COGNITIVE FUNCTION IN KOREAN WOMEN DIAGNOSED WITH EARLY STAGE BREAST CANCER

by

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DEDICATION

To my dad, mom, brother, and sister

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ABSTRACT

Cognitive deficits have been reported in western women following chemotherapy for breast cancer (BC). Attention and working memory deficits may negatively impact women's abilities in performing in daily activities, dealing with stressful situations, and maintaining health-related quality of life. However, little is known about cognitive deficits in Korean women with BC. Furthermore, no research has examined cultural effects on cognitive deficits although cultural context can influence cognitive processing, thereby affecting performance and responses.

This study investigated the incidence and severity of attention and working memory deficits in Korean women treated with chemotherapy for early stage BC and explored factors contributing to cognitive deficits. Based on the biobehavioral-neurocultural framework, demographic, general health, and medical characteristics, physical and psychological symptoms (fatigue, anxiety and depressed mood, sleep problem, and symptom distress), and cultural characteristics (cultural attitude of collectivism, housework burden, childrearing burden, and self-blame tendency about BC diagnosis) were considered as potential covariates. Assessment with established neurocognitive measures and self-reports of cognitive function and potential covariates was conducted in 32 BC participants about four months following chemotherapy and in 32 non-BC participants after negative screening mammography. Comparative statistics and multiple regression analyses were used.

BC participants showed higher incidence and greater severity of cognitive deficits than non-BC participants. Specifically, BC participants had lower scores on neurocognitive tests, worse performance in the attention network test, and lower scores on perceived cognitive function than non-BC participants. These group differences were medium to large. Being in the BC group, older age, and lower educational level significantly predicted poorer cognitive performance while being in the BC group was found to be a predictor of better effectiveness of cognitive function. Interestingly, the number of symptoms regardless of severity was found to be an important predictor of worse performance and lower effectiveness in cognitive function. Depressed mood significantly predicted lower effectiveness in cognitive functioning. Cultural attitude of collectivism was a significant predictor of poorer cognitive performance, while having a daughter and lower childrearing burden predicted better effectiveness in cognitive functioning. These factors should be considered when designing therapeutic interventions to improve cognitive function in Korean women with BC.

CHAPTER I

INTRODUCTION

Since 2001 breast cancer has been a significant health concern for Korean women. According to the latest cancer incidence data reported by the National Cancer Information Center in South Korea, primary breast cancer accounts for about 15% of all female patients newly diagnosed with a malignant neoplasm (Korean Statistical Information Service, 2011a). When compared to the prevalence of breast cancer in other countries, South Korea has one of the lowest breast cancer incidence rates. However, the recent 10-year trends in incidence of breast cancer suggest an increase in the percentage of newly diagnosed breast cancer in Korea (Korean Statistical Information Service, 2011a; SEER, 2011). Specifically, an average percent change (APC) for the rates of breast cancer incidence is 6.5% in women from 1999 (incidence rate: 25 per 100,000 women) to 2008 (incidence rate: 42 per 100,000 women). This APC score is much higher than those of other western countries which ranged from -1.9% in the United States (from 1998 to 2006) to 2.5% in Estonia (from 2001 to 2005). Moreover, breast cancer mortality in Korea has gradually increased from 4.8% in 2000 to 7.6% in 2009, a trend that contradicts that of western countries as well as other East Asian countries, which all have decreasing mortality rates (Korean Statistical Information Service, 2011a; Shin et al., 2010; SEER, 2011). This rising incidence and mortality in Korean women confirm that breast cancer is a significant life-threatening illness leading to physical, psychological, and cognitive distress in women's lives.

As the incidence of primary breast cancer in Korea has increased, attention has been increasingly directed towards treatment-related adverse effects such as nausea, hair loss, fatigue, and depression (S. H. Kim et al., 2008; Kim & Seo, 2010; Kim, 2010; Park, Jun, Kang, Joung, & Kim, 2009; Woo & Kim, 2007; Yang, 2005; Yang, 2003; Yoo, Lee, & Yoon, 2009). However, the incidence of cognitive problems in Korean women with breast cancer has remained unexplored although recent studies conducted in western countries reported that women undergoing chemotherapy for early stage breast cancer have compromised cognitive function (Wefel, Saleeba, Buzdar, & