the blood-brain barrier and activate glial cells in the central nervous system (CNS) to further TNF- α production in the brain. The synthesis of TNF- α in the CNS is related to the induction of nitric oxide synthase (Chen et al.). As a result, the generation of reactive nitrogen species, including nitric oxide, increases (Tangpong et al., 2007). In addition, the neurotoxicity associated with doxorubicin-induced TNF- α resembles the free radical mechanisms implicated in Alzheimer's disease (Tangpong et al.).

The presence of the apolipoprotein (APOE) E4 allele may predispose patients to cognitive impairment (Ahles & Saykin, 2002; Ahles et al., 2003). APOE is "a complex

glycolipoprotein that facilitates the uptake, transport and distribution of lipids” and appears to have a role in neuronal repair after injury (Ahles & Saykin, 2007, p. 198). The E4 allele is associated with Alzheimer’s disease and poor recovery from stroke and traumatic brain injury. Some prospective trials to evaluate CRCI now include genetic measurements to assess whether a genetic predisposition to more significant and longer-lasting injury from chemotherapy exists (Ahles & Saykin, 2007). Those prospective trials may help answer the question of whether some patients are genetically predisposed to long-term damage, and results could have significant impact on treatment options for cancer.

Chemotherapy for Breast Cancer

The decision to offer adjuvant chemotherapy to women diagnosed with non-metastatic invasive breast cancer (stages I-III) is based on a number of factors associated with the risk of recurrence. Primary considerations include tumor size, hormone receptor status, lymph node status, and tumor grade (NCI, 2009a). Women at intermediate or high risk of recurrence typically are offered adjuvant chemotherapy. Combination chemotherapy and hormonal therapy (with selective estrogen receptor modulators or aromatase inhibitors) is common for women who are estrogen receptor (ER) and/or progesterin receptor (PR) positive. Women with over-expression of the human epidermal growth factor receptor two (HER-2) neu oncogene also are offered treatment with the anti-HER-2 monoclonal antibody, trastuzumab. Data related to treatment efficacy are limited for women over the age of 70 years as many clinical trials exclude the elderly due to the presence of comorbidities and reductions in performance status.

The National Coalition of Cancer Survivors publishes evidence-based treatment guidelines for the treatment of breast cancer (NCCN, 2009). Numerous chemotherapy

regimens are listed as preferred (category 1 level of evidence). Most of these regimens contain an anthracycline (doxorubicin), cyclophosphamide, and a taxane (docetaxel or paclitaxel). Many of the older regimens, no longer listed as category 1, contain fluorouracil and methotrexate. As mentioned above, the anthracyclines, cyclophosphamide, and fluorouracil are associated with oxidative stress. Taxanes are associated with the release of proinflammatory cytokines and known to cause peripheral neuropathies. Methotrexate has been associated with neurotoxicity in studies done to evaluate CRCI (Scherwath et al., 2006; Tchen et al., 2003).

Challenges with Neurocognitive Testing

Standard neurocognitive tests have been developed to evaluate cognitive performance across domains such as attention and concentration, executive function, information-processing speed, language, motor function, visuospatial skill, learning and memory (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005). A number of these tests have been shown to have some sensitivity to CRCI in patients with breast cancer. Jansen et al. (2007) conducted a meta-analysis of the various neurocognitive tests used to detect CRCI in patients with breast cancer. They reviewed 13 studies and utilized meta-analysis software to calculate standardized mean difference effect size and a 95% confidence interval. Effect sizes were interpreted as negligible (< 0.20), small (.20-.50), medium (.50-.80) and large (greater than .80). Tests that were used in at least two or more studies were included in the analysis and 30 tests were examined. Only 6 of the tests were sensitive to CRCI in 4 of the 8 cognitive domains (language, motor function, visuospatial skill, and verbal memory) (see Table 1). The authors noted that “most of the neurocognitive tests used in the studies performed to date do not appear to be sensitive enough to detect changes in cognitive function” (p. 1004).

Table 1

Neurocognitive Tests Shown to be Sensitive to CRCI in Patients with Breast Cancer

Domain	Test	Effect Size
Language	HSCS Language Subtest	Small
Motor Function	Grooved Pegboard	Large
	Fepsy Finger Tapping Test	Moderate
Visuospatial skill	RCFT Copy Test	Moderate
	WAIS Block Design Subtest	Moderate
Verbal Memory	HSCS Memory Subtest	Small

HSCS = High Sensitivity Cognitive Screen, RCFT = Rey-Osterrieth Complex Figure Test,

WAIS = Wechsler Adult Intelligence Scale

Adapted from Jansen et al., 2007.

Learning and memory sometimes is divided into visual and verbal memory (Nail, 2006). Abstract reasoning also is periodically assessed as a component of neurocognitive testing (Freeman & Broshek, 2002). Results provide insight into specific areas of brain injury based on individuals' performance on tests designed to elicit objective data related to the specific cognitive domains (see Table 2) (Ahles & Saykin, 2007; Jansen, Miaskowski, Dodd, & Dowling, 2007).

A number of challenges exist related to neurocognitive testing for CRCI. One of the major challenges is the selection of appropriate assessment tools. Cognitive changes observed in this patient population are subtle. Tests designed to assess gross changes in neurocognitive function associated with severe dementia or head injury are not appropriate for patients experiencing CRCI. Patients who are well educated with high baseline cognitive function may continue to score normally on neurocognitive tests, even though they perceive deficits that interfere with their daily function and quality of life (Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). The Mini-Mental State Examination (MMSE) has been criticized for those reasons (Meyers & Wefel, 2003). At best, the MMSE may be used as a baseline screen to exclude patients from a prospective trial who have significant cognitive deficits prior to the initiation of therapy.

The array of neurocognitive tests that would normally be employed to conduct a full cognitive assessment may range in length from four to seven hours (Freeman & Broshek, 2002). Patient burden should be a consideration in determining the extent of testing that occurs in each session. An additional challenge exists for patients experiencing the fatigue associated with a cancer diagnosis and treatment (Butt et al., 2008). Several hours of testing may not be practical. In addition, in the context of a clinical trial, the time and expense

Table 2

Domains of Cognitive Function: Corresponding Components and Brain Anatomy

Cognitive Domain	Definition	Components	Associated Anatomy
Attention & Concentration	Enable ability to triage relevant inputs, thoughts, and actions while ignoring those that distract or are irrelevant. Ability to focus and sustain attention.	Arousal Selective attention Sustained attention or vigilance Directed attention	Ascending reticular activating system Frontal subcortical network Rt hemispheric prefrontal and parietal regions Prefrontal cortex (cingulated cortex, amygdala)
Executive Function	Higher order cognitive Processes that include Initiation, planning, hypotheses generation, cognitive flexibility, decision making, self-regulation, judgment, feedback utilization, and self-perception.	Initiation Planning Cognitive flexibility Self-monitoring Self-regulation	Anterior cingulated cortex Dorsolateral prefrontal cortex
Information-Processing speed	Ability to rapidly process simple and complex information. Linked to all other cognitive domains due to tactile, auditory, verbal and visual nature of input.		Parietal and frontal lobes
Language	Ability to comprehend and communicate written and spoken symbolic information	Verbal or written expression Reception Repetition	Supplementary, motor, prefrontal cortices Wernicke's area Broca's area
Motor function	Performance related to speed, strength, and coordination.	Speed Strength Coordination Dexterity Apraxia	Frontal lobe (premotor and primary motor areas), parital lobe (somatosensory areas), cerebellum, brain stem.

Table 2 continued

Cognitive Domain	Definition	Components	Associated Anatomy
Visuospatial skill	Ability to process and interpret visual information regarding where things are situated in space.	Perception Construction	Primary visual cortex in posterior occipital lobe, temporal lobes, parietal lobes
Learning and Memory	Ability to acquire, store, and access new information	Learning	Reticular activating system, dorsolateral prefrontal cortex, parietal cortex, medial temporal lobe, amygdale, orbitofrontal cortex
		Short-term memory	
		Long-term memory	
		Recall	
		Recognition	Frontal and anterior temporal lobes
		Verbal memory	Prefrontal cortex
		Visual memory	Left hemisphere
			Right hemisphere

Ahles & Saykin 2007; Freeman 2002; Jansen et al. 2005, 2007

involved in extensive testing may preclude a complete examination from being included in the protocol (Freeman & Broshek). A multidisciplinary workshop held in 2004 yielded the suggestion of a two-stage approach to cognitive assessment, depending on the question that was being asked (Tannock et al., 2004). When the goal is demonstration of a cognitive change in a large sample of patients in a clinical trial, brief validated assessment such as the Functional Assessment of Cancer Therapy-Cognitive Function scale (FACT-*COG*, a self-report measure) (Wagner, et al, 2009) may be appropriate (stage 1). Workshop participants acknowledged that most brief measures do not have sensitivity for impaired executive function and therefore might lead to underreporting of deficits. Patients who demonstrate a change in cognitive function by brief objective assessment can then be referred for more thorough evaluation with conventional neurocognitive testing (stage 2) (Tannock et al.).

Studies conducted to date have employed a variety of different neurocognitive tests to evaluate cognitive function. For results to be compared, the use of consistent tests would be very advantageous. One of the recommendations of the multidisciplinary workshop was to identify tests sensitive to the subtle changes observed with *CRCI* as well as to develop and validate self-report forms (Tannock et al.). As important as objective tests of cognitive function are, patient perception of cognitive function and the resultant impact on *QOL* remain important aspects of the assessment process (Minisini, et al., 2004).

Additional challenges of the current process of neurocognitive testing for patients experiencing *CRCI* revolve around the difficulty in replication of a real-life situation. Typically, neurocognitive testing occurs in a laboratory-like environment that has little overlap with a patients' everyday experience (Schagen, et al., 2002). Current testing procedures are criticized for low ecologic relevance and sterile conditions with minimal

distraction. Patients with cancer who self-report CRCI describe an inability to multitask, which is difficult to replicate in a testing situation (Cimprich, So, Ronis, & Trask, 2005).

Assessment of cognitive function in participants with cancer is further complicated by a number of potentially confounding variables such as age, education, hormonal status, anemia, fatigue, anxiety, and depression (Nail, 2006). Controlling for these factors still yields the independent presence of cognitive change in patients who have received chemotherapy (Ahles et al., 2002). However age and education are significant predictors of cognitive performance. More years of education have been associated with better performance on measures of cognitive function (Cimprich, et al., 2005). Cimprich et al. (2005) studied pre-treatment factors related to cognitive functioning in newly diagnosed women with breast cancer. Cimprich noted that younger women may have perceived even small fatigue-related losses in attention that interfered with usual levels of functioning but were not detectable on testing. Older women demonstrated decreased ability to direct attention prior to any treatment and thus may be at higher risk for treatment-related changes in cognitive function. Cimprich also noted that depression is positively correlated with patients' self-report of cognitive changes. Hypotheses generated about the discrepancy between self-report and objective testing include the rationale that subjective measures reflect perceived changes while objective measures only assess current performance and do not reflect changes over time. Thus subjective measures may be sensitive to smaller effect sizes than those of objective measures available today (Jacobs, Jacobsen, Booth-Jones, Wagner, & Anasetti, 2007).

Importance of Self-Report

Substantive work remains to be done to identify the neurocognitive tests most sensitive to CRCI and to develop new tests more closely related to real-life situations where cognitive changes are noted (Ahles & Saykin, 2007). The importance of assessing patients' perceptions of cognitive change cannot be ignored (O'Shaughnessy, 2003). Patients' self-report of perceptions of cognitive change may be more sensitive to subtle deficits in function than standard neurocognitive tests (Schagen, et al., 2002). Researchers are beginning to advocate the position that patient-reported cognitive function is an important endpoint in its own right due to the profound impact of perceived cognitive function on QOL and evidence of an association between patient-reported cognitive decline and with increased cognitive effort demonstrated by neuroimaging (Ferguson, McDonald, Saykin, & Ahles, 2007; Lai, et al., 2009; Saykin, et al., 2006; Scherwath, et al., 2006; Wagner, et al.).

Patients' description of the lived experience of CRCI may provide rich data that are useful in more accurately defining the types of cognitive changes that result from chemotherapy. Ahles and Saykin (2001) noted that the use of quantitative instruments may obtain data less rich in describing the cancer experience. They offered the example of comparing responses to a quantitative survey with questions about the impact of chemotherapy on job performance. Use of the quantitative survey yielded the information that a patient was able to work in the same profession following chemotherapy. Results of the qualitative assessment indicated that while the patient may have remained in the same profession, the decision was made to move to a less demanding position or not to compete for a promotion due to impairment of cognitive function (Ahles & Saykin, 2001). Work-related limitations may contribute to additional impact on QOL.

CRCI can have a dramatic effect on survivors' quality of life, such as changes in the ability to maintain a job/role, participate in enjoyable activities and have an absence of distress (Ahles & Saykin, 2001; Boykoff et al., 2009; Tannock et al., 2004). Patients have expressed concern about CRCI and their subsequent ability to resume previous professional, scholastic, and social activities (Wefel et al., 2004). No data are available on the percentage of patients who miss or lose work because of this adverse event. Estimating the cost of CRCI is difficult because prospective trials to ascertain a more precise incidence, risk factors and specific impact on quality of life are ongoing. CRCI is a significant concern because of the prevalence of the symptom experience and patients' concerns about the impact on QOL. Given the significance of CRCI to patients, appropriate measures should be taken to educate patients and families about the potential for CRCI, assess and diagnose the CRCI, and recommend interventions to assist patients in coping with changes in function they experience.

Study Purpose and Aims

The purpose of this qualitative descriptive study was to provide an in-depth description of the experience of CRCI for women with breast cancer. Specific aims of the study were to: 1) Describe the experience of CRCI for women with breast cancer who have received chemotherapy treatments; and 2) Identify information about CRCI that women would find useful prior to initiation of chemotherapy and following the onset of CRCI .

Research Questions

The study was designed to answer the following research questions: 1) How do women who have received chemotherapy for breast cancer describe the experience of CRCI?; 2) What information about CRCI would women who have received chemotherapy

for breast cancer have found helpful prior to initiation of treatment?; and 3) What information about CRCI would women with breast cancer have found helpful once changes in cognition are experienced?

Outcomes

Information gleaned from this study adds to the body of knowledge related to the experience of CRCI from the patients' perspective by providing a comprehensive description of the phenomenon. Participants' descriptions of information they would have found helpful prior to therapy and after experiencing cognitive changes will be used to support the development of appropriate educational tools. Enhanced understanding of CRCI by oncologists and oncology nurses and appropriate patient/family education is necessary to obtain full informed consent prior to initiating chemotherapy. Recognition and acknowledgement of CRCI by HCPs and pre-treatment education will decrease frustration and dissatisfaction for women with breast cancer. A deeper understanding of the patient experience with CRCI may lead to refinement of existing or development of more sensitive, neurocognitive tests to measure CRCI. As the experience of CRCI in patients with breast cancer becomes better defined, the knowledge may be used to begin to explore the experience of CRCI in patients with other types of malignancies treated with chemotherapy.

Summary

CRCI is estimated to occur in up to 83% of patients with breast cancer and has been identified as a national research priority. Mechanisms of causality remain unclear as do the specific relationships with potentially confounding and/or exacerbating factors. No standard for assessment has been determined. A number of issues relate to the lack of sensitivity of current objective methods to measure cognitive function in this patient population. Self-

report is gaining favor as the most sensitive measure of the subtle changes in cognitive function experienced in conjunction with chemotherapy.

Very little literature exists to describe the patient experience. Patients' descriptions of their perceptions of the phenomenon are necessary for providing appropriate education, revising current neurocognitive tests to achieve more ecologic validity or developing new tests that are more sensitive to the subtleties of CRCI. The following chapter includes a review of literature pertinent to this study. Gaps in the literature are identified in support of the research questions and hypotheses.

Chapter 2: Review of Literature

The review of the literature begins with an overview of studies conducted to demonstrate evidence of CRCI in patients with breast cancer. A review of work done to evaluate the timing of the occurrence of CRCI as a late effect of chemotherapy as well as comparisons of dose intensity follows. Exploration of the potential for hormonal influence such as decreased estradiol levels associated with both treatment-induced menopause and aromatase inhibition is reviewed. Hormone levels potentially are confounding factors for changes in cognitive function as a normal part of the aging process. A summary of neurocognitive tests and self-report measures used for each of the studies reviewed are noted in Table 3. The volume and variety of neurocognitive testing demonstrates the lack of standardization or agreement as to the best objective measures of cognitive function for patients who have received chemotherapy. Study results supporting the role for patients' self-report of CRCI as a valid measure are discussed. A summary of contradictory findings is provided. Results of relevant qualitative research performed to describe the patient experience of CRCI and patients' need for acknowledgement and education are reviewed. This chapter concludes with a summary of gaps in previous research lending support for this research proposal.

Evidence for CRCI in Breast Cancer

Early work related to the quest for objective evidence for chemotherapy-related deterioration in cognitive function for women treated for breast cancer was published by Wieneke and Dienst (1995). They evaluated 28 women (ages 28-54) with early stage disease (I, II) who had no evidence of metastases or comorbidities and were treated with standard-dose chemotherapy: cyclophosphamide, doxorubicin, and fluorouracil (CAF) and/or

Table 3

Summary of Neurocognitive Tests and Self-Report Measures

Reference & Title	Neurocognitive tests	Self-Report Measures
Ahles & Saykin, 2002 Neuropsychologic impact of standard-dose systemic Chemotherapy in long-term Survivors of breast cancer and Lymphoma	Wechsler Adult Intelligence Scale III Vocabulary Wide Range Achievement Reading Subtest California Verbal Learning Wechsler Memory Scale Revised Logical Memory Verbal Memory Finger Tapping and Thumb-Finger Sequencing Continuous Performance Vigilance and Distractibility Subtests	Squire Memory Self-Rating Questionnaire Center for Epidemiological Study Depression Scale Spielberger State-Trait Anxiety Inventory
Bender et al., 2006 Cognitive impairment associated with adjuvant therapy in breast cancer	Digit Vigilance Trail Making Rey Auditory Verbal Learning Rey Osterrieth Complex Figure Four Word Short Memory	
Bender et al., 2007 Memory impairments with adjuvant anastrozole versus tamoxifen in women with early-stage breast cancer	Digit Span Digit Vigilance Rey Auditory Verbal Learning Rivermead Behavioral Memory Rey Osterrieth Complex Figure Grooved Pegboard National Adult Reading-Revised	Beck Depression Inventory Profile of Mood States Tension/Anxiety Subscale
Brezden et al., 2000 Cognitive function in breast cancer patients receiving adjuvant chemotherapy	High Sensitivity Cognitive Screen	Profile of Mood States
Castellon et al., 2004 Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen	Controlled Oral Word Association California Verbal Learning Wechsler Memory Scale Logical Memory and Visual Reproduction Wechsler Adult Intelligence Scale Digit Symbol Rey Osterrieth Complex Figure California Computerized Assessment Package Paced Auditory Serial Additional	Beck Depression Inventory Spielberger State-Trait Anxiety Inventory Medical Outcomes Study Short Form-36

Table 3 continued

Reference & Title	Neurocognitive tests	Self-Report Measures
Cimprich & Ronis, 2001 Attention and symptom distress in women with and without breast cancer	Mini-Mental State Exam Digit Span Symbol Digit Modalities Necker Cube Pattern Control	Symptom Distress Scale Profile of Mood States Depression Subscale
Cimprich et al., 2005 Pre-treatment factors related to cognitive functioning in women newly diagnosed with breast cancer	Digit Span Trail Making Test Three Shapes Three Words	Attentional Functional Index Symptom Distress Scale Profile of Mood States
Downie et al., 2006 Cognitive function, fatigue and menopausal symptoms in breast cancer patients receiving adjuvant chemotherapy: Evaluation with patient interview after formal assessment	High Sensitivity Cognitive Screen	Functional Assessment of Cancer Therapy- General, Fatigue, Endocrine Symptoms
Jenkins et al., 2006 A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer	Wechsler Memory Scale-III National Adult Reading Wechsler Adult Intelligence Scale Rey Osterrieth Complex Figure Stroop Digit Span Letter Cancellation Spatial Span Letter/Number sequencing	General Health Questionnaire Broadbent Cognitive Failures Questionnaire Functional Assessment of Cancer Therapy- Questionnaires for Breast, Fatigue and Endocrine Symptoms
Jenkins et al., 2004 Does hormone therapy for the treatment of breast cancer have a detrimental effect on cognition? A pilot study	Wechsler Memory Scale-III Verbal Memory, Visual Memory, Working Memory	Beck Depression Inventory General Health Questionnaire Cognitive Failure Questionnaire
Klemp et al., 2006 Evaluating the effects of chemotherapy on cognitive function and quality of life in pre-menopausal women with breast cancer	High Sensitivity Cognitive Screen	Cognitive Difficulties Scale RAND 36-Item Health Survey Breast Cancer Prevention Trial Symptom Check List Beck Depression Inventory Center for Epidemiological Studies Depression Scale Functional Assessment of Cancer Therapy- Anemia
Mar Fan et al., 2005 Fatigue menopausal symptoms and cognitive function in women after adjuvant chemotherapy for breast cancer: 1- and 2-year follow-up of a prospective controlled study.	High Sensitivity Cognitive Screen Mini-Mental State Exam Conner's Continuous Performance Trail-Making	Functional Assessment of Cancer Therapy Questionnaires for Breast, Fatigue and Endocrine Symptoms

Table 3 continued

Reference & Title	Neurocognitive tests	Self-Report Measures
Paganini-Hill & Clark, 2000 Preliminary assessment of cognitive function in breast cancer patients treated with tamoxifen	Clock Drawing Task Necker Cube Narrative Task	Geriatric Depression Scale
Schagen et al., 1999 Cognitive deficits after postoperative chemotherapy for breast carcinoma	Rey Auditory Verbal Learning Complex Figure Digit Span Digit Symbol Trail Making D2 Stroop Dutch Aphasia Society Word Fluency Subtest Fepsy Finger Tapping Fepsy Visual Reaction Fepsy Binary Choice Fepsy Visual Searching Dutch Adult Reading	Hopkin's Symptom Checklist European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30
Schagen et al., 2002	Same as above	
Scherwath et al., 2006 Neuropsychological function in high-risk breast cancer survivors after stem-cell supported high-dose therapy versus standard-dose chemotherapy: Evaluation of long-term effects	Trail Making Test Battery for Attentional Performance Test d2 Cancellation Wechsler Memory Scale-Revised Rey-Osterrieth Complex Figure Regensburger Wortflussigkeits Leistungsprufsystem Achievement Measure System Hamburg-Wechsler Intelligence Scale-Revised	
Shilling et al., 2003 The effects of hormone therapy on cognition in breast cancer	Wechsler Memory Scale-III Verbal Memory, Visual Memory Working Memory	Beck Depression Inventory General Health Questionnaire Cognitive Failure Questionnaire
Tchen et al., 2003 Cognitive function, fatigue and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer	High Sensitivity Cognitive Screen Mini Mental State Exam Conner's Continuous Performance Trail-Making	Functional Assessment of Cancer Therapy Questionnaires for Breast, Fatigue and Endocrine Symptoms

Table 3 continued

Reference & Title	Neurocognitive tests	Self-Report Measures
van Dam et al., 1998 Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: High-dose versus standard-dose chemotherapy	Rey Auditory Verbal Learning Complex Figure Digit Span Digit Symbol Trail Making D2 Stroop Dutch Aphasia Society Word Fluency Subtest Fepsy Finger Tapping Fepsy Visual Reaction Fepsy Binary Choice Fepsy Visual Searching Dutch Adult Reading	Hopkin's Symptom Checklist European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30
Von Ah et al., 2009 Cognitive function in breast cancer survivors compared to healthy-age and education-matched women	Auditory Verbal Learning Digit Span Digit Symbol Controlled Oral Word Association	Center for Epidemiological Studies Depression Scale Squire Memory Self-Report
Wefel et al., 2004 The cognitive sequelae of standard-dose adjuvant chemotherapy in women with Breast cancer	Wechsler Adult Intelligence Scale Revised Digit Span, Digit Symbol, Similarities, Block Design Trail Making Verbal Selective Reminding Nonverbal Selective Reminding Multilingual Aphasia Examination Controlled Oral Word Association Booklet Category	Functional Assessment of Cancer Therapy-Breast
Wieneke & Dienst, 1995 Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer	Wechsler Adult Intelligence Scale Intelligence Quotient National Adult Reading Digit Span/Digit Symbol Paced Auditory Serial Addition Trail Making California Verbal Learning Rey Osterrieth Complex Figure Block Design Grooved Pegboard	Beck Depression Inventory

cyclophosphamide, methotrexate, and fluorouracil (CMF) within the previous 12 months. Some participants also received hormonal therapy with tamoxifen. Chemotherapy must have been completed at least two weeks prior to neurocognitive testing and participants were excluded for history of neurological disorder, serious head injury, psychiatric illness, substance abuse, or concomitant medications known to affect cognitive function. Participants were evaluated for cognitive performance across nine domains: attention and concentration, verbal and visual memory, abstract conceptualization, mental flexibility and processing speed, visuospatial ability, motor function, estimated premorbid intelligence and depression. In this study, 75% of women treated with chemotherapy scored within the range of moderate cognitive impairment. The majority of the sample had some college education (93%) and 86% (n = 24) received CMF. Tamoxifen was received by 39% (n = 11). The mean time since completion of chemotherapy was six months. No significant differences were attributed to time since treatment, type of regimen received, or depression. Study limitations included small sample size, retrospective design, and the potential for over inclusion of participants who had already voiced cognitive complaints, thus creating a sample bias.

A similar study was conducted by Brezden et al. (2000). Three groups were evaluated: participants currently receiving cyclophosphamide, epirubicin, and fluorouracil (CEF) or CMF for at least two cycles (Group A), participants who had completed chemotherapy at least one year ago who were without disease recurrence (Group B) and healthy controls (Group C). Participants were aged 25-70 years and had no history of gross cognitive dysfunction, psychiatric illness, and drug or alcohol abuse. Six cognitive domains were tested: memory, language, visuomotor, spatial, attention and concentration, and

executive function. Participants also were assessed for mood, including anxiety and depression. The sample consisted of 107 women (Group A: $n = 31$, Group B: $n = 40$, Group C: $n = 36$). Sixteen women in Group B were currently taking tamoxifen and two women had taken tamoxifen previously. Significant differences in cognitive function were seen between those currently receiving chemotherapy (Group A) and healthy controls (Group C) ($p = .009$). Analysis of covariance was used to examine the impact of age, education level, and menopausal status. The significance of the difference between Group A and Group C did not change. No significant differences were seen between participants receiving FEC versus CMF.

Efforts continue to define the incidence and risk factors for CRCI. Von Ah, Harvison, Carpenter, and Unversagt (2009) examined cognitive function in breast cancer survivors ($n = 52$) compared to age-and-education matched healthy controls ($n = 52$) through a cross-sectional, case-control design. Neurocognitive testing was conducted in person or over the phone for the following domains: short and long-term memory, attention, concentration, working memory, executive function, language, processing speed, and self-report of mood and memory. Eligible participants were >40 years of age, >1 year post chemotherapy, and without evidence of major medical, neurologic, or psychiatric illness, head injury, epilepsy, stroke, brain tumors/infection/degeneration. Statistical testing controlled for age, education, format of test administration (in person versus phone), hormonal therapy, and time since completion of chemotherapy. Breast cancer (BC) survivors had clinically significant impairment in one or more cognitive tests (36%). BC survivors less than 4 years after completion of chemotherapy scored significantly lower on tests for delayed recall.

Dose Intensity and Timing of CRCI

Late effects of chemotherapy are of interest due to the potential for impact on quality of life for cancer survivors. Schagen et al. (1999) evaluated 39 women with breast cancer to examine the late effects of cyclophosphamide, methotrexate, and fluorouracil (CMF) on cognitive function. Twenty participants completed six courses of CMF followed by 3 years of hormonal therapy with tamoxifen. Nineteen did not receive hormonal therapy. Age-matched, lymph node negative breast cancer patients who did not receive systemic adjuvant therapy served as controls ($n = 34$). Eligible participants were free of relapse or metastatic disease and must have been at least six months post completion of chemotherapy. Participants were excluded for history of neurologic or psychiatric illness, concomitant medications that might affect neurocognitive testing (such as benzodiazepenes or anti-depressants), alcohol or drug abuse. Neurocognitive testing was conducted almost two years following chemotherapy (mean = 1.9 years) and slightly over two years following local therapy for the controls (mean = 2.4 years). An array of 14 tests was used to evaluate the domains of verbal function, memory, attention/concentration, information processing speed, motor function, visuoconstructional function, and mental flexibility. Participants also were asked to rank the extent of impact experienced in daily life as a component of semi-structured interviews. Quality of life (QOL), anxiety and depression also were measured. Additional variables entered into multivariate stepwise logistic regression analysis included age, intelligence quotient, time since treatment and fatigue. Problems with concentration were reported by 31% of the participants who received chemotherapy and 21% reported problems with memory, both of which were significantly higher than the controls ($p = .007$, $p = .022$). QOL for physical and cognitive functioning scales also were significantly lower

than controls ($p = .035$, $p = .01$). Twenty-eight percent of participants who received chemotherapy demonstrated cognitive impairment compared to 12% of controls. Age, time since treatment, anxiety, depression and fatigue did not significantly contribute to the regression model. The risk for cognitive impairment in the chemotherapy group was highly increased ($p = .013$). No correlation was seen between self-report of cognitive changes and objective measures. However, there was a correlation between the self-report of cognitive changes, anxiety, depression, and QOL. The risk for objective changes in cognitive function was not affected by anxiety, depression, fatigue, or time since chemotherapy. In this study, no differences were seen in the patients who were treated with tamoxifen.

Schagen et al. (2002) continued their previous work in this area by conducting a study to evaluate cognitive function in women with breast cancer who were four years post chemotherapy. Participants from two earlier studies (described in the two previous paragraphs) were considered eligible if they were free of recurrence (Schagen, et al., 1999; van Dam, et al., 1998) and at least one year had passed from the previous neurocognitive assessment. Participants had received high-dose cyclophosphamide, thiotepa, and carboplatin (CTC, $n = 22$), standard-dose fluorouracil, epirubicin, and cyclophosphamide (FEC, $n = 23$) or conventional cyclophosphamide, methotrexate, and fluorouracil (CMF, $n = 27$). Participants were compared to 27 healthy controls. Eligible participants from the study described above and participants from an earlier study (van Dam et al., 1998) were included in a follow-up study. The same measures described above were used in the follow-up study. At the time of the follow-up assessment, no significant differences were seen between the three groups. The authors concluded that the effects of CRCI may be transient.

The first randomized study to compare two chemotherapy regimens of different intensity was conducted by van Dam et al. (1998). In this study 34 women treated with high-dose chemotherapy plus tamoxifen were compared to 36 women who received standard-dose chemotherapy plus tamoxifen, and 34 controls who received local therapy only (mastectomy followed by radiation therapy or in conjunction with breast-conserving surgery). High-dose participants received four standard cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by high-dose cyclophosphamide, and thiotepa and autologous stem cell transplant. Standard-dose participants received four or five cycles of FEC. Eligible patients must have completed chemotherapy at least six months prior to the study. Participants were evaluated with an array of 13 neurocognitive tests and measures for quality of life (QOL), anxiety, and depression. Age and education level were taken into consideration. Semi-structured interviews were conducted to evaluate participants' self-reports of cognitive changes. The results indicated that 32% of the high-dose participants experienced cognitive impairment compared to 17% of the standard dose participants and 9% of controls. No relationship was seen between objective cognitive measures and self-reports. As noted earlier, patients' self-report of cognitive changes may be a more sensitive indicator of change than presently available neurocognitive tests (Schagan, et al. 2002). No relationships were seen for time since last therapy, anxiety, or depression and cognitive function. Participants in the high-dose group were at 8.2 times higher risk for cognitive impairment than controls ($p = .006$). Participants in the standard-dose group were at 3.5 times higher risk than controls ($p = .056$).

Since the work of van Dam et al., one additional study has been conducted to compare the impact of high-dose chemotherapy to standard dose regimens (Scherwath, et al.,

2006). Scherwath et al. compared 24 high-dose participants with 23 standard-dose participants and 29 controls (women diagnosed with early disease that received surgery and radiation therapy). High-dose participants received four cycles of epirubicin and cyclophosphamide (EC) followed by high dose cyclophosphamide, thiotepa, and mitoxantrone (CTM). Standard-dose participants received EC followed by cyclophosphamide, methotrexate and fluorouracil (CMF). All hormone receptor positive participants received tamoxifen. The mean time since completion of chemotherapy was five years. Comprehensive neurocognitive testing was conducted to assess the following domains: attention, memory, and executive function. Participants who demonstrated impairment in four or more of the eighteen test parameters were classified as impaired in global neurocognitive performance. Impairment was demonstrated in 8% of the high-dose group, 13% of the standard-dose group and 3% of controls. The authors concluded that CRCI was substance dependent as opposed to dose dependent and credited methotrexate as the most neurotoxic agent of the two regimens. No correlations were seen between tamoxifen use and changes in cognitive function. Study results indicated that CRCI most frequently affected cognitive functions in the attention domain. Least impairment was noted for executive function, a finding that was unexpected given the support for changes in executive function provided by other studies. The authors acknowledged that this unexpected outcome may be due to the use of tests with insufficient sensitivity for measuring subtle cognitive impairments (see Table 3).

Timothy Ahles and Andrew Saykin have contributed significantly to the state of the science about CRCI. In 2002 they published results of a study to evaluate the neuropsychologic impact of standard dose systemic therapy in long-term survivors of breast

cancer and lymphoma. They compared the results of neurocognitive testing for patients with breast cancer ($n = 35$) and lymphoma ($n = 36$) who had received chemotherapy to patients who had received local therapy only, such as surgery or radiation therapy ($n = 35$, $n = 22$, respectively). Survivors in both groups had to be at least 5 years post completion of their chemotherapy and without signs of CNS disease, history of CNS treatment, such as intrathecal treatment or radiation therapy to the brain, head injury, or neurologic disorder, or current administration of medications known to alter neuropsychologic functioning. A standard array of neuropsychologic tests were selected to measure function in nine cognitive domains and all participants completed an 18-item self-report measure for perceived changes in memory functions. Participants also completed instruments that measure anxiety, depression, and fatigue. Demographic information was collected on age, gender, and education level as well as the type of therapy received, including hormonal therapy. Significantly lower scores were seen for participants receiving systemic versus local therapy ($p < .04$). The domains of verbal memory ($p < .01$) and psychomotor functioning ($p < .03$) were most affected. A neurocognitive performance index was calculated based on participants' scores on all the neurocognitive tests. Significantly more participants who received systemic therapy had low index scores (39% vs. 14%, $p < .01$) and reported greater problems with working memory ($p < .02$). No significant differences were seen among the participants who had received hormonal therapy (tamoxifen) with those that had not. No significant differences were seen between the participants with breast cancer versus those with lymphoma, lending support to the hypothesis that the phenomenon of CRCI may be similar for different types of malignancies. The authors noted that the chemotherapy regimens were very consistent for the two disease populations. The authors concluded that

the study results demonstrated support for the hypothesis that systemic chemotherapy has a negative impact on cognition and that a subgroup of survivors may experience long-term cognitive deficits.

Baseline Cognitive Impairment

Results of prospective trials are beginning to be published. The first longitudinal trial to be conducted was designed to evaluate cognitive function at baseline, approximately three weeks following the completion of chemotherapy and any related medications known to have CNS activity (such as antiemetics) and 1 year post completion of chemotherapy (Wefel, et al., 2004). The short-term post-chemotherapy time point was about 6 months after the baseline assessment. The long-term time point was about 18 months after the baseline assessment. Cognitive testing was selected to evaluate the domains of attention, processing speed, learning, memory, executive function, visuospatial function, and motor skill. Depression, anxiety, and self-report of quality of life also were measured. The sample consisted of 18 participants who had received fluorouracil, doxorubicin, and cyclophosphamide (FAC). At baseline, 33% of the participants were classified as having cognitive impairment (impairment on 2 or more neurocognitive tests) and 24% exhibited impairment on verbal learning and memory compared to normative data adjusted for age, education, and gender ($p = .02$). No mean group differences were seen between the short term and long term time points. No statistically significant correlations were seen between cognitive performance and depression or anxiety at any time point. Within subject analyses indicated that 61% of participants experienced a decline in cognitive function between baseline and the short-term time point. No significant differences were seen for QOL. For participants experiencing cognitive declines, 45% exhibited improvement at the long-term

time point and 45% demonstrated stable cognitive function. The authors noted that despite the absence of a statistically significant mean group decline in cognitive function associated with FAC, a subset of women demonstrated a decline in function. The most commonly affected domains were attention, learning, and processing speed.

The discovery by Wefel et al. that a third of women with breast cancer may experience cognitive changes prior to the initiation of chemotherapy was preceded by some research done by Cimprich and Ronis (2001). Cimprich and Ronis (2001) defined one component of cognitive function as the capacity to direct attention (CDA), further described as the cognitive ability to actively block or inhibit a competing stimulus in purposeful or goal-directed activity (Cimprich, et al., 2005). Aging has been associated with a loss of CDA in both men and women (Cimprich et al., 2005). Cimprich et al. published results of a study in which women aged 55-79 who were newly diagnosed with breast cancer ($n = 47$) were evaluated for CDA and symptom distress before surgery, two weeks postoperatively, and three months postoperatively. Healthy matched controls ($n = 48$) were evaluated at similar time frames. The breast cancer group scored significantly lower than the healthy controls for CDA and symptom distress at baseline ($p = .005$) even though mean scores for CDA for both groups were within normal ranges for healthy adults. Regression analysis was performed to assess the impact of age alone and group (breast cancer versus controls). Age alone accounted for 6% of the variance at baseline with an additional 12% of the variance explained by group ($p = .006$). Other variables (education, marital status, health problems, and depression) did not explain a significant proportion of the variance.

Cimprich et al. continued their work with a subsequent study designed to further evaluate the relationship of CDA with pertinent demographic and medical factors such as

age, menopausal status, education level, and comorbidities as potential predictors of CDA prior to treatment for breast cancer (Cimprich, et al., 2005). Cognitive testing for two measures of CDA, memory, and self-report of cognitive function was performed for 184 women with early stage disease (0, I, II) about 23 days after diagnosis by biopsy and about 18 days prior to surgery. Symptom distress and mood state also were measured. Cognitive performance was within the normal range of healthy adults although participants' self-report of cognitive function indicated that 50% reported moderate effectiveness and 25% reported lower effectiveness. No significant relationships were seen between self-report and objective performance for attention or memory. Age was significantly correlated with attention and memory as well as to self-report of cognitive function. Younger participants had poorer effectiveness perception of cognitive function. Significant differences were shown for memory ($p < .05$) and attention ($p = .04$) between pre and postmenopausal women. No significant differences were seen for perimenopausal women. More years of education were associated with better cognitive performance but no correlation was seen with self-report of cognitive function. A relationship was seen between ratings of symptom distress and self-reports of cognitive effectiveness. Age and years of education were significant predictors of CDA prior to treatment. Symptom distress and mood scores were significant predictors of self-report of cognitive effectiveness. The authors suggested that younger women may perceive even small fatigue-related losses in attention that interfere with cognitive function but are not discernable with objective testing. Older women were hypothesized to be at greater risk for treatment-related losses in CDA over time. The authors stated that age may explain the observed relationship between menopausal status and cognitive functioning. As in previous studies, the authors acknowledged that the objective cognitive tests may not be

sensitive enough to detect subtle changes in function or to replicate the complexity of the demands of daily life.

Hormonal Influence on CRCI

Attribution of causality for CRCI in patients with breast cancer is complicated by the impact of estrogen inhibition on cognitive function. The majority of breast cancer is diagnosed in postmenopausal women (approximately 75%) (Klemp, Stanton, Kimler, & Fabian, 2006) as the average age at diagnosis is 61 (NCI, 2009b). Decreases in serum estradiol levels have been associated with changes in cognitive function. Abrupt menopause is typically observed in premenopausal patients who receive chemotherapy. Subsequent changes in cognitive function may be more pronounced in this population that does not have the more gradual onset of diminished estradiol levels normally experienced as women age. Studies designed to control for the use of hormonal therapy (selective estrogen receptor modulation with tamoxifen, or aromatase inhibition with anastrozole or letrozole) have produced conflicting results.

Paganini-Hill and Clark (2000) conducted a study with 1163 patients with breast cancer who took part in an earlier population-based case-control study. Of these, 710 had taken tamoxifen and 453 had not. Participants were stratified between past and current use as well as duration of therapy. Standard-term tamoxifen users were defined as those who took tamoxifen for five years. Participants completed three neurocognitive tests that were supplied and returned by mail. Little difference was seen between standard-term tamoxifen users and never users. However, standard-term users reported seeking attention from their physicians for memory problems (3.8% vs 1.5%, $p = .04$) and those currently receiving tamoxifen demonstrated a lower score on the narrative writing task ($p = .03$). The authors

concluded that current use of tamoxifen may adversely affect cognition. This study was limited by the lack of personal administration of the three neurocognitive tests as no direct observation of tests performance was possible nor was the opportunity to verify participants understood the instructions.

The effects of hormone therapy on cognition in breast cancer recently was studied as a component of the anastrozole, tamoxifen and combined (ATAC) trial (Jenkins, Bloomfield, Shilling, & Edginton, 2005; Shilling, Jenkins, Fallowfield, & Howell, 2003). Women on this trial with no evidence of disease ($n = 94$) were compared to a convenience sample of healthy post-menopausal women ($n = 35$). No patients on this trial received chemotherapy. Neurocognitive tests were conducted to assess auditory-verbal memory, visual memory, working memory and attention, processing speed, vigilance, and intelligence. Participants also completed instruments to measure anxiety and depression as well as a 25-item self-report instrument to describe cognitive impairment. Participants receiving hormonal therapy had significantly lower scores for immediate verbal recall ($F = 4.57, p = .034$) and processing speed ($F = 3.96, p = .049$). No differences were seen between the groups for the remaining domains. The authors concluded that hormone therapy did not affect overall cognitive performance, but did impair performance on tests of verbal memory and processing speed.

Another study conducted to evaluate the impact of chemotherapy on cognitive function also explored the impact of hormonal therapy (Castellon, et al., 2004). Participants were part of a larger study (the Cancer and Menopause Study- CAMS), who were between two and five years from diagnosis, age 50 years or younger, with no evidence of disease recurrence. Participants were excluded for history of neurologic or psychiatric disorder, current or past history of drug or alcohol use disorder, or use of any medications that might

impact neurocognitive performance. Participants were diagnosed with early stage disease (I, and II) and were compared to healthy, age-matched women recruited specifically for this study. Measures included instruments to assess function across eight cognitive domains, in addition to depression, anxiety, and fatigue. The sample consisted of breast cancer survivors ($n = 53$) and healthy comparison controls ($n = 19$). Of the breast cancer survivors, 17 received only local therapy, 18 received chemotherapy alone and 18 received chemotherapy with the addition of tamoxifen. Most of the women received cyclophosphamide, methotrexate and fluorouracil (CMF, 41%) while 38% received a doxorubicin containing regimen with either cyclophosphamide alone or with CMF. The remainder received doxorubicin, cyclophosphamide, and a taxane (ACT, 9%). Significant differences in performance for verbal learning ($p = .03$) visuospatial functioning ($p = .005$), and visual memory ($p = .01$) were seen for the women receiving systemic therapy versus local therapy. Global neurocognitive performance scores also were significantly lower for the systemic treatment group ($p = .01$). Women who received both chemotherapy and tamoxifen had the lowest group means on five of the eight cognitive domains and significantly lower global neurocognitive performance scores than the women who received chemotherapy alone ($p = .02$). As with many studies, lack of correlation was seen between self-report of cognitive function and the objective measures potentially due to the lack of sensitivity of available neurocognitive tests (Jacobs, et al. 2007). Significant correlation was observed between poor cognitive performance with depression ($r = .44, p < .01$), anxiety ($r = .42, p < .05$), and fatigue ($r = 1.39, p < .05$). The authors acknowledged that study limitations included small sample size and cross-sectional design. The authors concluded that the study provided

support for CRCI in a subset of breast cancer survivors and that adjuvant tamoxifen may have subtle but lasting cognitive effects in breast cancer survivors.

A more recent study was conducted to compare memory impairment seen with adjuvant anastrozole versus tamoxifen for women with early-stage breast cancer (Bender, et al., 2007). Due to evidence to support lower serum estradiol levels with aromatase inhibition compared to selective estrogen receptor modulation, Bender et al. hypothesized that anastrozole would have a more profound effect on cognitive function than tamoxifen. A cross sectional design was used to evaluate cognitive function, depression, anxiety, and fatigue for 31 postmenopausal women who had received tamoxifen ($n = 15$) or anastrozole ($n = 16$) for a minimum of 3 months. Cognitive testing was conducted for the domains of attention, learning and memory, psychomotor efficiency, mental flexibility, visuospatial ability, and general intelligence. The variables of age, years of education, time on hormonal therapy, depression, anxiety, and fatigue were controlled. Women receiving anastrozole had significantly lower scores on measures of learning and memory. However no significant difference was noted for any of the other cognitive domains. Hierarchical regression was calculated for the controlled variables (block 1) and the addition of anastrozole and chemotherapy for each cognitive test of learning and memory. Anastrozole contributed a unique explanation of variance for the models of verbal learning and memory (12-35%) as compared to the variance explained by chemotherapy (.1-6%). Study limitations included small sample size, cross-sectional design, and lack of baseline measures prior to initiation of chemotherapy and hormonal therapy.

Klemp et al. (2006) evaluated the effects of chemotherapy on cognitive function and QOL for premenopausal women with breast cancer. The sample consisted of 20 women with

breast cancer receiving chemotherapy with doxorubicin and cyclophosphamide, epirubicin and cyclophosphamide, trastuzumab or carboplatin and docetaxel. Cognitive function, depression, fatigue, QOL, serum estradiol levels and hemoglobin levels were measured at baseline, half-way through chemotherapy, and approximately three weeks following the completion of chemotherapy (prior to the initiation of any hormonal therapy or radiation). Cognitive domains included: memory, language, attention and concentration, visuomotor, spatial, and executive function. Patients receiving either adjuvant or neoadjuvant (50%) chemotherapy were eligible. Estradiol levels significantly decreased from baseline ($p = .009$). Participants reported menopausal symptoms that caused depression ($p = .001$) and affected QOL. Participants perceived impairment of concentration and memory although impairment was not demonstrated on the objective neurocognitive tests. Cognitive function scores actually improved over time which the authors attributed to practice effect.

Additional work related to the impact of menopausal symptoms and fatigue to cognitive function was conducted by Tchen, et al. (2003). A sample of 110 women receiving adjuvant chemotherapy nominated an age-matched volunteer to total 100 matched pairs for evaluation. Eligible participants were age 60 or younger and had completed at least three courses of chemotherapy at the time of assessment. Preferred time for assessment was within two to six weeks of the previous chemotherapy treatment. Premenopausal status was defined as menses within the past 3 months, perimenopausal as menses within 3-12 months, and postmenopausal as no menses for >12 months. Participants were tested for cognitive performance in the following domains: verbal memory, language, visuomotor, spatial, attention and concentration, and executive function. Reaction time and psychomotor speed also were assessed in addition to self-report of fatigue, menopausal symptoms and QOL. The

majority of participants were receiving combinations of cyclophosphamide, epirubicin, fluorouracil, doxorubicin, and methotrexate. Five participants were receiving tamoxifen. Hemoglobin levels were collected and included in multivariate analysis for possible effects on cognitive function and fatigue. Participants receiving chemotherapy demonstrated poor cognitive function compared to controls ($p = .0008$). Co-variables of age, education, and menopausal status did not alter the statistically significant difference between the group receiving chemotherapy and the controls ($p = .008$). Fatigue was more significant in the chemotherapy group ($p < .0001$). Sixty-two percent of participants were menstruating prior to starting chemotherapy, but only 25% were menstruating at the time of the assessment. Participants receiving chemotherapy had significantly more severe menopausal symptoms ($p < .0001$) and lower QOL scores ($p < .0001$). Objective tests of cognitive function were not correlated with fatigue, menopausal symptoms or QOL, however strong relationships were seen between fatigue and QOL ($p < .0001$), menopausal symptoms and QOL ($p < .0001$), and fatigue and menopausal symptoms ($p < .0001$). The authors noted that only 16 participants had moderate or severe cognitive dysfunction (less than expected), so the study was insufficiently powered to make definite conclusions about the influence of fatigue, menopausal symptoms, type and number of courses of chemotherapy, hemoglobin level on the probability of cognitive dysfunction. Scores for objective tests of cognitive function were not correlated with scores for QOL. The authors stated that they believed methotrexate to be the most neurotoxic of the chemotherapeutic agents. Since only 11 patients in this study were receiving a methotrexate containing regimen the relationship between specific drugs and cognitive effects could not be evaluated. They noted feeling reassured that the fluorouracil, epirubicin, cyclophosphamide, (FEC) regimen was more intensive but did not

lead to an increase in cognitive dysfunction. The authors stated that the study results did not support a hormonally mediated mechanism for causing cognitive dysfunction.

Follow-up to the work was published in 2005 (Mar Fan, et al., 2005). Participants were re-evaluated at 1 and 2 years of follow-up. The proportion of patients with moderate-severe cognitive impairment decreased from 16% to 4% after 2 years. No significant difference was seen between patients who received hormonal therapy and those that did not. Similar levels of QOL were reported by both participants who received chemotherapy and controls at 1 and 2 years of follow-up. The authors did acknowledge that practice effect might have masked a small effect of tamoxifen on cognitive function. Over the 2 year follow-up period, a very small number of participants received an aromatase inhibitor. No conclusions were drawn related to aromatase inhibition versus selective estrogen receptor moderation with tamoxifen.

Prospective longitudinal studies provide the benefit of being able to compare baseline data about cognitive function to changes that may occur during or after completion of chemotherapy. One such study published in 2006 (Bender, et al., 2006) was designed to compare changes in cognitive function across three groups of breast cancer survivors ($n = 46$). Bender et al. evaluated women with stage I or II breast cancer with hormone receptor negative disease who received chemotherapy alone ($n = 19$), to women with hormone receptor positive disease who received chemotherapy in addition to hormonal therapy with tamoxifen ($n = 15$). The control group was comprised of women with ductal carcinoma in situ who received neither chemotherapy nor tamoxifen ($n = 12$). Cognitive function was measured after surgery in the non-treatment group and just prior to initiation of adjuvant therapy in both treatment groups (Time 1). Additional measurements were conducted within

1 week after completion of chemotherapy (Time 2) and at a comparable time for the non-treatment group. Time 3 measurement was conducted 1 year after Time 2. The neurocognitive test array was selected to measure the domains of attention, learning and memory, psychomotor speed, mental flexibility, visuoconstructional ability, executive function, and general intelligence. Participants' also completed a self-report measure for perceptions of cognitive function. Potential moderators of cognitive function also were assessed, including: depression, anxiety, fatigue, and concomitant medications. The chemotherapy regimens all included cyclophosphamide, however the regimens were not consistent related to the other antineoplastic agents (methotrexate, fluorouracil, doxorubicin, and a taxane). Attrition occurred for all three groups (10 at Time 2 and 14 at Time 3) due to drop-outs for "being too busy" (80%) or progression of disease (20%). The attrition rate was not different across the groups and no significant differences were seen between women who dropped out and women who remained on study. Women scoring higher on the depression measure were noted to perceive more cognitive problems. No interaction was seen for anxiety or fatigue with cognitive function. No significant differences in cognitive function were seen at baseline. The performance of the treatment groups for memory measures deteriorated over time. Overall, women receiving chemotherapy alone or with tamoxifen had significantly worse performance on memory tests over time than the women in the non-treatment group ($p = .026$) at Time 3. Women who received only chemotherapy performed better than women who also received tamoxifen ($p = .043$) at Time 3. Women who received both chemotherapy and tamoxifen demonstrated deterioration in tests of immediate recall between Time 2 and Time 3 ($p = .017$). The broadest deteriorations were seen for visual memory and verbal working memory by the women who received both chemotherapy and

tamoxifen. The authors concluded that CRCI was domain specific as opposed to diffuse. The authors attributed the difference to the pre-treatment baseline evaluation that is a component of prospective trials. Very little objective variation from baseline was seen at Time 2, although participants' self-report of changes in cognitive function were immediately evident at the conclusion of therapy. As with many other studies, there was no correlation between objective and subjective measures of cognitive function. The authors recommended shorter measurement intervals in future studies to try and more precisely capture when objective changes in cognitive function occur. Strengths of this study included baseline evaluation of cognitive function and evaluation of cognitive function at uniform times after completion of chemotherapy. Limitations included the small sample size, attrition rate, and lack of consistency for chemotherapy regimens. The authors noted that their study results reinforce the subtlety of cognitive changes related to chemotherapy and that the deficits may be limited to memory. They also stated that CRCI may be manifested with recall of recently learned information, particularly in situations where distractions occur and women with CRCI have difficulty working effectively in cognitively challenging situations.

A prospective trial by Jenkins et al. (2006) was conducted to study the effects of adjuvant chemotherapy and hormonal therapy on cognition in women with early stage breast cancer. Cognitive testing was performed for 85 women scheduled for chemotherapy, 43 scheduled for hormonal and/or radiation therapy, and 49 healthy controls at baseline (T1), post chemotherapy or 6 months (T2), and at 18 months (T3). Hormonal therapy regimens included tamoxifen, goserelin, and aromatase inhibitors. No group differences were observed, but individual declines were seen in 20% of chemotherapy patients, 26% of hormonal therapy patients, and 18% of controls at T2 and T3 (18%, 14%, 11%). Participants

who experienced a treatment-induced menopause showed more decline at T2 ($p = .086$). Self-reports of cognitive function were associated with QOL scores ($p < .0001$), but no correlation was seen with objective cognitive tests. A majority of participants receiving chemotherapy noted changes in memory (83%) and concentration (80%) at T2. Improvements were seen at T3 (60%, and 45%). Reliable predictors of cognitive performance were determined to be age, intelligence, and years of education. No association was seen for objective cognitive performance with chemotherapy, hormonal therapy, QOL and psychological distress. The authors noted that most of the participants in the chemotherapy group received low dose fluorouracil, epirubicin, and cyclophosphamide (FEC). The authors concluded that the study results suggested only a small proportion of women receiving adjuvant therapy for breast cancer experience objective declines in cognitive function and those experiencing treatment-induced menopause, particularly in the initial period following chemotherapy, appear to be at greatest risk.

Self-Report of CRCI

Participants who took part in the studies by Tchen et al. and Mar Fan et al. (described above) also had the opportunity to participate in semi-structured interviews performed to gather descriptive information about the symptoms and subsequent meaning and impact on participants' day-to-day lives (Downie, Mar Fan, Houede-Tchen, Yi, & Tannock, 2006). Every second patient recruited during a defined time interval of the larger study was invited to participate in the interviews and complete an assessment of cognitive function as well as a self-report questionnaire (Functional Assessment of Cancer Therapy- General, Fatigue and Endocrine Symptoms Subscales). The sample included 21 participants without evidence of recurrence or metastases and no history of major physical or psychiatric illness. Patients

were excluded for psychotropic medications with the exception of benzodiazepines or serotonin reuptake inhibitors. Participants were asked about whether they had noticed changes in memory, concentration and attention, verbal ability, thinking speed, spatial ability/orientation, and the ability to plan and organize (executive function) as well as fatigue or menopausal symptoms. If participants answered yes to any of these areas, they were then asked to describe the symptom, how the symptom had changed from prior to the start of chemotherapy, how the symptom changed their life, how they coped with the symptom, and the level of severity with which they would rate the symptom (mild, moderate, or severe). In this mixed-methods design, the severity descriptors were assigned a numerical value (normal/borderline = 0, mild = 1, moderate = 2, severe = 3). Correlations were examined between the interview responses and participants' scores on the quantitative measures of cognitive function, fatigue, and menopause. Fatigue was reported by 90% of patients on the quantitative instrument and 100% in the interviews. Menopausal symptoms were reported on 94% of the quantitative instrument and 83% during the interview. Objective measures of difficulty with language (61%) and memory (48%) contrasted with those reported during the interview (78% and 95%). The biggest disparity occurred between objective measures of attention and concentration (10%) and those reported in the interview (90%). Significant correlations were seen between objective cognitive performance for fatigue ($p = .001$), menopausal symptoms ($p = .05$), and memory ($p = .008$). Participants said that fatigue, nausea, and cognitive problems interfered with the ability to maintain full-time employment. About 30% of participants were able to work part-time. Participants complained of changes in short-term memory, concentration, verbal fluency and word finding, processing speed, and executive function. These problems were described to be intermittent and unpredictable. No

participants complained of difficulty with verbal comprehension. Participants noted a great change in their ability to multi-task. Few participants noted difficulty with spatial ability, however about 10% complained of decreased sense of direction and distance judgment. Several noted changes in their ability to drive due to trouble with concentration, memory, and processing speed. The authors acknowledged that the sample size was large for qualitative investigation, but small for statistical analysis. The authors concluded that quantitative self-report measures and semi-structured interviews are important to gain a comprehensive and clinically relevant understanding of the symptom experience.

The importance of self report for CRCI has been emphasized in the literature. Lynne Wagner and colleagues continue to develop the Functional Assessment of Cancer Therapy-Cognition instrument (Wagner, Sweet, Butt, Lai, & Cella, 2009). The results of qualitative interviews and focus groups were used to generate the self-report measure of chemotherapy-related cognitive function. Due to the profound impact of perceived cognitive impairment on functional abilities and quality of life, Wagner et al. advocate the position that patient-reported cognitive function is an important study endpoint.

Further support for the importance of self-report of CRCI was generated by the work of Andrew Saykin in which an association was seen between patient self-report of cognitive changes and neuroimaging (Saykin et al. 2006). In this work neuroimaging was used to compare decline in gray matter volume between older adults with self-report of memory complaints and normal performance on memory tests with individuals demonstrating mild cognitive impairment on testing as well as healthy controls. Results of the study indicated that self-report of memory complaints was associated with gray matter loss prior to decreased performance on objective memory tests.

Contradictory Findings

Many aspects of the research conducted to date are contradictory, as evidenced by two recent meta-analyses conducted to examine the neurocognitive effects of cancer therapy and address the issue of the magnitude of cognitive impairment due to chemotherapy (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Falletti, Sanfilippo, Maruff, Weih, & Phillips, 2005). Anderson-Hanley et al. evaluated 30 studies involving various cancer therapies such as chemotherapy, radiation therapy, immunomodulatory therapy, and bone marrow transplant for a variety of malignancies ($n = 838$). They noted consistent statistically significant negative effect sizes across both normative and control methods for executive function, verbal memory, and motor function. Anderson-Hanley et al. concluded that no clear clinical implications could yet be drawn as more research is needed to clarify which treatments are associated with cognitive impairment and to further rule out the wide variety of possible mediating or moderating variables such as: total brain irradiation, central nervous system disease, and immunologic therapy, treatment intensity, severity of diagnosis, stress, fatigue, depression, inflammatory cytokines, and concomitant medications. Anderson-Hanley stated that the effect sizes across all the studies for executive function, verbal memory, and motor function indicated that cognitive performance for patients receiving systemic therapy was one third to almost one standard deviation below normative samples or control groups. This performance level is not as low as what would traditionally warrant a label of impairment by neurocognitive standards (-1 to -3 standard deviations). As such, the deficits may be difficult to observe. Anderson-Hanley et al. discussed the impact that subtle changes in cognitive function would have on individuals with average or above-average baseline function and the distress associated with the inability to continue performing in a

profession that requires peak cognitive skills. Anderson-Hanley et al. also noted that further research for CRCI may clarify the potential need for more detailed informed consent prior to initiation of chemotherapy. More knowledge about CRCI would serve to validate some patients' experiences while enhancing the pre-treatment anxiety of others. Specific knowledge regarding who is at greatest risk for CRCI may relieve those who are likely to experience smaller or more reversible declines in cognitive function.

Falleti et al. conducted a meta-analysis specific to CRCI in women with breast cancer. Only six studies met their inclusion criteria ($n = 208$) (five cross-sectional and one prospective). Their results were somewhat contradictory to much of the literature to date. Regression analysis indicated a significant negative logarithmic relationship ($R^2 = .63$) between effect sizes and time since last receiving chemotherapy, percentage of patients currently taking tamoxifen ($R^2 = .60$), and average age ($R^2 = .67$). No relationship was seen between the percentage of patients on tamoxifen and cognitive function. The prospective effect sizes indicated improvements in cognitive function from the beginning of chemotherapy to one year following treatment. Falleti et al. compared CRCI with the fatigue that occurs at the end of a normal day (twelve hours of wake time). Falleti et al. criticized studies that used multiple neurocognitive tests for each cognitive domain, stating that the more tests used to assess cognitive performance, the greater the probability that an individual would meet the criteria for impairment.

Descriptions of CRCI and the Breast Cancer Experience

Very few qualitative studies have been published that specifically relate to the experience of CRCI for women with breast cancer. Support in the literature exists for the need of information related to long-term sequelae from the treatment of breast cancer

(Cappiello, Cunningham, Knobf, & Erdos, 2007). Cappiello et al. recently conducted a qualitative study to “describe the information and support needs of women with early-stage breast cancer after treatment, as a basis for developing specific interventions” (p. 280). A series of 16 semi-structured interviews were conducted (8 in-person, and 12 by phone) for women with early stage breast cancer (0-IIIa) diagnosed within the past 5 years who had completed primary and/or adjuvant treatment (with the exception of hormonal therapy). Participants were questioned about physical symptoms at 3, 6, and 12 months following treatment. Fatigue was the most prevalent symptom reported. However difficulty concentrating was reported by 60% at three months. Difficulty remembering things was reported by 80% at three months. These symptoms persisted (55-75% respectively) throughout the first year following treatment. Participants also were asked to describe their emotions following treatment. Anxiety was common during the 1st year (ranged from 50-60%). Changes in mood (50%) and feeling sad (20%) diminished over time (20% and 5%). Participants described struggling to return to the life they led before their breast cancer diagnosis. The authors concluded that a need exists to provide comprehensive information and support to prepare women for the transition from cancer treatment to long-term survivorship. The authors acknowledged that the study was limited by the small, cross-sectional sample, homogenous demographics (90% Caucasian), and dependence on participants’ recall of symptoms the year following treatment.

Two recent works were completed to better understand the experience of CRCI for patients with breast cancer (Mulrooney, 2007; Thielen, 2009). Mulrooney conducted a phenomenological study to examine the experience of CRCI on day-to-day life. She interviewed 10 women who were within 15-52 months of completing their chemotherapy that

self-reported cognitive impairment. Participants were recruited from two larger studies being conducted at Dartmouth that included longitudinal standard neurological testing prior to and after chemotherapy ($n = 9$) and functional magnetic resonance imaging (fMRI) ($n = 1$). Each participant was interviewed twice. The second interview (4-8 weeks following the first) provided an opportunity for member checking as well as the collection of additional information after participants had some time to reflect on their experiences. Mulrooney also collected e-mails received from participants, field notes, and an electronic journal of her thoughts throughout the study. Participants were asked to describe how CRCI had interfered with their ability to function in any aspect of their day-to-day lives and what, if any, strategies they had devised for handling the problem. Mulrooney described a bracketing exercise to attempt to separate knowledge and prejudices about the phenomenon. Her data analysis procedure was well described. Mulrooney noted three themes from her analysis: 1) I just don't feel like me; 2) Trying my best to live with it; and 3) I am alive. The analysis process produced a final theme that participants believed CRCI was a result of necessary treatment to save their lives, and thus focused most on survival. Mulrooney summarized participants' difficulties with memory, learning, concentration, language, and multitasking ability. Concrete coping skills were described as: keeping a calendar, writing lists, putting frequently used items in the same place to prevent loss or dependence on family for assistance.

Thielen also conducted a phenomenological study of the experience of neurocognitive changes in women undergoing chemotherapy for breast cancer. The purpose of her study was to describe and enrich the understanding of what CRCI means to the individual and the effect it has on everyday life. Thielen hoped the insights obtained from the study would be

useful in the design of screening questionnaires, educational products, and interventional strategies. Thielen listed her research question as, “What is the lived experience of neurocognitive changes in women undergoing adjuvant chemotherapy for breast cancer?” Thielen outlined her presuppositions about breast cancer, side effects and the impact on women. Participants were recruited through an advertisement in the local newspaper and contacts in the offices of private oncology practices. Efforts were made to include women from diverse ethnic and racial groups. Eligible participants were women who self-reported changes in memory, attention, and/or concentration since undergoing chemotherapy. Participants could be currently receiving treatment or within 3 months of completion. Unstructured interviews were conducted with 13 women. Colaizzi’s method for phenomenological data analysis was used. Thielen identified the following eight themes: 1) Insidious recognition and delayed validation of cognitive changes; 2) Looking for answers in all the wrong places; 3) Attention: Can’t keep my eye on the ball; 4) Underwhelming information for an overwhelming experience; 5) Work department: Hold please!; 6) Missing label: Caution- women on chemotherapy on board; 7) Coping: not on the journey alone; 8) What the future holds.

Participants complained that they didn’t know what was happening to them which added to the distress associated with the cognitive changes they were experiencing. This complaint lends support to the need for HCPs to provide appropriate pre-treatment education and to validate patients’ experiences as they are identified or reported. Three of Thielen’s themes included the need for information and validation: 1) Insidious recognition and delayed validation of cognitive changes; 2) Looking for answers in all the wrong places; and

4) Underwhelming information for an overwhelming experience. Further analysis may have led to the combining of these three themes into one.

Participants described difficulty with concentration, distraction, and indecisiveness. Complaints included deficits in being able to remember names and telephone numbers and do simple math (short and long term memory and executive function). They associated these changes with decreased QOL. One participant was unable to return to work. Many participants did not have to work full time but expressed doubt over whether they would be able to do so due to the changes in cognitive function they experienced. Participants described difficulty driving due to impaired sense of direction and inability to remember how to get to familiar places. Family members were needed to assist with accurate administration of home medication due to inability to remember whether a dose had been taken or not. Most participants were hopeful that they could return to a pre-treatment cognitive state.

Thielen stressed the need for appropriate assessment and education of patients receiving chemotherapy for breast cancer. She recommended replicating this study with a more diverse sample demographically and geographically in addition to triangulation from patients' medical records regarding types of chemotherapy regimens.

Boykoff et al. recently published results of an exploratory pilot study to investigate post-treatment side effects of breast cancer survivors. Participants were at least one year post-completion of adjuvant radiation and/or chemotherapy. Both focus groups and in-depth interviews were conducted with 74 women (20 women participated in both) to explore the effects that cognitive impairment has on women's personal and professional lives. Eligible women self-reported changes in cognitive function. The investigators used terminology such as loss of words, forgetfulness, memory loss, or chemobrain when querying participants

about CRCI. Data were analyzed using ethnographic content analysis and codes that were developed a priori to the study. Participants reported 15 discrete, chronic symptoms attributed to cancer therapy. Cognitive impairment was reported by 70% of the sample. Participants described difficulty remembering numbers, trouble with word-finding, decreased processing speed, and diminished ability to read complex books. Lack of acknowledgement of CRCI by the medical community was a common complaint. Participants noted they wished they had received some warning about the potential for CRCI. A number of participants described lack of understanding from family and friends and many shared issues and concerns with maintaining their previous level of wage earning and work-related performance. Some coping strategies included the use of calendars and post-it notes as well as some social withdrawal due to difficulty in following conversation. The investigators acknowledged the importance of in-depth interviews as compared to questionnaires to truly learn about survivors' experiences and recommended further qualitative work to gain knowledge of the interplay between CRCI and resultant life experience.

Summary and Support for Current Research

The review of literature related to the experience of CRCI for women with breast cancer yielded a number of gaps and contradictions in the state of the knowledge. Controversy exists over whether potential predictive factors are related to CRCI or not. Results of several studies did not show significant correlation or impact on cognitive function for a variety of factors including: age, education level, menopausal status, time since treatment, treatment regimen, anxiety, depression, and fatigue (Brezden et al., 2000; Schagen et al., 1999, 2002; van Dam et al., 1998; Wieneke & Dienst, 1995). However, these results were contradicted by Castellon et al. (2004) who found a correlation between cognitive

impairment and depression, anxiety, and fatigue. Likewise, Jenkins et al. (2006) found age, intelligence quotient, and education level to be predictors of cognitive performance. Anxiety and depression have been shown to be related to a negative impact on quality of life and may contribute to enhanced perception of cognitive changes (Klemp et al. 2006).

Jenkins et al. (2005) found hormonal therapy to be associated with declines in verbal memory and processing speed and Bender et al. (2006) noted that combination chemotherapy and hormonal therapy was associated with higher levels of cognitive changes than chemotherapy alone or no therapy. Mar Fan et al. (2005) found no significant differences in cognitive function for women who received hormonal therapy.

The semi-structured interviews conducted by Downie et al. (2006) yielded information about the intermittence and unpredictability of cognitive changes women with breast cancer experienced. Mention was made of difficulty maintaining employment, multitasking, and sense of direction. This study provided support for both quantitative self-report measures and semi-structured interviews to better understand the symptom experience of CRCI. Bender et al. (2006) noted that patients' self-report of cognitive change was present immediately at the conclusion of chemotherapy as compared to a more delayed evidence on objective measures. This information matches the experience described by Saykin et al. (2006) whereby self-report precedes changes seen by neuroimaging.

Results of the qualitative work by Boykoff et al. (2009), Cappiello et al. (2007), Mulrooney (2007), and Thielen (2008) indicated that women with breast cancer would benefit from receiving comprehensive information and support related to the potential for cognitive changes from chemotherapy. Boykoff's results demonstrated a lack of acknowledgement of CRCI by the medical community as well as the importance of in-depth

interviews with cancer survivors. Thielen's descriptions of women who "didn't know what was happening to them" and the "need for information and validation" are strong indicators for the development of meaningful educational materials. Thielen described one woman who was unable to return to work as a result of cognitive changes. Very little information is available in the literature related to the impact of CRCI on the ability to maintain professional and personal roles.

Evidence of the lack of agreement and standardization of objective measures of cognitive performance for women with breast cancer who have received chemotherapy is clear. Lack of congruence between self-reports of cognitive changes and performance on neurocognitive tests has been demonstrated repeatedly. Self-report measures are credited with higher sensitivity than standard neurocognitive tests to the subtle changes in cognitive function experienced by women with high levels of baseline function.

Further qualitative exploration of the patient experience has the potential to significantly add to the state of the knowledge about CRCI. Obtaining rich, detailed descriptions from women with breast cancer about the experience of CRCI may validate earlier qualitative work. Ascertaining specific information that women with breast cancer would have found helpful prior to starting treatment with chemotherapy is necessary to provide a framework to develop meaningful educational tools. A better understanding of the experience of CRCI is needed to educate HCPs and lead to an improved process of informed consent as well as validation of the patient experience. The following qualitative descriptive research study was designed to add to the body of knowledge related to the experience of CRCI for women with breast cancer and desired timing and content of related education.

Chapter 3: Methods

The study was designed to address the following problem: Women with breast cancer complain of a lack of acknowledgement and education about the potential for cognitive changes related to chemotherapy. Cognitive changes can have a significant impact on cancer survivors' quality of life and lack of information regarding the potential risk for chemotherapy-related cognitive impairment (CRCI) prevents obtaining full informed consent prior to initiation of therapy. Lack of acknowledgement of CRCI by HCPs is a source of frustration and dissatisfaction to patients experiencing cognitive changes. The purpose of this qualitative descriptive study was to provide an in-depth description of the patient experience of CRCI for women with breast cancer.

Study Design

A qualitative descriptive design was selected to answer the research questions because this methodology is particularly suited to obtaining straightforward answers of interest to practitioners (Sandelowski, 2000) . Data were collected through the use of semi-structured interviews and a focus group. Triangulation of data between the interviews and focus group occurred as the data were analyzed and interpreted. This approach was used to enhance study credibility.

Setting

Participants were recruited from the University of Kansas Medical Center (KUMC) Breast Cancer Survivorship Center (BCSC). Participants also were recruited by referral from members of the Greater Kansas City Chapter of the Oncology Nursing Society. Self-referrals also were accepted by eligible interested women who became aware of the study through conversations with friends/family participating in the study.

The KUMC BCSC was selected for the study due to the large potential pool of eligible women (about 800) and interest on the part of the staff in the area of CRCI. The Managing Director of the BCSC was a member of the research team and has conducted research related to CRCI in women with breast cancer.

Sample

Purposive sampling (a qualitative sampling technique that involves deliberate, non-random recruitment of participants to meet pre-established eligibility criteria) was used for recruitment to the study. Eligible participants included adult women (18 or older) diagnosed with any stage of breast cancer, who were within 6-12 months of completing chemotherapy and self-reported changes in cognitive function. Self-report included voluntary, unsolicited description of changes in cognitive function to the potential participant's HCP (oncologist or oncology nurse) or the Managing Director of the KUMC BCSC. Examples of changes in cognitive function included (but were not limited to) complaints of mental foginess, difficulty concentrating, trouble with memory, inability to multitask or do mathematic calculations, and decreased sense of direction when driving.

The following additional inclusion criteria applied: ability to read, write, speak, and understand English in order to read and understand the informed consent and demographics questionnaire. Any questions related to the informed consent or questionnaire were explained in person by the investigator. Women were excluded from the study if they had evidence of severe cognitive impairment (exhibited lack of understanding and/or inability to repeat the purpose of the study during the process of informed consent with the investigator), central nervous system metastases, a history of mental illness, dementia, or Alzheimer's disease or were currently taking psychotropic medications (with the exception of

benzodiazepines or selective serotonin reuptake inhibitors prescribed for the treatment of anxiety or depression). Any standard-dose regimen of chemotherapy was accepted as was current or past hormonal therapy (selective estrogen receptor modulation or aromatase inhibition). Medical and medication history were confirmed by the referring HCP as initial eligibility was assessed prior to providing the investigator's contact information to interested women. Eligibility was confirmed by the investigator during the in-person meeting to obtain informed consent.

A sample size of approximately 15 participants for the semi-structured in-depth interviews was predicted to achieve data saturation. The sample size prediction was based on previous qualitative work conducted by Thielen ($n = 13$), Mulrooney ($n = 10$) and Capiello ($n = 16$). Sampling continued until no new information was obtained during the in-depth semi-structured interviews.

Procedures

Safety. Approval was granted by the KUMC Protocol Review Monitoring Committee and Human Subjects Committee prior to study recruitment and data collection. The study was explained to participants, questions invited, and signed consent obtained (see Appendix A). Participation was completely voluntary and participants were free to withdraw from the study at any time or could decline to answer specific interview questions. The consent form included an option to be contacted by the investigator to participate in a focus group following the completion of the semi-structured in-depth interviews and initial data analysis. Interview participants' information was kept confidential as all data were de-identified and stored in a secure, locked environment. Only first names were used in the focus group to maintain as much confidentiality as possible in the group setting.

Prior to enrollment the investigator reviewed the informed consent form with the participant and confirmed eligibility for the study. As part of this discussion, the investigator asked the participant to describe in their own words the purpose of the study and components of participation in order to assess the level of understanding. In the event that the investigator was concerned that the potential participant did not understand the purpose of the research or what would be requested of study participants, then the participant was to be thanked for their time and interest in the study, but not enrolled. This process for ascertaining capacity for consent is consistent with the procedure used within the KUMC Alzheimer & Memory Program (J Burns, Director, personal communication, October 30, 2009). Discussion with patients and careful review of the informed consent form to determine the capacity for medical decision-making also is supported in the literature (Jeste et al., 2003; Venesy, 1995).

Recruitment. The Managing Director of the KUMC BCSC and designated staff assisted with the identification of eligible women. Additionally, HCPs, i.e.: oncologists and oncology nurses practicing at the KUMC Breast Cancer Program, and members of the Greater Kansas City Chapter of the Oncology Nursing Society received a letter describing the study (see Appendix B) and a study synopsis outlining eligibility criteria (see Appendix C). HCPs were asked to recruit potential participants. A flyer was developed for use in discussing potential participation with eligible women (see Appendix D). The flyer was posted in the KUMC infusion center as well as the BCSC.

Eligible patients receiving care and follow-up at the KUMC Breast Cancer Survivorship Center were invited to participate by the Managing Director of the Survivorship Center and her staff, oncologists and oncology nurses. Women expressing an interest in

participation were provided with contact information for the investigator. Women interested in participating in the study contacted the investigator and the investigator then discussed the study and confirmed interest and eligibility. Initial contact between the investigator and potential study participants occurred by phone, e-mail or in-person. Informed consent took place in-person at the BCSC or a location mutually agreeable to the participant and the investigator such as participants' homes.

Prior to initiation of data collection, efforts were made to further refine the interview guide by consulting two key informants who were women with breast cancer that self-reported CRCI and were not eligible for the study. The key informants were identified by the Managing Director of the KUMC BCSC and the investigator. Both women were more than 12 months from completing chemotherapy. The first interviewee had previously participated in research related to CRCI conducted by the Managing Director of the KUMC BCSC. The second interviewee was known to the investigator through a previous introduction and had expressed interest in participating in the current study.

Following informed consent by the investigator, the key informants were invited to provide advice related to the development of the interview guide. The first informant was three years out from completion of chemotherapy and continued to report issues with CRCI such as difficulty with short term memory and word finding. The second informant had completed chemotherapy 15 months earlier and shared that she, her mother, and her aunt had experienced CRCI during and after chemotherapy for breast cancer. Both agreed the primary questions and probes in the interview guide were appropriately worded to answer the research questions. However, the second informant initially thought that "changes in memory and thinking" related to her worldview following the diagnosis of cancer and suggested

asking about “changes in memory” only. The first informant noted that she would have preferred to receive education about CRCI once her oncologist had confirmed a complete response to therapy. Both recommended interviewing women greater than 12 months from completion of chemotherapy due to the lingering sequela of fatigue and potential for lack of awareness of CRCI until all the other side effects of treatment and the concerns related to dealing with the diagnosis and treatment were reduced. The key informants confirmed the original guide was appropriate, so the original version was retained.

Data collection. Data were collected over a period of six months. Demographic information were collected in the form of a questionnaire (see Appendix E) for all participants including: age at diagnosis, current age, marital status, ethnicity, menopausal status at diagnosis, current menopausal status, employment status at diagnosis, current employment status, level of education, stage of disease at diagnosis, time since last chemotherapy, chemotherapy regimen (agents, frequency, duration), and hormonal therapy status.

The semi-structured interview guide was used to elicit information from participants through the use of open ended questions (see Appendix F). The guide was revised based on information provided by key informants identified at the beginning of the study and results from on-going data analysis as new areas of questioning were identified. The guide consisted of four primary questions and a series of related probes used to enhance participant response if needed. The four open-ended questions were designed to stimulate a rich description of the experience of CRCI and participants’ views on desired timing and content of related education.

The semi-structured in-depth interviews (approximately 60 minutes in length) were conducted at the KUMC Breast Cancer Survivorship Center or at a location of the participants' choosing that was agreeable to the investigator, such as participants' homes. Interviews were audiotaped and transcribed verbatim.

Upon completion of the interviews and initial data analysis, participants who provided consent to be contacted for follow-up were invited to participate in a focus group comprised of 5-8 women. The purpose of the focus group was to provide the opportunity for member checking (participant feedback and validation) to assure that study results and interpretations from the data collected during the interviews were an accurate reflection of participants' experience of CRCI and recommendations for education.

During the focus group, the investigator reviewed a summary of pooled responses to questions posed during the in-depth semi-structured interviews and the themes identified during the data analysis. Focus group participants were asked to provide feedback related to the summary and identified themes. Samples of specific suggestions for educational content gleaned from the interviews were reviewed with the focus group participants. Feedback and validation was obtained. The feedback was used to further refine the description of the experience of CRCI, related educational needs, and specific suggestions for educational content. One focus group was sufficient to complete the member checking process based on the congruence of the initial analysis and interpretation of study results with the responses obtained from member checking during the focus group.

The focus group was conducted in a conference room at the KUMC Breast Cancer Survivorship Center. The investigator facilitated the focus group session (90 minutes in length). Prior experience with focus group facilitation was gained by the investigator

through conducting focus groups for the Oncology Nursing Society Board of Directors (Krebs, et al., 1996). Ground rules for focus groups participation were reviewed with all participants at the beginning of the session. Only first names were used to protect participants' privacy as much as possible. Participants were instructed that information shared during the group session was not to be shared with anyone outside the group. Participants also were instructed to speak one at a time and to provide all participants an equal chance to speak during the session. The investigator encouraged participants to openly and constructively disagree with any study findings they did not feel accurately reflected the experience of CRCI or their recommendations for education.

The focus group session was scribed by a graduate student from the University Of Kansas School Of Nursing. The scribe was prepared for assisting with the focus group by the investigator. The preparation included a review of pertinent literature, a discussion of rationale for focus group research, and a description of group facilitation techniques. Expectations for note-taking during the focus group session were reviewed. Selected recordings and transcripts of the in-depth interviews were shared and reviewed and initial data interpretations were discussed in preparation for the presentation of data to the focus group. The investigator and the scribe performed an on-site assessment of the KUMC BCSC conference room to review the data to be presented, discuss seating, and test the recording devices to assure successful audio capture for the purpose of accurate transcription. The focus group session was audiotaped and transcribed verbatim. The scribe's notes were used as an aid for debriefing following the session as well as transcription of the audiotape.

Qualitative descriptive methodology is appropriate when seeking a thorough, in-depth description of an experience as well as investigating research questions that are of special

relevance to practitioners and for which the literature is limited (Sandelowski, 2000). In-depth interviews were selected as the qualitative strategy to answer the research questions in order not to limit participants' responses. The use of open-ended questions allowed participants to share information freely outside the constraints of a structured survey. This strategy provided an opportunity to learn details of the participants' perception of the experience of CRCI that may not otherwise have been shared. Focus group participation provided participants an opportunity to validate their perceptions and experiences with other survivors. Focus group responses were used as a mechanism for member checking to confirm the interpretations of the data obtained from the in-depth interviews and explore additional questions that were raised.

Data Analysis

Qualitative content analysis of participants' audiotaped responses to the interview guide was used to analyze the data from the interviews to answer the research questions: 1) How do women who have received chemotherapy for breast cancer describe the experience of CRCI?; 2) What information about CRCI would women who have received chemotherapy for breast cancer have found helpful prior to initiation of treatment?; and 3) What information about CRCI would women with breast cancer have found helpful once changes in cognition are experienced?

Data were simultaneously collected and analyzed in an iterative process designed to continuously modify the semi-structured interview guide, if needed, as new insights were acquired and new questions identified about participants' experience of CRCI (Sandelowski, 2000). Field notes were used to supplement study transcripts. These notes facilitated the

inclusion of both manifest and latent content for analysis in order to ascertain the deepest possible meaning of the descriptions provided by participants.

Inductive analysis procedures were used to prepare, organize, and report the data (Elo & Kyngas, 2007). Transcripts were organized into meaning units (such as words, phrases, sentences, or paragraphs that conveyed like content deemed important to understanding the participant experience). The meaning units were coded and grouped into categories. NVivo 8 qualitative software was used for the organization and coding of the transcripts (NVivo 8, 2008 QSR International Pty Ltd.). The abstraction process continued until primary themes were identified (Elo & Kyngas). Refinement of categories and themes continued throughout the member checking, peer and expert review process. Participants' direct quotes were used as the data were analyzed and reported to provide a rich description of the experience of CRCI and recommendations for education prior to treatment and once changes in cognition were experienced.

Credibility Assessment

The credibility of the qualitative content analysis was strengthened through the use of member checking, peer review, and data triangulation. Member checking was conducted through the focus group held after the conclusion of the semi-structured in-depth interviews and initial data analysis.

Peer review was conducted with the focus group scribe as data from the in-depth interviews were analyzed. The scribe conducted a quality check of a sampling of three audiotapes and transcriptions to verify accuracy. Results of the quality check were used to discuss the evolution of the investigator's interview style to less talking and more listening. Selected transcripts were shared and discussed as coding was conducted and categories

identified. The scribe concurred with the categories that emerged as data were analyzed. Expert review was conducted with select members of the investigator's dissertation committee who have expertise in qualitative content analysis. Initial interpretations were shared with the Dissertation Committee Chair prior to conducting the focus group. Suggested revisions were made to the presentation to enhance clarity and stimulate rich discussion of the results. The revised presentation and focus group participants' comments about the investigator's interpretations of the data were shared with one committee member who made suggestions to the development of overarching themes and the need to personalize the study results. Some wording was simplified, such as the revision of the use of the term "comparisons" to "feels like" for reporting results related to analogous experiences to CRCI. Quantification of the sample demographics and study categories was added.

Data collection procedures were supplemented by regular journaling of thoughts, feelings, observations, and insights by the investigator. Journal notes were used to provide an audit trail as data analysis was conducted and decisions made related to identification of categories and themes from participants' descriptions of the experience of CRCI and desired timing and content of related education. Field notes were recorded following each in-depth interview and the focus group. Prior to data collection, the primary investigator documented preconceived notions about the patient experience of CRCI. The investigator noted expectations that: 1) Women notice CRCI early in the course of chemotherapy; 2) Women want to have education about CRCI prior to initiating chemotherapy; 3) Women want to receive as much information about CRCI as possible; and 4) Women prefer the education about CRCI to be provided by an oncology nurse. This process served to identify biases prior to the start of the research. The investigator made a conscious effort to separate herself from

these ideas in an effort to be totally open to the information shared by participants. In particular, the investigator noted preconceived ideas about the timing of cognitive changes and women's preferences related to receipt of education about CRCI.

Limitations of the Study

Homogeneity of the sample related to the level of education may limit the generalizability of the study results. All but one participant were educated beyond the high school level. The experience of CRCI may vary for women with less education and potentially lower baseline cognitive function. Peer review was conducted with a non-oncology nurse who served as scribe. The scribe was very familiar with the study so was in a good position to provide input on data interpretations. The scribe's lack of oncology experience may have contributed to missing some nuances associated with the diagnosis of cancer. However this limitation may have been balanced by bringing a fresh perspective to the data. Coding was performed by a single investigator and was therefore subject to the biases and interpretations of one individual, although this was mediated by the expert-review and advice of the dissertation committee.

Chapter 4: Results

Eighteen women responded to the three primary questions in the interview guide: 1) How would you describe your experience with changes in thinking and memory during chemotherapy?; 2) What information would you have found helpful prior to starting chemotherapy?; and 3) What information would you have found helpful once you began to notice changes in your thinking and memory? These three primary questions in the interview guide were designed to answer the three research questions: 1) What is the experience of CRCI for women with breast cancer who have received chemotherapy; 2) What information about CRCI would women who have received chemotherapy for breast cancer have found helpful prior to the initiation of treatment?; and 3) What information about CRCI would women with breast cancer have found helpful once changes in cognition are experienced? The fourth primary question in the interview guide, “Is there anything else you would like to share about your experience?”, was used at the conclusion of each interview after the investigator performed a member check by verbally summarizing the major points discussed during the interview.

Qualitative content analysis was initiated immediately following completion of the first interview. The coding process began as the audiotape was transcribed and continued with each subsequent interview. Participants’ responses to the interview questions were grouped into meaning units and categories were assigned as patterns were recognized. The iterative process of data analysis prompted additional member checking during the interviews to verify whether or not the descriptions of the experience of CRCI were consistent among participants. Due to the specificity of the research questions, data analysis and coding initially yielded two main themes that were congruent with the research questions and

consistent with the structure of the interview guide: 1) Experience of CRCI, and 2) Recommendations for Education. As the iterative process of data analysis continued, the frequency with which participants described various methods of coping with CRCI led to the decision to reflect Coping Strategies as the third main theme. Further analysis, with input from the results of expert review, refined the themes to more accurately reflect the personal nature of the experience of CRCI and the impact on participants' lives.

The overarching theme was identified as *Life with Chemobrain*. This theme encompasses all the participants' descriptions of the experience of CRCI, the coping strategies they employed, and the education they would have liked to have received. The overarching theme is comprised of three subthemes. The first subtheme is *Life with Chemobrain: How I Changed*. Participants provided rich descriptions of the changes in cognition they experienced during and after chemotherapy for breast cancer. The first subtheme includes participants' descriptions of how CRCI "feels" as well as deficits in short term and verbal memory, ability to focus, and ability to multitask. The second subtheme, *Life with Chemobrain: How I Cope*, consists of participants' descriptions of strategies they use to cope with changes in cognition such as systems of documentation for things to remember, focusing on one task at a time, allowing sufficient time to accomplish tasks, and giving themselves permission to make mistakes. The third subtheme is *Life with Chemobrain: How to Teach Me*. Participants provided specific advice related to their preferences for the timing, content, and amount of education about CRCI. The underlying basis for their recommendations was the need for education to be individualized to account for differences in learning styles and the timing of participants' educational needs. Details about the study sample and themes follow.

Sample Description

In-depth interviews were conducted with 18 women who were within 6-12 of months of completing chemotherapy. Ages ranged from 26-61 (see Table 4). Sixteen participants were married and two were divorced. No changes in marital status occurred since participants were diagnosed with breast cancer. The sample was comprised both of Caucasian (15) and African American (3) participants. Prior to chemotherapy 12 women were premenopausal. After chemotherapy only 4 were still menstruating. The majority of the sample worked full time. One participant changed to part time status during treatment and three were not presently working, two of whom attributed loss of employment to cognitive changes. Participants were well educated. Most of the women were diagnosed with stage II breast cancer, although all four stages of disease were represented in the study. The primary chemotherapy regimen was Adriamycin® (doxorubicin) and Cytosan® (cyclophosphamide), followed by Taxol® (paclitaxel) (n = 12) or Taxotere® (docetaxel) (n = 5). Five received Herceptin® (trastuzumab) in addition to the primary regimen. Two also received Avastin® (bevacizumab). Other regimen components included Xeloda® (capecitabine) (n = 1), and Abraxane® (paclitaxel protein-bound particles for injectable suspension) (n = 1). One woman could not remember the names of her chemotherapy agents. The duration of treatment ranged from 4-8 months. Participants' responses regarding the frequency of chemotherapy administration were too varied to summarize due to the wording of the questionnaire and some uncertainty on the part of participants about how to answer this question as many of them had received more than one regimen with varying levels of administration frequency. Reported menopausal symptoms included hot flashes, trouble sleeping, weight gain, and feeling irritable. Over half the sample continued to experience

Table 4

Participant Demographics, N = 18

Category	n	Category	n
<u>Current Age</u>		<u>Marital Status</u>	
25-30	3	Married	16
31-35	1	Divorced	2
36-40	3		
41-45	3	<u>Ethnicity</u>	
46-50	1		
51-55	5	Caucasian	15
56-60	0	African American	3
61-65	2		
<u>Job Status*</u>		<u>Education Level</u>	
Full Time	11	High School	1
Part Time	2	College	11
Not Working	3	Graduate School	6
Homemaker	2		
Lost job	2		

*Participants could select more than one response

Table 4 Continued

Category	n	Category	n
<u>Stage at Diagnosis</u>		<u>Hormonal Therapy</u>	
I	4	Yes	10
II	8	No	8
III	3		
IV	1		
Not sure	2		
<u>Menopausal Status Pre-Treatment</u>		<u>Menopausal Status Post-Treatment</u>	
Pre	12	Pre	4
Post	5	Post	12
Peri	1	Peri	1
Not sure	0	Not sure	1
<u>Menopausal Symptoms*</u>		<u>Other Symptoms</u>	
Hot flashes	6	Anxiety	7
Trouble sleeping	8	Depression	6
Weight gain	5	Fatigue	10
Feeling irritable	2		

*Participants could select more than one response

fatigue following the cessation of chemotherapy while about a third noted anxiety or depression.

Life with Chemobrain: How I Changed

Participants provided poignant descriptions of the many changes in their lives resulting from CRCI. Participants' descriptions of these changes were coded into seven categories including: deficits in "short term memory", trouble with word finding (verbal memory), "lack of focus" and decreased executive function, decreased performance, "It feels like..." (analogies of how CRCI "feels"), other physical factors, and the trajectory of CRCI. Participants' own words were selected as examples for each category and the quotes are provided in Table 5.

Deficits in "short term memory". Nine participants acknowledged a significant change in their short term memory. Deficits included difficulty retaining information in a variety of settings such as casual conversation with friends or family, work or school related activities, and reading or movies. Participants described frequently finding themselves in a room and not remembering the purpose for being there. Several participants noted frequently misplacing items such as cash, keys, and cell phones. One young woman shared:

I put a 20 dollar bill somewhere the other day and for the life of me I can't remember where I put it. I mean I had it in my pocket and it's like, well, it was going to fall out when I went for a run and I slid it somewhere. It's in my house and I'm going to find it someday and it's going to be great. I tucked it underneath something. And I don't remember what I did with it.

Table 5

Select Quotes for *Life with Chemobrain: How I Changed Categories*

Category	Quote
Deficits in short term memory	<p>Yeah...not so much long term, but more recent...short term...So even to the kids, like....did you brush your teeth? And you know, 2 minutes later, did you brush your teeth? Like I couldn't remember, did you say? You know, and my kids would say I answered you 5 times! And I'm like... so sorry, I do not remember hearing youI don't remember asking and I don't remember hearing you answer (chuckling).</p> <p>And it was more a short term memory thing? I could remember something that happened in the previous calendar, school year, somebody who'd visited or applied, or went through the process but I couldn't remember if I'd sent someone a contract or if I had done this step in the process.</p>
Trouble with word finding (verbal memory)	<p>And that's part of memory. I mean you've got your vocabulary stored but if you can't...I've noticed myself saying in the last few weeks when I'm on tours I can't think of the word I wanted to use. And I'll say ...we'll stop and be like...uuuhh, like tongue-tied kind of. Fumbling for a word, and then I'll figure it out. And I'll feel kind of stupid, cause I'm not that way, I haven't been that way. But when I was going through chemo we had a joke, I'd always say, chemobrain, chemobrain today. Don't trust what I'm saying because it's chemobrain. Um, and I think that's definitely, for me, I'm a very verbal person and to not be able to come up with the word is very frustrating and it feels awkward.</p> <p>So after talking with somebody for awhile I start losing words. I can't finish my thought. And I'm a fairly verbal person. And people that know me will say ...I talked about anybody, I enjoy ...sometimes the words just don't come.</p>
Lack of focus and decreased executive function	<p>I've always been a reader. And I used to like be able to read even, you know, like thrillers or mysteries and stuff and now I just stay on...and it took me (sighing) boy you know I did books on....and I've always used to enjoy books on tape, or CD or whatever...but I did ONLY those probably for a year because I couldn't concentrate</p>

or focus on reading a book, you know I couldn't sit down with , even, like a simple little romance novel and focus on reading it. I couldn't do it.

Yeah...I mean you know and I would lay in bed, and it's like I couldn't even watch TV you know, I couldn't even concentrate on the TV

And then I'll really lose my focus because when that happens I just feel like I said, I could be in a conversation and here talking to you but yet I'm not a 100% there.

I get lost a lot easier driving (chuckling). I have two GPS's. This is funny, it actually happened this morning. I have two GPS units. I have a GPS and one on my phone and I typically take printed directions with me now also and I could not find where I was going to a meeting this morning. 45 minutes later I finally figured out where I was supposed to be. And at that point I had missed the meeting (laughing).

Sometimes I'm driving and then I'll ...I won't remember ...oh I already went through that intersection or, you know there's like a blank moment of...where am I going? (laughing) you know...oh right...that's what I'm doing...you know. It's not like you're completely unsafe in the car, it's not that, it's just you may be...it's the same process of where you might be running upstairs or downstairs and then all of the sudden you can't remember what it was that I was doing and ...it's sort of the same thing, but you do notice it in the car...which I would never have done before.

I've caught myself lately ...when I go through an intersection, I look around and I think did I look at the light to be sure it was the right color before I went through the intersection? And it's all part of that sort of relearning how to drive. Relearning what was automatic to me before is not. And sometimes, I don't think like speeding is an issue but it's more just the general operation of the car. I'll just be like, I'm on the road now, I need to remember that there's a stop light or I need to put my blinker on to turn, or am I turning into the right lane so, it is a lot of those common things that you think you have ingrained in you that are sort of fuzzy. And it's not like I think I can't drive but I do notice myself catching myself and I'll lookmy reaction time is different. I think that's true. You know when you're watching a stop light and where as I might have gone when it turned green, now I'm sort of Ok...look around...be sure we all have the same signal here, we're all doing the same thing. I'm going to go, you're stopping,. But it's very

strange. Now that I think about it. And, my daughter is old enough to drive and she's been driving me to school and I feel so much more comfortable sitting and being a passenger.

I had 2 chemo treatments and it was a day of treatment and my hair was starting to fall out and um, I was...I got off the highway to go to McDonalds to grab a little something to eat. And I was sitting at a stop light and was looking this way for merging traffic (looks left) and I thought that I was stopped but I wasn't and I hit the person in front of me. And (inhales audibly) so that was just like you know like even, um, knowing if I was moving or not. You know like I couldn't ...I couldn't tell that I was moving.

Decreased performance

Well...even when I started chemo...and I was trying to work...um, it was pretty much...really what consisted of my work was going in one or two hours and trying to think of what I hadn't like shown somebody what to do, you know? And um, (sighing) it was um, kind of difficult while being on the chemo to go through a full thought process. Um, and um, then, you know for those 3 months there were things that I would forget to do at work now whether that was chemo related or hysterical related or whatever you know...but like I forgot to pay, like, a certain tax or whatever. They used that against me to fire me.

I was very aware that was going on ...I couldn't remem...I'd go out to you know...if somebody would make an appointment and I'd start pulling things ..couldn't remember sizes, couldn't remember what they said they wanted. Let's see did they say wanted that, or didn't want that. You know, that kind of thing. It really impacted the job.

"It feels like"....

It was like being pregnant and just not, um, I just felt like I was pregnant again. And it's like, it's frustrating. Just not being able to remember, uh, things slipping by, uh, you know somebody tells you a date and not being able, several days later being clueless that they even told you that date. It's um, just no recall.

I would relate it to being pregnant ...maybe, you know like um you know, like I said I was sharing my brain. You know with the fetus? (chuckling) And you know doing, just not able to pay attention to everything and forgetting things.

Other physical factors

Fatigue

Especially when I was so sleep deprived. So, um, but, like, I couldn't think about putting together a grocery list or you know,

like that was way beyond my capability.

Um, I mean when I was exercising I was feeling better, and so my memory was better. So I don't know that it was linked to exercise, I just think it was linked to how I was feeling. Um, so, I can't say that it was exercise related. And there were many times that I would have wished that I could have exercised but I couldn't have gotten out of bed. So....

Yes, excellent. Although I will say, maybe it was memory and just the level of exhaustion to maintain friendships is real hard because you have to expend the energy to do it and unless peoplethe true friends are still there. The people that are kind of on the periphery are likeyeah. But that's probably the fatigue.

Well, I think it's related first to fatigue, its' definitely is fatigue and as your body's going through that change of that chemical going through your body, and then I think eventually your lack of focus, your lack of memory starts occurring and you know if you're not reading the news or you're not reading a book you're not going to remember thingsso I think it's a buildup effect of losing that process...

Um, so, but I do think it is improving as far as my memory, word finding, and things like that. Except when I'm tired.

Clumsiness and decreased balance

I've noticed a great lack of coordination. I can't stand on one foot to put on pants or put on shoes or, without leaning up against somethingbalance....I have always been very coordinated. I have considered myself athletic. It irritates the heck out of me that I can't do that.

I don't remember ever falling down this much as I do. I uh, and dropping things. I routinely drop things. And it's one of those moments where you go, I swear I had a grip on that. I swear I had that in my hand. How did...how did that fall? But...um, and some days more than others I'll have very full clumsy days. And one thing I've found that ...and I don't know if this has any relation whatsoever, but looking at days where I'm nutritionally better...I eat more protein um, I drink more water ...I'm clearer and feel better in general and I'm not nearly as clumsy. So I have no idea if that's related but it also coincides with feeling more energetic and able to get to the gym, and run a little longer on the treadmill and....so I have no idea if nutrition would help on that level or if

it's just that you're giving yourself more energy and....

Neuropathy

I worry now because I have this weird, when I touch my fingers sometime....it hurts (touching left pinky). Have you heard of that? It's more pain. I know people say numbness and tingling...

I lost all these down to here (indicating fingers) and then my toes, they had to dial everything back towards the end cause ...and I had to fight with them for it cause you know if it gets too far, it won't regrow. I mean that's part of the reason I wasn't super active cause my feet were so numb that it felt like your toes were curling under. That's what it felt likeit actually hurt. My fingers were always cold and numb but my feet actually hurt. And so they dialed my taxol back towards the end and then I was on Neurontin to try to help try to stimulate the nerve growth which I haven't got all mine back. I feel like sometimes lose a little bit in my thumbs, a little sensation but I know that some people never get that back either.

Trajectory of CRCI

Uh, you know I think because your going through treatment you're in such a fog anyway. Um, you're feeling 50-60% of normal that, I don't know....and I wasn't working as regularly. I didn't pay as much attention to whether I was on top of things and I was forgiving myself a lot of thing I normally.....sleeping more all those kinds of things. So I just didn't really pay attention to how on top of it I was. So I have to say, it probably wasn't until I was completely done with treatment that I really began noticing it. And then I kind of thought, well...I'm still getting a lot of drugs, but I'm really realistic. But I think it really was more after treatment was done.

Uh, definitely during, uh, probably....gosh, probably after I'd had a couple treatments, so 3...3 maybe 4 weeks in.

No, not really. Jennifer told me I would probably start to see some improvement after a year. I'm waiting!

I feel like they've gotten better. Um...I mean it...I could just remember things like what's on the grocery list or what are we doing this weekend. Those sorts of repetitive conversations ...did I really say this? Or did you tell me that? Or like my husband and I? We have a lot more of those conversations it seems like. Last, um associated with date, last August or September that's kind of when I would have been right at...it seems kind of like it has slowed down a bit. Uh, I seem to struggle the most with things here at work. But again that's more associated with longer timelines.

I think just being patient with yourself you know related to the memory lossI think I've noticed that um, it has kind of resolved itself over time. And the instances are getting further and further apart. So I'm still hopeful that eventually it'll just go away. Um, but, now that I think about it the work that I've been trying to do and hearing my boss, or my husband or whoever say, it's ok you know. It'll go away. Be patient and many, many times I've kind of watched that process. And looking back , now I'm done! Now it'll all go away.But it doesn't happen that way. And logically I know that now you just kind of lose that perspective for a little while.

I feel like the longer it's been, it seems to happen less often. Um, but then when it does, like just this morning ...uuuhhh, I thought this was getting better. You know and every time it happened I'm like UURRRHH (clenching hands).

Another participant noted, “I was at a conference yesterday. I couldn’t begin to count the number of times I misplaced my cell phone or the number of times I had to completely empty out my purse to find it”.

Participants were unable to remember appointments, tasks they needed to do, or items from conversations without writing things down. One example follows:

When someone tells me something like at work, I really have to....you know I have to write things down. ‘Cause if I don’t, two minutes after they told me what they wanted me to do, a lot of times I can’t remember.

Trouble with word finding (verbal memory). Complaints of word finding occurred for 100% of the sample population. Participants described “forgetting names, not completing sentences” and “not being able think of the word”. One participant shared a story about preparing dinner for the family:

My aunt called and said, well what are we having? Um, I don’t remember. So what are you making? Well, I know what I’m making I don’t remember what it’s called. But I know how to make it. And I can’t remember what we’re having. Imagine how stupid that feels! You know, we were having Swedish meat balls! That’s what it was! But, I couldn’t remember what we were having.

“Lack of focus” and decreased executive function. Nine participants described being unable to focus or concentrate, contributing to issues such as maintaining their train of thought in conversation. Six participants described lapses in focus and decreased executive function contributing to issues with driving familiar routes and in other various aspects of driving such as coming to a complete stop at intersections, correctly responding to traffic signals, and the necessary steps to refuel the vehicle. Another example of decreased

executive function involved inability to follow a recipe when cooking. Additionally, one participant's husband has taken over handling the bills (the process of writing the checks, stamping, and mailing). She described herself as "not trustworthy enough to do it" and that her husband "wasn't sure where the bills would end up".

Several participants mentioned losing the ability to multitask and/or the need to focus on one thing at a time. When referring to cooking, one participant noted:

I mean... because I'm slower at it for physical reasons and I used to be able to like...you know, do 3 or 4 different things at a time in the kitchen, but now I got to do one thing at a time. 'Cause I have to focus on it.

Decreased performance. Two participants indicated that cognitive changes contributed to the loss of employment. One of these participants historically had worked >60 hours a week as a company comptroller and was the "go-to" team member for problem resolution due to her organizational skills and ability to balance multiple activities. Now, she describes looking at the job descriptions in the newspaper and struggling to find the type of employment where she would have a one-focus job. The second of these participants worked in a retail position as a personal shopper. Subsequent to her changes in cognition she described being unable to remember her clients' preferences, sizes, or previous requests for merchandise. One young woman working on her master's degree described herself as having a photographic memory prior to chemotherapy. She related never having to read something more than once and maintaining an A average in her classes. During chemotherapy she had to drop a class as she could no longer succeed with her current pattern of study habits. She maintained an A in the class until beginning treatment but subsequently was at risk for failing the class due to her inability to retain information from reading and class work for the

examinations during and after treatment. She has adapted her study methods and is now maintaining a B average. She described having an extensive vocabulary and expressed significant frustration at not being able to think of the words she wants to use in expressing herself. She, as well as other participants in the study, described the use of word substitution in order to maintain a conversation. This same young woman indicated she never needed to write down appointments prior to therapy. She said she could remember her own, as well as her mother's and her children's appointments without difficulty. However on the day of her scheduled interview for this study she admitted having no recollection of having scheduled the appointment and actually was not dressed or expecting anyone to come by. Participants noted that overall speed of performance was slowed due to the need to read things several times and changes in their processing speed.

Some differences existed between whether participants found work or casual settings to be more problematic for their performance. One participant noted that she had the most difficulty in casual conversation. She described being focused and "on-point" during business interactions as she was using a good deal of energy to stay focused on the task at hand. In a more social or casual setting she found herself to be more relaxed and therefore less focused. Most participants described the greatest difficulty with short term memory and word finding in situations in which they were stressed or anxious. Focus group participants noted "taking longer to get things done at work" due to the need to read things multiple times and "slower thinking".

"It feels like....". A very rich component of participants' descriptions of the experience of CRCI was what CRCI "feels like". Participants described the experience of cognitive changes to be analogous to being pregnant, drinking too much, or the effects of

heavy allergy medicine. Comparisons were made to aging as well as the cognitive changes associated with Alzheimer's disease. Complaints included feeling like one's grandmother or someone's "daffy old aunt". One participant described a strong family history of Alzheimer's and expressed the fear that the cognitive changes she was experiencing now would predispose her to an earlier onset of Alzheimer's in the future. Another participant related her experience to the female protagonist in the movie "Mr. and Mrs. Bridge" in which the character is seen sitting in the car in the garage without a clear notion of what to do next. This participant described pulling up to the gas station to refuel her vehicle and having no idea how to release the gas cap. She described sitting in the car for 15 minutes before she was able to remember the steps involved. She said this happened to her on two occasions. She referred to the experience as "pulling a Mrs. Bridge". Participants also used the term "fog" to describe the feelings of being unable to think clearly and expressed frustration at feeling stupid.

Other physical factors. As participants described the experience of CRCI, a number of other physical factors consistently were discussed. Most women (72%, $n = 13$) described experiences with fatigue during and after treatment and 55% ($n = 10$) described ongoing issues with fatigue. Participants acknowledged that cognitive issues were more pronounced when they were tired and noted some improvement in mental clarity after napping or "getting enough rest".

Clumsiness and decreased balance was an issue for almost a third of the participants (27%, $n = 5$). Participants described no longer being able to stand on one leg to put on a sock, losing their balance going down a slope, dropping things and stumbling more than they used to do. Almost half (44%, $n = 8$) of the participants had experienced neuropathy in their feet

($n = 2$), toes ($n = 4$), fingers ($n = 4$) or fingers/toes ($n = 2$) and 27% ($n = 5$) still had some residual numbness. However, only one participant with residual neuropathy complained of clumsiness or balance issues (see Table 6).

Table 6

Comparisons of Physical Factors and Other Reported Symptoms (n = 18)

Age	Anx	Dep	Ftg	Sleep	Neuro Ever	Neuro Now	Neuro Loc	Clum/Bal	Total
61				X	X	X	Toe (rt great)	X	4
61	X	X	X		X		Feet		4
55	X		X		X	X	Fingers		4
52					X		Feet		1
52			X					X	2
51			X	X					2
51									0
48	X	X	X						3
45	X	X	X	X				X	5
45			X						1
41		X		X					2
40	X		X	X					2
37				X				X	1
37			X	X					4
35					X		Fingers/ Toes		2
28					X	X	Toes		2
27	X	X	X	X	X	X	Fingers/ Toes		6
26	X	X			X	X	Fingers	X	1
Total	7	6	10	8	8	5		5	

Anx = Anxiety, Dep = Depression, Ftg = Fatigue, Neuro Ever = neuropathy during and/or after treatment, Neuro Now = neuropathy now, Neuro Loc = location of neuropathy, Clum/Bal = Clumsiness and/or Balance issues

Trajectory of CRCI. Variability was noted related to participants' perceptions of when they began to notice cognitive changes. Most participants noticed changes during chemotherapy with the majority of these being after 1-2 months of treatment. One participant described noticing changes immediately after receiving her first treatment. Three participants did not notice changes until after therapy. One of these women noticed changes 4-5 months after completing chemotherapy and one did not notice changes until several months later.

Most participants described noting some improvement in their cognitive changes over time. Some women mentioned beginning to notice improvement one to two months following the completion of chemotherapy. Word finding, however, appeared to be the primary residual deficit, with all participants complaining about this problem at the time of the interviews. Five (27%) of participants noted that improvement may have been hampered by recovery from subsequent surgeries after chemotherapy related to breast reconstruction and the effects of anesthesia. One woman's quote reflecting the effects of anesthesia on cognition follows:

Um, well I had my surgery after chemo and so I went right from chemo treatment into, and then I did a double mastectomy and um, and so I had, you know, from that um anesthesia, you know and all that in my body I was, you know, it took a long time to get out of that kind of funk. So, um, so I would say maybe ... maybe like Julyish I was feeling pretty normal and feeling good, and exercising again and all that. And then in August I had my final surgery, my reconstruction surgery. And um, and so then um, it took me awhile to get over that anesthesia too. And so I think I probably started feeling normal again um, probably a couple months after that.

Participants' descriptions of the experience of CRCI (Life with Chemobrain: How I Changed) were consistent. The investigator began to note data saturation around the tenth interview related to complaints about short term memory, lack of focus, and decreased executive function. All of the participants complained about issues with word finding and a significant percentage experienced difficulty with reading and driving. Participants expressed concern about decreased performance at work and school, with two participants attributing loss of employment to CRCI. Comparisons of CRCI to "being pregnant" or exposure to substances such as alcohol or allergy medicine provide a potent description of what CRCI "feels like". The other physical factors of residual fatigue, clumsiness/decreased balance and neuropathy are important in understanding the impact of CRCI on participants' daily lives and raise a number of research questions for exploration. The trajectory of CRCI was variable, however most participants did experience some improvement over time.

Life with Chemobrain: How I Cope

Participants described coping with the effects of CRCI in a number of ways. Primary coping strategies included: writing things down, importance of support and validation, helping others, depending on others, focusing on one task at a time, not rushing, and giving oneself permission to make mistakes. Participants also described attempts at intervention for CRCI including exercise, mind stimulation, getting enough rest, meditation/yoga, and good nutrition.

"*Writing things down*". The most common strategy described for coping with changes in memory and thinking was writing things down (see Table 7). Participants varied slightly in the method they selected such as the use of phone calendars, day planners, notebooks, lists, and sticky notes. However almost everyone (88%) described the need to

Table 7

Life with Chemobrain: How I Cope Categories

Category	n	%
Coping Strategies		
<hr/>		
Writing things down	16	88
Importance of support	15	83
Helping others	9	50
Depending on others	7	38
One task at a time	3	16
Not rushing	3	16
Permission to make mistakes	2	11
Intervention Strategies		
<hr/>		
Exercise	5	27
Mind stimulation	5	27
Getting enough rest	3	16
Meditation/yoga	2	11
Nutrition	1	5

make note of things they wanted to remember shortly after receiving information due to their difficulties with short term memory loss.

Importance of support and validation. Most participants acknowledged the importance of the support of family, friends, and coworkers. In general, participants described the reactions of others to the cognitive changes to be that of patience and understanding. However a few participants did share that family members (such as husbands or children) expressed frustration at having to frequently repeat themselves due to the participant's inability to retain information.

One participant discussed the need for validation of her cognitive changes by her spouse. She expressed frustration that her husband didn't acknowledge the difficulty she was experiencing. She was one of the three participants who compared CRCI with the cognitive changes experienced during pregnancy. As she and her husband have five children, she noted that the cognitive changes she experienced during and after chemotherapy might seem "normal" to her husband since she had been pregnant so much of their married life.

Younger participants noted dealing with very different issues than most of the women they encountered in the infusion room and therefore requested a different type of support. For example participants in their 20's and early 30's expressed a desire for being matched with someone their own age as a support mechanism (age-matched support). Younger participants noted concerns about fertility and finding a mate. These issues were not a concern for older survivors and contributed to a lack of connection and support from other survivors.

During the course of the interviews, participants expressed frustration at the lack of communication and validation by HCPs. As a result of the interviews, participants exhibited

enthusiasm for research being conducted to learn more about CRCI and noted a sense of “relief” that others were experiencing similar issues.

Helping others. Several participants indicated a strong desire to help others through their experience of chemotherapy. Some wanted to volunteer in infusion rooms to provide inspiration to those just starting treatment. Others wanted to start a support group in their area or develop a mechanism to provide meals to newly diagnosed women receiving treatment. Participants described the desire to “give back” and to “make something positive” out of their experience with breast cancer.

Depending on others. A few participants described depending on their spouse, children, or coworkers to help them remember certain things. One participant mentioned the need to tell coworkers what she had accomplished at the end of the day.

I couldn't remember if I'd sent someone a contract or if I had done this step in the process. And so I was leaving myself sticky notes. And every day, it was kind of a joke in our office. We're all very tight knit. But every day I would leave and I would say I need to tell you these things in case I get hit by a bus tonight. But I think really what I was doing was I needed to tell somebody else what I had done so I could say to her, did I do that?

One task at a time and not rushing. Focusing on one task at a time was mentioned by several participants as they described a decreased ability or inability to multitask compared to their ability prior to chemotherapy. Taking one's time and not rushing were mentioned as strategies to increase success at completing tasks. One participant described a situation where she was cooking dinner when one of her kids came into the kitchen and needed to have a permission note to attend a field trip the next day. The participant said she had to delegate the

rest of the meal preparation to the other children because she could not work on both tasks at the same time. She acknowledged that multitasking was not difficult for her prior to chemotherapy. Establishing achievable deadlines for a task was one method mentioned for preventing a rushed timeline.

“Permission to make mistakes”. Participants varied in their reaction to cognitive changes as some expressed more distress (complaints of feeling frustrated or upset) than others at not being able to find words or remember things. One participant shared that she didn’t get stressed out over not being able to remember things because everyone makes mistakes. She described an overall life philosophy of not worrying too much about things she couldn’t control. Another participant advised women not to “stress about it” when they “mess up”. “Life’s too short and you’ve just got to move forward”. Others expressed a higher level of frustration at on-going cognitive issues and appeared to exhibit more distress.

Exercise. Exercise was mentioned as an important interventional strategy by eleven (61%) of the participants. However, only a few participants were able to exercise during treatment. Those who described returning to exercise following treatment indicated a perception of benefit to cognitive function (n = 5). Others acknowledged that the reduction in fatigue that allowed resumption of exercise may have contributed to cognitive improvement. One participant described the benefits of leaving the work setting to “work out for 30-60 minutes” allowing her to return to her job with more mental clarity.

Mind stimulation. Many participants recommended initiating efforts to “stimulate their mind” such as sudoku, crossword puzzles, or other “brain teaser” activities. Despite the difficulties with reading participants recommended trying to read some each day as a way to “work their brain”.

“Getting enough rest”. Association between cognitive changes and fatigue was mentioned frequently. Participants described the need to get enough rest or take short naps during the day to sharpen their mental acuity. One participant shared that she was thankful she worked from home. The autonomy allowed her the flexibility to rest for 30 minutes when she needed to “sharpen her focus”. Another participant described the need to “power nap” during the day as she would become so fatigued during social interactions that she would “hit a wall” and need to rest due to mental “fogginess”.

Meditation/yoga. Additional strategies suggested to assist with focus were meditation and yoga. The one participant who suggested meditation as a strategy reiterated the idea during the focus group session. However, she acknowledged she had not yet tried meditation herself. Yoga was mentioned by another participant who enrolled in a class to help her with coordination and balance.

Nutrition. One participant described being able to exercise more and “feeling clearer” when she ate more protein and stayed hydrated.

Life with Chemobrain: How to Teach Me

One third (33%, $n = 6$) of the participants were told about the potential for cognitive changes during or following chemotherapy by members of their health care team prior to receiving therapy. Participants were adamant about the need to know about this potential side effect up front. Frustration was described as “feeling like they were going crazy” when cognitive changes began to occur for which they were unprepared. However, one participant recommended waiting until near the end of treatment to discuss cognitive changes due to the major issues that women are coping with at the beginning of treatment such as fear of dying, loss of their breast(s) and the risk for cardiac damage from anthracyclines.

The primary basis for participants' recommendations for education related to chemobrain was the need for individualized care. Variation was seen in the extent of information that was desired as well as the delivery method. Participants were divided between wanting extensive information as early as possible so they could make appropriate plans and begin to assimilate the information, versus those who preferred very brief, general information. Five participants described being overwhelmed with the volume of written information that was provided about chemotherapy and side effects prior to treatment. One woman described her experience in receiving a bag of booklets and pamphlets from her surgeon, medical oncologist, and radiation oncologist. As a result, she read very little of the information that had been provided. Eight participants expressed the desire to have someone sit down with them and assess how they preferred to learn and their readiness to learn.

Participants did not identify any one person on the health care team whom they felt was the best suited to provide the information. However, they described wanting someone who was not rushed with whom they could spend enough time to gain comfort in asking sensitive questions. One participant suggested that education specialists be used so the variation in adult learning styles could be accommodated. Focus group participants stated that the ideal person to fill this role would be a cancer survivor, so that the person providing the information would have firsthand knowledge of the experience and would approach the topic with great sensitivity. They also recommended that the person be assigned at the beginning of treatment and maintain the relationship throughout treatment and subsequent follow-up. The benefit of a consistent relationship with an individual who "knew them" and was skilled in education was noted to be of great value.

One participant described wanting not to be treated only as a patient but to be recognized and acknowledged as an individual for whom the diagnosis and treatment would have an impact on her day to day life. Several women noted that the paradigm of the treatment milieu de-individualized the person being treated due to the need to put their lives and schedules on hold to fit into the schedule structure imposed by the treatment facility.

Participants shared their thoughts on the educational content and style they would have found beneficial. Suggestions included providing a simple one page handout with large font and no medical jargon. A compilation of pertinent statements from participants for the description of CRCI to women preparing to start chemotherapy was validated by the focus group and is summarized in Table 8.

Participants wanted a description of the likely cognitive changes such as trouble with short term memory, and trouble with word finding. They wanted to know what was meant by cognitive changes. As one participant joked, “Does it mean that I’ll roll over in bed one morning and not recognize my husband? What does it really mean?”

Information for spouses and children was desired. Many participants discussed the lack of information geared to describing CRCI for their family members and felt that education was important in order for the family to anticipate and understand CRCI.

Recommendations included suggestions to reconsider taking classes during chemotherapy or to be aware that existing study patterns or test-taking skills may be affected. Participants desired information on the incidence and duration of CRCI as well as any information about effective interventions. A number of suggestions were made regarding inclusion of ideas for coping strategies. Participants’ recommendations related to educational content were validated with the focus group and are summarized in Table 8.

Table 8

Recommendations for Education about CRCI

Category

Suggested Statements to Describe CRCI

Some women have experienced memory changes during and after receiving chemotherapy.

These changes have been compared to the type of memory changes experienced during pregnancy or when taking allergy medicine.

Some women describe feeling as if they were in a fog.

Not all women have this experience, but those who do describe issues with short term memory and difficulty finding the right word.

Others have described difficulty with driving and sense of direction, following written instructions (like recipes), or maintaining focus when reading.

Many women experience improvements in memory and thinking over time.

Table 8 continued

Recommendations for Education about CRCI

Category

Suggested Recommendations for Educational Content

Choose a method of writing down important things or activities you want to remember such as a notebook, day planner, or phone that you keep with you at all times.

Get enough sleep to feel rested (this may include naps).

Start or maintain activities to stimulate your mind such as word puzzles, crosswords, sudoku or word finding games.

Give yourself permission to focus on one thing at a time.

Use a GPS unit if you have trouble with driving directions.

Choose only activities that are important to you and allow yourself plenty of time to complete tasks so as to reduce stress.

Consider use of relaxation techniques such as meditation or yoga.

Maintain some form of regular exercise (this does not need to be strenuous).

Don't beat yourself up for not remembering things as you used to be able to before chemotherapy.

Tell your family and friends you may need help remembering things and ask for their patience and support.

Be aware that your reading retention may change during and after chemotherapy. This may affect your study habits or test taking ability.

When asked what information they would have liked to receive once they began to experience cognitive changes, participants acknowledged the desire for “someone regularly to ask them” if they were experiencing any difficulty with memory as a “part of the assessment”. Participants suggested that the educational content described above could be reinforced throughout treatment. They also wanted reassurance that CRCI would resolve. Focus group participants noted that CRCI might not resolve and agreed that educational content should be carefully designed so as not to mislead. The recommendation was to include a statement such as “many women experience improvement in memory and thinking over time”. Participants also wanted to be kept informed about any information on effective interventions.

Exemplars

Interviews with two participants in particular yielded a very complete description of the experience of CRCI. The two exemplars that follow are drawn from those two interviews in which both participants volunteered information about almost all of the components of CRCI identified during the study. Pseudonyms were used to maintain confidentiality.

Exemplar 1. Prior to her breast cancer diagnosis, Rachel, a woman in her 40’s, left bedside nursing to become a full time homemaker and do the bookkeeping for the family business. During chemotherapy, she described her frustration at not remembering her rationale for data entry. She noted that she experienced similar issues when she was pregnant. She also described significant difficulty remembering names and maintaining social relationships. When introduced to a Director of Music candidate for her church she told the candidate and his wife up-front that she would not be able to remember their names. Later she felt she had been rude, but didn’t want to expend the social energy to explain her

situation that early in the relationship. Rachel said that the cognitive changes were exacerbated by fatigue. She was surprised by how draining social interaction could be, due to the difficulties in having conversations with word-finding issues and trouble focusing on the verbal and nonverbal cues in order to respond appropriately. A sample from Rachel's interview follows:

I do the family business book work and I like to be able to go down there and understand what I'm doing and be able to come back a week later and understand what I had done the week before. When I was pregnant [it feels like....], just like when I was in therapy (chemotherapy) at the end of the year when I'm going through the books again I'm like...why did I do this? Why did I put that and enter it this way? I have no clue! And it was the same thing going through the book work this year ...I don't think it was quite as bad but it was just like...ok...I don't know....you know I can't tell you why, [decreased performance] I... but a lot of it too, it's just....in functioning, but when I'm tired it gets worse [other physical factors]. The fatigue is really..... Just yesterday I was at a friend's house and ...I have to take a power nap, in the middle of the day orand I didn't get that. And in trying to talk to her, one thing that I realized is that the energy required in interpersonal relationships is a whole lot more than I ever imagined. So talking, I can function at home but to get out with people where I am required to read their emotions or read...you know just that whole...I don't think we realize how much energy we put into interpersonal relationships and when all of your energy is put into trying keep up with the conversation and making sure you're acting appropriately? It's like I'm exhausted. So after talking with somebody for awhile I start losing words [trouble with word

finding]. I can't finish my thought. And I'm a fairly verbal person.....sometimes the words just don't come.

Exemplar 2. One of the younger participants particularly was distressed over the residual effects on cognition. Emily is only 26 years old and she feels like she lost 4 months of her life during chemotherapy. She continues to experience issues with short term memory and directional sense. Emily describes her experiences as follows:

After chemo everything is sort of foggy. I keep making the joke to my husband that this is a whole new experience for me, Spring in this city, because I slept through last Spring. And I really do not remember much of those four months. It's very foggy. Since then I don't think I realized how much of a fog I was walking around in. A lot of that's starting to clear, but I do find that it's extremely hard to concentrate for very long at all. I can concentrate in short bursts of 20 to 30 minutes tops. And then I'm just thinking about a million things, sort of have drifted and I find it's a lot harder to be as efficient at work as I was before ["lack of focus"]. I was always very organized and worked very efficiently, and I have a hard time being that way now [decreased performance]. I have to write things down in 3 or 4 places because I'll forget it and can't remember where I wrote it down [deficits in short term memory]. I get lost a lot easier driving [decreased executive function]. I have two GPS units and I typically take printed directions with me now also and I could not find where I was going to a meeting this morning. Forty-five minutes later I finally figured out where I was supposed to be. And at that point I had missed the meeting. I find that I get sort of confused about what word I'm trying to use [trouble with word finding]. I sort of feel like my grandmother who has Alzheimer'sit's like...I sit there and have a

conversation and neither one of us can find the correct word [“it feels like...”]. So you know I just find that everything is a little more of a struggle to remember and to focus and to concentrate in general. I have to concentrate a lot harder to accomplish what I used to be able to do sort of easily.

Information provided in the exemplars highlights issues with word finding, attention/concentration, memory, and difficulty with driving as well as the coping strategies of writing things down and taking naps during the day to refresh mental clarity. Participants’ quotes demonstrate some of the difficulties with verbal expression and social interaction. The additional effort needed to accomplish day-to-day tasks is evident.

Summary

The purpose of this qualitative descriptive study was to provide an in-depth description of the experience of CRCI for women with breast cancer. Specific aims of the study were to: 1) Describe the experience of CRCI for women with breast cancer who have received chemotherapy treatments; and 2) Identify information about CRCI that women would find useful prior to initiation of chemotherapy and following the onset of CRCI. The study purpose and aims were achieved by analyzing the data resulting from the in-depth interviews and focus group. A rich description of the experience of CRCI was obtained, including information about how women cope with CRCI and recommendations for education. The three research questions were answered as follows.

Research question 1: how do women who have received chemotherapy for breast cancer describe the experience of CRCI?. Participants described the experience of CRCI as frustrating and provided details about deficits in short term memory, trouble with word finding, lack of focus and decreased executive function, and negative impact on performance.

Half of the women complained of difficulties with reading and driving. Other physical factors were described including residual fatigue, clumsiness/decreased balance, and neuropathy. The trajectory of CRCI was variable. Most of the women described improvements in cognitive function over time with the exception of word finding. Participants shared a number of coping strategies including: writing things down, the importance of support and validation, depending on others, taking on one task at a time, and giving oneself permission to make mistakes. Younger women made requests for age-matched support. Interventions that were recommended included exercise, mind stimulation, getting enough rest, meditation/yoga, and nutrition.

Research question 2: what information about CRCI would women who have received chemotherapy for breast cancer have found helpful prior to the initiation of treatment?.

Participants wanted to know about CRCI prior to initiation of chemotherapy. The need for an individualized approach to education was stressed, including an assessment of preferred learning styles and a selection of type and volume of educational materials to meet the need for information. Participants desired interaction with a HCP who has expertise in education, was not rushed, and who, ideally, had personal experience with cancer and cancer treatment. The women noted the need for education for their family members. Recommendations were made for the educational content to be concise and free of medical jargon. Any information on incidence, recovery, and interventions was strongly desired.

Research question 3: what information about CRCI would women with breast cancer have found helpful once changes in cognition are experienced?. Participants stressed the need for on-going assessment of CRCI by HCPs as well as reinforcement of education about CRCI throughout therapy and follow-up. Reassurance of recovery and any information on

interventions was requested. The following chapter contains a discussion of the research findings, conclusions, and recommendations for future research.

Chapter 5

Discussion, Conclusions, and Recommendations for Future Research

Discussion

The study results provide evidence of self report of changes in cognitive function across a number of domains, including attention and concentration, short term memory, verbal memory, motor and executive function. Participants' complaints of lack of focus and inability to concentrate are examples of changes in the attention and concentration domain. Short term memory deficits included the inability to remember the content of conversations or various tasks to be done and frequently losing objects such as keys and cell phones. Decreased verbal memory was described as inability to remember individuals' names and pervasive difficulty with word finding. Motor function was impaired for some participants who complained of changes in coordination and balance. Several examples of decreased executive function were reported such as difficulty with the steps involved in refueling a vehicle, paying the bills, or making out a grocery list.

Information gleaned from the in-depth interviews was consistent with the research of Downie et al. (2006), i.e., complaints of changes in short term memory, concentration, verbal fluency and word finding, processing speed, executive function; change in ability to multitask, and trouble driving due to decreased sense of direction and trouble with concentration, memory and processing speed. Consistency also was seen between the results of the current study and the work conducted by Thielen (2008), i.e., trouble remembering names, returning to the workplace, driving, impaired sense of direction, and remembering how to get to familiar places, and Boykoff et al. (2009), i.e., trouble with word finding, decreased processing speed, and diminished ability to read complex books; use of calendars

and post-it notes as well as some social withdrawal. Congruence with results discussed by Mulrooney (2007) also was noted (keeping a calendar, writing lists, dependence on family for assistance with memory).

Participants acknowledged the importance of validation of CRCI by both HCPs and family members. This need for validation may be congruent with the phenomenon of participants' self-report of cognitive changes being more accurate than the results of current objective measures of cognitive function. Participants expressed frustration at the lack of validation of cognitive changes by family members but acknowledged that the changes participants perceived might not be noticeable to others. This hypothesis is consistent with that of Jacobs et al. (2007) who noted subjective measures may be sensitive to smaller effect sizes than those of available objective measures. Support of family, friends, and coworkers was noted to be very important to successful coping and included assistance with memory as well as patience and understanding concerning cognitive changes. Age-matched support was desired by younger participants due to the differences in issues they faced as a result of cancer and chemotherapy, such as fertility and finding a mate.

Responses to the demographic questionnaire yielded information about anxiety, depression, fatigue, and trouble sleeping. Further information about residual fatigue was obtained during the interviews as was information about past and current neuropathy and complaints of decreased balance and coordination (see Table 6). Notably, 17 of the 18 participants reported one or more symptoms in addition to CRCI. Fatigue was the most commonly reported symptoms ($n = 10$), followed by trouble sleeping ($n = 8$), neuropathy ($n = 8$), anxiety ($n = 7$), and depression ($n = 6$).

Fatigue and sleep disturbance are two of the most commonly reported symptoms for cancer survivors (Beck, Dudley, & Barsevick, 2005) and sleep disturbance is a common menopausal symptom. The majority of participants reported experiencing fatigue during chemotherapy (72%) and 55% continued to complain of residual fatigue at the time of the interviews. Similarly, 44% of the sample acknowledged trouble sleeping.

Neuropathy is commonly experienced by survivors who receive a taxane as a component of chemotherapy (Taxol®, Taxotere®). Seventeen participants received a taxane, one of whom received both Taxol® and Taxotere®. One woman could not remember the names of the agents used for her chemotherapy regimen. Slightly less than half of the participants noted neuropathy (44%) during treatment and 27% mentioned residual effects.

These findings are consistent with the results of a recent secondary analysis of a data set for women with ovarian cancer. The secondary analysis was conducted to explore the potential relationship between receiving chemotherapy and complaints of memory problems (Myers, Sousa, Donovan, 2010). Women with ovarian cancer who had received chemotherapy ($n = 638$) were statistically significantly more likely ($t(82.70) = -3.12, p < .01$, mean difference = -1.04 , CI from -1.7 to $-.38$) to complain of memory problems than those who had not received chemotherapy ($n = 68$). Regression analysis demonstrated that fatigue ($\beta = .18, p < .01$) neuropathy ($\beta = .07, p < .05$) and sleep disturbance ($\beta = .16, p < .01$) were significant predictors for complaints of memory problems in addition to mood swings ($\beta = .23, p < .01$). Further exploration of the potential relationships between fatigue, neuropathy, trouble sleeping, and CRCI is warranted. Given the potential predictive nature of fatigue, neuropathy, and trouble sleeping for complaints of memory problems, residual side effects may be predictive of long-term CRCI.

Fatigue has been noted to be a potentially confounding variable for CRCI (Nail, 2006) yet studies in which confounding variables have been controlled still yielded the independent presence of cognitive changes (Ahles et al., 2002). Results from the secondary analysis described above in conjunction with results from the present study lend support to the need for further examination of a moderator effect of fatigue on CRCI.

Clumsiness and/or issues with balance and coordination were reported by 27% of the sample. This finding was not mentioned in the qualitative work performed by Theilen, Mulrooney, or Boykoff. A comparison was made between the participants who experienced neuropathy (n = 8) and those complaining of balance and coordination issues (n= 5) (see Table 6). One participant was common to both groups and did note residual neuropathy (right great toe). This result was surprising as neuropathies can contribute to decreases in motor coordination (complaints of dropping items) or issues with gait (complaints of tripping or stumbling). The lack of commonality between the two groups may indicate the presence of an unidentified factor that contributes to balance and coordination issues. Further work may be warranted in this area of investigation.

Other confounding factors mentioned in the literature include anxiety and depression. Participants were asked to report whether they were currently experiencing either of these states on the demographic questionnaire. Seven participants documented anxiety (38%) and 6 reported depression (33%). Five participants noted both anxiety and depression (27%). Fatigue accompanied anxiety and depression for three participants (16%). Four participants noted both depression and fatigue (22%). Trouble sleeping was reported by 44% of the sample and occurred in conjunction with depression (16%), anxiety (16%), and fatigue (33%). Two patients reported all four symptoms (11%). In this study anxiety, depression, and

trouble sleeping were reported less frequently than fatigue. Some overlap among the four symptoms was noted, providing support for further analysis of concurrent symptoms.

Participants varied in the amount of distress related to CRCI they expressed during the interviews. The study was not designed to quantify levels of distress or to detect age-related patterns related to the amount of distress described. However, study results in the literature indicate distress may be heightened for younger women who may be more perceptive of subtle changes in cognitive function (Cimprich et al., 2005). The two women who appeared to express the least amount of distress related to CRCI in this study were 51 and 52 years of age. Future studies should include some rating of symptom distress related to cognitive changes.

Two participants related loss of employment to cognitive changes. One participant described significant changes in school performance during and after chemotherapy. The majority of participants was employed full time and did not report a change in work status since diagnosis of breast cancer. Focus group participants validated reports of slower time frames to complete work-related tasks due to decreases in processing speed and difficulties with reading and comprehension. These results are consistent with a recent qualitative study conducted by Munir, Burrows, Yarker, Kalawsky, and Bains (2010) where women reported poor concentration, memory problems, difficulties in thinking quickly, and issues with reading comprehension having an impact on their work performance. However participants in the Munir study felt cognitive effects were independent of fatigue.

The majority of participants acknowledged the importance of receiving information about CRCI prior to receiving chemotherapy, thereby reinforcing the need to educate about this potential side effect as a component of providing informed consent. Thirty-three percent

of participants were informed about CRCI prior to therapy by a HCP. This percentage is lower than that reported by Myers and Teel, where 44% of nurses educated patients and families about CRCI. However in the current study three participants noted they received information about CRCI from their oncologist. Strides are in progress towards provision of much desired education, however further improvement is needed to meet women's needs.

Participants expressed a desire to be informed of any intervention that could help improve their cognitive function. A number of potential interventional strategies are under study such as neurostimulants, exercise cognitive retraining (ClinicalTrials.gov, 2010), and biofeedback (J. Alvarez, Ed.D., Lake Erie Brain Performance Institute, LLC., personal communication, March 8, 2010). Participants described a number of strategies used for coping with changes in cognitive function. These strategies are an important component of the educational content that should be provided to women with breast cancer prior to initiation of chemotherapy.

The desire to "give back" or to "find something positive" in the diagnosis and treatment of breast cancer was consistent with the literature regarding "finding meaning in the cancer experience (Lee, 2008; O'Connor, Wicker, & Germino, 1990). Four of the participants in this study shared a strong desire to help others through the experience and be an inspiration to women receiving chemotherapy.

During the course of recruitment for this study a number of women expressed an interest in participation, but were not eligible because of being longer than twelve months from completion of chemotherapy. These women expressed frustration at not being allowed to participate as they continued to self-report CRCI. The two key informants who were interviewed prior to data collection both recommended collecting data from women greater

than 12 months after completion of chemotherapy. All but three participants (16%) in the current study described experiencing some improvement in cognitive function over time with the majority noting improvement beginning within 1-2 months of completing therapy. A subset of patients (approximately 17-34%) may experience long-term cognitive changes after completion of chemotherapy (Ahles and Saykin, 2007). A logical next step to follow the current study would be to explore the experience of CRCI for women with breast cancer who are greater than 12 months from the completion of chemotherapy as the experience may vary as a factor of time.

Contribution to Theory Development

The study results contribute to the development of the Revised Conceptual Model of Chemotherapy-Related Changes in Cognitive Function Based on the Theory of Unpleasant Symptoms (see Figure 1) (Myers, 2009). The model depicts fatigue, depression, and anxiety as concurrent symptoms and neurotoxicity as an associated toxicity. Additionally anxiety and depression also are shown as psychosocial mediating factors. The model also depicts consequences of CRCI to functional ability. Results of the current study provide support for the impact of CRCI on functional ability related to self-reported deficits for job and school performance. Results of the current study suggest that the concurrent symptom of fatigue may require further evaluation as a potential moderating factor of CRCI in the model. The study results also suggest some support for the concurrent occurrence of fatigue, anxiety, and depression, and sleep disturbance. The model has been updated to reflect these two revisions (see Figure 2). Prospective quantitative studies are needed to further examine these revisions to the model.

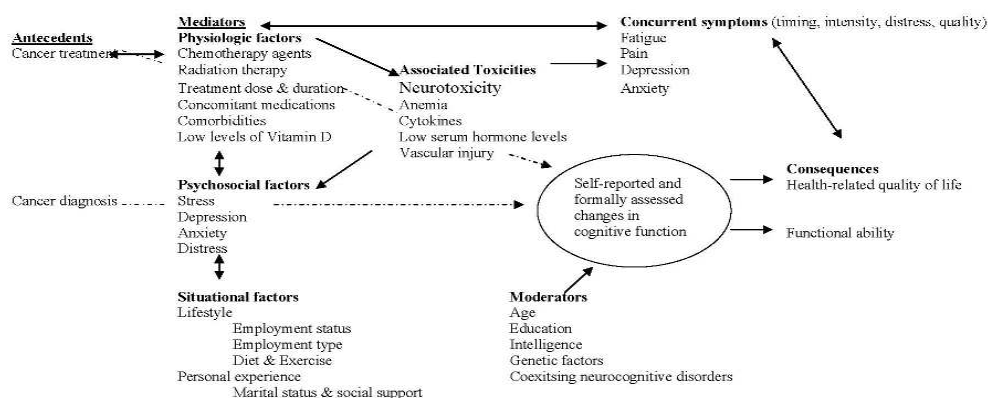


Figure 1. Revised Conceptual Model of Chemotherapy-Related Changes in Cognitive Function Based on the Theory of Unpleasant Symptoms. From “A comparison of the theory of unpleasant symptoms with the conceptual model of chemotherapy-related changes in cognitive function,” by J. S. Myers 2009. *Oncology Nursing Forum*, 36(1), E1-E10, Copyright 2009 by Oncology Nursing Society. Reprinted with permission.

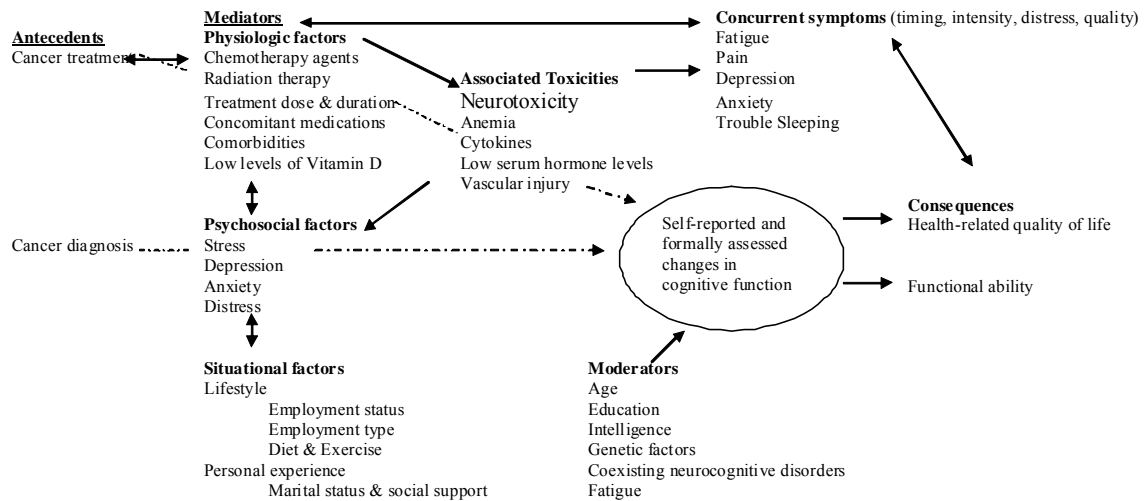


Figure 2. Revised Conceptual Model of Chemotherapy-Related Changes in Cognitive Function Version 2

The overarching study theme, Life with Chemobrain, and two of the primary themes, How I Changed, and How I Cope, reflect the consequences of CRCI on health-related QOL and alterations to functional ability. The third primary theme, How to Teach Me supports women with breast cancer's desire to be provided with information about the phenomenon of CRCI. This desire, as well as participants' suggestions for interventional strategies, is not captured by the model referenced above. However, the study themes provide a framework for enhanced understanding of CRCI and can be used to educate HCPs about the phenomenon (see Figure 3). The framework can be used to guide content to include information about the experience of CRCI, common coping strategies, and information important for inclusion in the development of an approach to patient/family education.

Conclusions

Based on interviews with the women who participated in this study, women with breast cancer who self-report cognitive changes during and following chemotherapy described issues with short term memory, trouble with word finding, difficulty with focusing, reading, and driving. Women acknowledged the importance of support as well as validation of the experience by those close to them. Women who self-reported CRCI employed a variety of coping strategies including writing things down, depending on others to assist them with remembering important tasks and events, exercise, focusing on one task at a time, and giving themselves permission to make mistakes. Women described obtaining cognitive benefit from exercise and getting enough rest. Women also recommended mind stimulation, meditation/yoga and good nutrition.

Women diagnosed with breast cancer wanted to know there was a potential for experiencing CRCI prior to initiating treatment with chemotherapy. Women wanted an

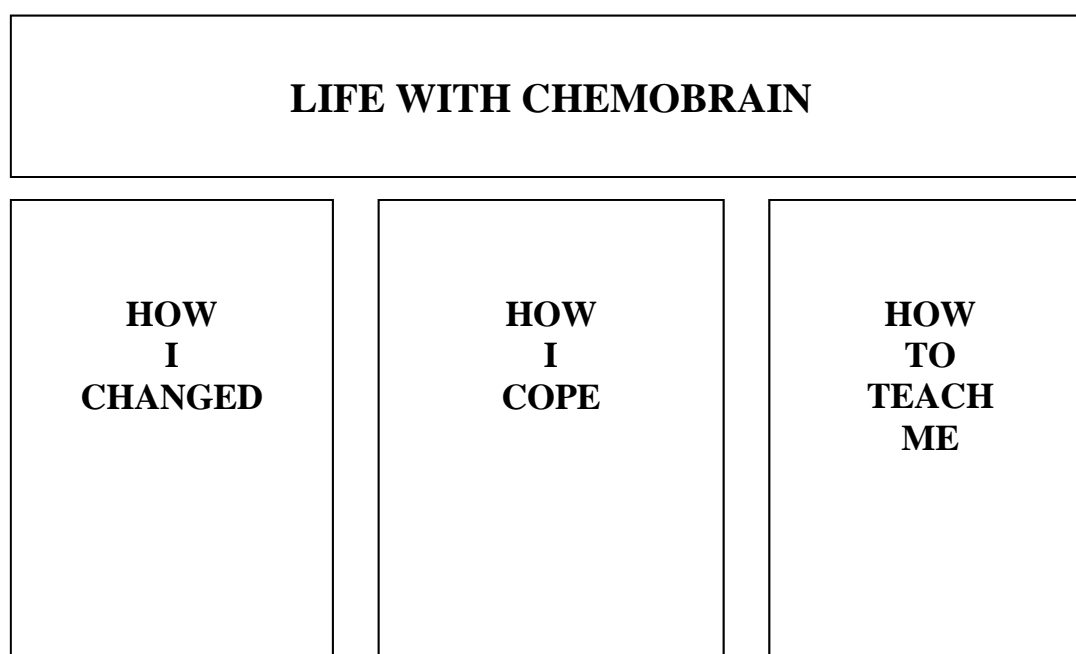


Figure 3. Life With Chemobrain Thematic Framework

individualized approach to education including an assessment of their preferred learning style and desired timing for receiving information. Women preferred to receive information from an HCP who has demonstrated expertise in education and ideally would like involvement by an individual who is a cancer survivor. Women with breast cancer wanted a tailored approach to the volume of information provided and wanted to be able to choose the format, such as one-on one conversation, written materials, or a list of pertinent websites. Education content should include information on the incidence and duration of CRCI (once known), a description of the phenomenon, and recommendations for intervention (once known) and coping strategies. The need for education of family members (including both significant others and children) was emphasized by participants.

Women described wanting on-going assessment for changes in cognitive function while they were receiving chemotherapy. This assessment could be as simple as a question related to whether they were experiencing any changes in memory. They recommended on-going reinforcement of education about CRCI throughout and following the course of therapy.

Participant's verbal responses to the semi-structured interview questions provided important information about the experience of CRCI and direction for development of an educational approach that would have been difficult to capture as a result of a quantitative survey. Live interviews offered the opportunity to further explore participants' descriptions and to observe both manifest and latent behaviors. Direct interaction between the investigator and the participant allowed additional questions to be asked and facilitated detailed participant responses that survey techniques do not provide.

Recommendations for Future Research

As expected, based on current standards of care for treating breast cancer, the majority of participants received an anthracycline (doxorubicin, Adriamycin®), cyclophosphamide (Cytosan®) and a taxane (paclitaxel, Taxol®; docetaxel, Taxotere®; or paclitaxel protein-bound particles for injectable suspension, Abraxane®). These agents have been associated with oxidative stress and the release of proinflammatory cytokines, and thus potentially are associated with resultant changes in cognitive function. Further work in animal modeling is needed to confirm causality and mechanism of action related to CRCI.

Results from this study support the need for further exploration of the relationships between fatigue, neuropathy, trouble sleeping and CRCI. The study results also support work in the area of examining the relationships between CRCI, neuropathy, clumsiness, and changes in balance and coordination. Future prospective quantitative studies should include hierarchical regression analysis to further examine the potential moderating effect of fatigue on CRCI.

Intervention studies are needed to identify strategies to prevent, minimize, or resolve CRCI. Areas of interest include exercise, cognitive retraining and nutrition (i.e. hydration and protein).

Results from this study may be helpful in the development of self-report instruments to quantify CRCI. Current instruments such as the Functional Assessment for Cancer Therapy- Cognition (FACT-COG) do not contain items related to difficulties with reading or driving. Further work is needed to explore whether difficulties with reading and driving are seen in larger populations of breast cancer survivors, those greater than 12 months from

completion of chemotherapy, and survivors of other tumor types who have received chemotherapy.

Participants' requests for individualization of educational methods and specific recommendations for educational content should be incorporated into plans of care and appropriate educational materials developed. Pilot testing of educational methods and tools is needed to demonstrate success and patient satisfaction.

A logical next step moving forward from the current study would be to conduct a similar study for women with breast cancer who are greater than 12 months from completion of chemotherapy. The experience of CRCI may differ based on the length of time since the completion of chemotherapy. Enhanced understanding of the CRCI trajectory may provide information necessary to identify individuals at high risk for CRCI as well as the development of appropriate interventions. Utilization of brief measurement tools such as the FACT-COG to further describe the sample would be of benefit, as would the use of tools to explore the level of distress and impact on quality of life related to CRCI. Revision of the demographic questionnaire used in the current study is recommended to include a question related to recent surgical procedures in which general anesthesia was used. Ultimately, the research in this area needs to be expanded beyond women with breast cancer to include survivors of other tumor types.

Implications for Nursing

The results of this study include an in depth description of the experience of CRCI and specific recommendations for the development of an educational approach and materials for women with breast cancer who will be receiving chemotherapy and their families. Oncology nurses are on the front-line for patient assessment, and patient/family education

about breast cancer, treatment, and related sequelae. Oncology nurses play an important role in obtaining informed consent prior to the initiation of therapy. Practical application of the study results will serve to validate the experience of CRCI for women with breast cancer and contribute to patient satisfaction with the delivery of care. Oncology nurse researchers should utilize the study results to support further nursing research in the area of CRCI.

Personal Reflection

I learned a great deal during the course of conducting this qualitative, descriptive study. I was granted an opportunity to see the experience of coping with a diagnosis of breast cancer and learning to live with the changes in cognitive function resulting from the treatment through the eyes of 18 survivors. As they shared their stories and experiences with me I could sense their frustration with the health care system and their sense of loss related to changes in their lives. I learned that our present methods of patient education are not meeting the needs of breast cancer survivors, and likely not survivors of other types of malignancies. In spite of the challenges around the time constraints of providing patient care in the current environment, we need to creatively craft solutions to allow staff the time and development of expertise to individualize educational plans of care.

On a more personal note, I confirmed the fact that I miss regular patient contact and find that aspect of conducting research intensely satisfying. With the help of the expert reviewers on the study team, I validated the ability to move outside of my typical linear mode of approaching the world and was able to begin to develop the skills necessary to be successful at qualitative research methodology. One such skill is the ability to synthesize participants' descriptions into meaningful categories and then further personalize the study

results into themes that capture the essence of the experience being described while remaining true to participants' words.

I was troubled by the fact that many of the participants hoped I would be able to tell them specific information regarding expectations for improvement in cognitive function and a time frame for returning to baseline performance. I found this painful and worried that I was taking their time to learn more about CRCI without being able to provide them with effective interventions or what they so desperately wanted to hear, i.e., that CRCI will eventually completely resolve. As a result of conducting this study I am even more committed to continuing to investigate CRCI. My next step is to disseminate these study results, to be followed by the development of future research to continue to add to the body of knowledge about CRCI.

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Appendix A

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Chemotherapy-Related Cognitive Impairment: The Breast Cancer Experience

RESEARCH CONSENT FORM

Chemotherapy-Related Cognitive Impairment: The Breast Cancer Experience

You are being asked to join a research study. You are being asked to take part in this study because you have received chemotherapy for the treatment of breast cancer. You do not have to participate in this research study. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

Research is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to stop early. Either way, you can still get medical care and services at the University of Kansas Medical Center (KUMC).

This consent form explains what you are being asked to do if you are in the study. It also describes the possible risks and benefits. Please read the form carefully and ask as many questions as you need to, before deciding about this research.

You can ask questions now or anytime during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating.

This research study will take place at the University of Kansas Medical Center (KUMC) with Cynthia Teel PhD, RN and Jamie Myers RN, MN, AOCN as the researchers.

BACKGROUND

Some women with breast cancer who have received chemotherapy have reported changes in thinking or memory (cognitive function). Examples of these changes may include trouble concentrating or focusing on tasks, trouble finding the right word in conversation, trouble with solving math problems, or trouble with sense of direction when driving. The changes in thinking or memory may affect women's day-to-day activities during or after treatment for breast cancer. Research has shown that many women may not have received information about the risk for changes in thinking or memory before beginning chemotherapy for breast cancer. A better understanding of what the experience is like may help physicians and nurses provide important information to women prior to and during chemotherapy.

PURPOSE

By doing this study, researchers hope to learn how women with breast cancer describe the experience of chemotherapy-related changes in thinking or memory and what information women would find helpful prior to starting chemotherapy and once they begin to experience changes in thinking or memory.

PROCEDURES

If you are eligible and decide to participate in this study, your participation will last
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approximately 60 minutes for the main study and approximately 60-90 minutes if you are willing to be contacted for follow-up information. As a part of the main study, you will be asked to complete a questionnaire. The questionnaire includes 18 questions. You will be asked to complete multiple choice and short answer questions about your age, marital status, education level, menstruation history, and questions about the type of treatment you received. The time it takes to complete the questionnaire is about 10 minutes.

You will be asked to take part in an interview with the researcher, Jamie Myers. The interview can take place at the University of Kansas Medical Center (KUMC) Breast Cancer Survivorship Center or at a place of your choosing that is acceptable to both you and the researcher, Jamie Myers. The location for the interview must be a quiet place where you and the researcher can talk privately without disturbing others. You will be asked to describe your experience with changes in thinking or memory during and/or after chemotherapy.

Approximately 15 women will be interviewed for this study. Once all the interviews are completed (over the course of a few months), you may be contacted to take part in a small group interview with 5-8 other women who have taken part in this study. The purpose of the small group interview is to review what has been learned during the single interviews and find out if the study results reflect the experience of changes in thinking or memory that women with breast cancer describe during and after chemotherapy. The small group interview will take place at the University of Kansas Medical Center (KUMC) Breast Cancer Survivorship Center and will be led by the researcher, Jamie Myers. One additional research team member will be present to take notes during the focus group.

If you are willing to participate in a small group interview, the researcher, Jamie Myers will review a summary of the study results with the group. You will be asked to make comments as to whether your experience with changes in thinking or memory has been correctly described. Your comments and suggestions will be used to revise the research.

Both types of interviews will be recorded. The researcher, Jamie Myers, and one additional research team member will listen to the recording. The recording will be typed up word for word for use in the study. Your name will not be used in conjunction with the recording or the typed version.

RISKS

There is a risk that sharing your experiences with changes in thinking or memory may bring up uncomfortable or painful memories about your breast cancer, chemotherapy, or changes to your day-to-day activities. If you are uncomfortable or embarrassed by any questions, you are free not to answer these questions. You are free to withdraw

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from the study at any time.

There may be other risks of the study that are not yet known.

NEW FINDINGS STATEMENT

You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

You may or may not benefit from this study. Sharing your experiences may provide comfort that you are not the only person to have experienced changes in thinking or memory after chemotherapy for breast cancer. Participating in this study will not affect your diagnosis or the outcome of your treatment.

Researchers hope that the information from this research study may be useful in educating doctors and nurses about the experience of women with breast cancer who have changes in thinking or memory after chemotherapy. Researchers hope that this information will help doctors and nurses provide important information to women with breast cancer before starting chemotherapy and after changes in thinking or memory occur.

ALTERNATIVES

Participation in this study is voluntary. Deciding not to participate will have no effect on the care or services you receive at the University of Kansas Medical Center.

COSTS

There is no cost for being in the study.

PAYMENT TO SUBJECTS

There is no payment for this study.

INSTITUTIONAL DISCLAIMER STATEMENT

If you think you have been harmed as a result of participating in research at the University of Kansas Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Under certain conditions, Kansas state law or the Kansas Tort Claims Act may allow for payment to persons who are injured in research at KUMC.

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CONFIDENTIALITY AND PRIVACY AUTHORIZATION

The researchers will protect your information, as required by law. Your name will not be associated with any of the study results. The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in any publication or presentation about the study.

Your health information is protected by a federal privacy law called HIPAA. By signing this consent form, you are giving permission for KUMC to use and share your health information. If you decide not to sign the form, you cannot be in the study.

The researchers will only use and share information that is needed for the study. To do the study, they will collect health information from the study. You may be identified by information such as name, address, phone, date of birth, social security number, or other identifiers. Your health information will be used at KU Medical Center Dr. Cynthia Teel, Jamie Myers, members of the research team, the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies. Study records might be reviewed by government officials who oversee research, if a regulatory review takes place.

All study information that is sent outside KU Medical Center will have your name and other identifying characteristics removed, so that your identity will not be known. Because identifiers will be removed, your health information will not be re-disclosed by outside persons or groups and will not lose its federal privacy protection.

Your permission to use and share your health information remains in effect until the study is complete and the results are analyzed. After that time, researchers will remove personal information from study records.

QUESTIONS

Before you sign this form, Jamie Myers or other members of the study team should answer all your questions. You can talk to the researchers if you have any more questions, suggestions, concerns or complaints after signing this form. If you have any questions about your rights as a research subject, or if you want to talk with someone who is not involved in the study, you may call the Human Subjects Committee at (913) 588-1240. You may also write the Human Subjects Committee at Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

You may stop being in the study at any time. Your decision to stop will not prevent you from getting treatment or services at KUMC. The entire study may be discontinued for any reason without your consent by the investigator conducting the study.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to Dr. Cynthia Teel. The

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mailing address is Cynthia Teel, PhD, RN, University of Kansas Medical Center School of Nursing, 3901 Rainbow Boulevard, Kansas City, KS 66160. If you cancel permission to use your health information, you will be withdrawn from the study. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your cancellation.

CONSENT

Jamie Myers or the research team has given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you say that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered. **You will be given a signed copy of the consent form to keep for your records.**

 Print Participant's Name

 Signature of Participant Time Date

 Print Name of Person Obtaining Consent

 Signature of Person Obtaining Consent Date

WILLINGNESS TO BE CONTACTED FOR FOLLOW-UP & SMALL GROUP INTERVIEW

By signing this portion of the form, you say that you freely and voluntarily consent to be contacted by the researcher, Jamie Myers, to take part in a small group interview.

The best way to contact you to arrange follow-up is:

___ Phone
 List preferred phone number: _____

___ E-mail
 List preferred e-mail address: _____

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____ US mail:

List preferred mailing address: _____

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Appendix B

LETTER TO HEALTH CARE PROFESSIONALS: DESCRIPTION OF THE STUDY

Dear Oncologist or Oncology Nurse,

I am seeking your help to recruit participants for a research study. As part of my doctoral dissertation research, I am conducting a qualitative study designed to provide an in-depth description of the **experience of chemotherapy-related cognitive impairment (CRCI) for women with breast cancer**. Enclosed are the study synopsis and eligibility criteria, as well as a flyer providing a description of the study and my contact information.

After reviewing the synopsis and flyer, if you have patients in your practice that are eligible, I am asking you to let them know about the study and ascertain interest. Please provide interested eligible women with the flyer and my contact information. I would be happy to talk with you by phone or in person if you have questions or would like more information. I hope you will encourage any eligible women to consider participation. If you are willing, I can provide copies of the flyer for your waiting area and/or staff to use in talking with patients

The desired outcomes for this study are to gain a better understanding of the patient experience and guide development of appropriate educational tools to use with women about to receive chemotherapy and for those who begin to report changes in cognitive function. I appreciate your time and consideration on this matter.

Warm regards,

Jamie S. Myers RN, MN, AOCN
913-449-5996 (cell)
jmyers@kumc.edu

Appendix C

Study Synopsis

Specific aims of the study are to:

- Describe the experience of CRCI for women with breast cancer who have received chemotherapy treatments
- Identify information about CRCI that women would find useful prior to initiation of chemotherapy and following the onset of CRCI

Inclusion Criteria

- Adult women (aged 18 or older)
- Diagnosed with any stage of breast cancer
- Within 6-12 months of completing standard-dose chemotherapy
- Previous or current hormonal therapy is acceptable
- Self-report changes in cognitive function (such as changes in ability to concentrate, remember, or focus on tasks; difficulty with finding the right word or phrase or doing mathematical calculations; or problems with sense of direction when driving)
- Able to read, write, speak, and understand English

Exclusion Criteria

- Evidence of central nervous system metastases
- History of mental illness, dementia, or Alzheimer's disease
- Currently taking psychotropic medications (with the exception of benzodiazepines or selective serotonin uptake inhibitors prescribed for the treatment of anxiety or depression).

About 15 women will be asked to participate in a semi-structured in-depth interview.

All participants will be asked to complete a demographic questionnaire including information about age at diagnosis, menopausal status, stage of disease, regimen and duration of therapy.

Willing participants may be contacted to participate in a focus group to check for agreement with the research findings and elicit suggestions for revision.

There is no cost for participation in the study and no reimbursement to patients for participation.

Human Subjects Committee approval has been obtained through the University of Kansas Medical Center (KUMC).

**Appendix D
Flyer**

**Are you a woman who has experienced changes
in thinking or memory since receiving
chemotherapy for breast cancer?**

If so, (and you are within 6-12 months of completing chemotherapy) you are invited to take part in an interview to describe your experience. I am an oncology nurse who is interested in learning more about the changes in thinking or memory (cognitive function) that some women with breast cancer experience with chemotherapy. The purpose of this study is to learn more about this experience in order to help doctors and nurses to better understand what women may go through and to develop some useful educational materials.

Participation in this study would involve:

- Completing a questionnaire (about 10 minutes)

AND

- Taking part in an interview with me (about 60 minutes)
- If you are willing to be contacted again in the future, you may be asked to take part in a small group interview with me and 5-8 other women who have/had breast cancer and chemotherapy and report some changes in thinking or memory

To be eligible for this study you must be:

- A woman with a history of breast cancer
- Within 6-12 months of completing chemotherapy
- Age 18 or older
- Able to write, speak, read, and understand English

If you would be interested in participating, or learning more about this research **study**, please contact me:

Jamie Myers RN, MN, AOCN
913-449-5996
jmyers@kumc.edu

Appendix E

Demographics Questionnaire

Date: _____

1. How old were you when you were diagnosed with breast cancer? _____

2. How old are you now? _____

3. What is your marital status?

___ single

___ married

___ divorced

___ widowed

___ in a relationship

4. Has your marital status changed since you were diagnosed with breast cancer?

___ yes ___ no

If so, how?

___ married

___ separated

___ divorced

___ widowed

___ in a relationship

___ other (please describe)

5. What is your ethnicity?

- | | |
|--|---|
| <input type="checkbox"/> White, non-Hispanic | <input type="checkbox"/> Native Hawaiian/Pacific Islander |
| <input type="checkbox"/> Black, non-Hispanic | <input type="checkbox"/> Two or more races, non-Hispanic |
| <input type="checkbox"/> American Indian | <input type="checkbox"/> Hispanic/Latino |
| <input type="checkbox"/> Asian | <input type="checkbox"/> Other (please describe) |

6. What is was your menopausal status before you received chemotherapy?

- Pre-menopausal (still menstruating)
- Peri-menopausal (greater than 3 months and less than 6 months since last menstrual period)
- Post-menopausal (no longer menstruating, greater than 6 months since last menstrual period, or post hysterectomy)

7. What is was your menopausal status now?

- Pre-menopausal (still menstruating)
- Peri-menopausal (greater than 3 months and less than 6 months since last menstrual period)
- Post-menopausal (no longer menstruating, greater than 6 months since last menstrual period, or post hysterectomy)

8. What is your employment status? You may check more than one if appropriate.

- full time home-maker
- part time home-maker
- no longer able to function as a home-maker
- employed full time
- employed part time
- retired
- on medical leave from my job
- not presently working

9. Has your employment status changed since you were diagnosed with breast cancer?

- yes no

If so, how?

- changed jobs
- missed promotion
- lost job
- went part-time
- retired
- other (please describe)

10. What is your highest level of education?

grade school

high school

college

graduate school

11. What was the stage of your initial diagnosis with breast cancer?

Stage 1

don't know

Stage 2

Stage 3

Stage 4

12. When was your last chemotherapy for breast cancer (approximate month and year)?

13. What were the names of the chemotherapy drugs you received to treat your breast cancer?

5FU (fluorouracil)

methotrexate

adriamycin

taxotere

cytoxan

other (please describe)

taxol

don't know

herceptin

epirubicin

14. How often did you receive your chemotherapy?

every 3 weeks

every 2 weeks

every 1 week

other (please describe)

15. Over how many months (or cycles) did you receive chemotherapy?

16. Have you received hormonal therapy to treat your breast cancer (such as Tamoxifen, Nolvadex, Femara, Letrozole, Arimidex, Anastrozole, Exemestane, Aromasin, Goserelin, Zoladex)?

yes

no

If yes, are you currently receiving hormonal therapy?

yes

no

17. Are you having any symptoms related to menopause?

- hot flashes
- trouble sleeping
- feeling irritable
- weight gain
- other (please describe)

18. Are you experiencing any of the following?

- anxiety
- depression
- fatigue

Appendix F

Interview Guide:

Primary Questions:

- 1) How would you describe your experience with changes in thinking or memory during chemotherapy?

- 2) What information would you have found helpful prior to starting chemotherapy?

- 3) What information would you have found helpful once you began to notice changes in your thinking or memory?

- 4) Is there anything else you would like to share about your experience?

Potential Probes

- a. When did you first notice the changes in thinking or memory?
- b. Did the changes get worse or better during therapy?
- c. Have you noticed any changes or improvement after therapy was completed?
 1. If so, tell me about the sequence of events (time-line)

- d. What did you find that made your thinking ability or memory better?
- e. What did you find that made your thinking ability or memory worse?
- f. What did you find that helped you cope with the changes in thinking ability or memory?
- g. What impact have these changes had on your relationships (family/friends/co-workers).
- h. What impact have these changes had on your job (or ability to function day-to day).
- i. How have these changes affected other aspects of your life?
- j. Did you receive any information about changes in thinking or memory prior to receiving chemotherapy?
- k. When would have been the best time to receive information about changes in thinking or memory?
- l. Who would you have liked to provide you with this information?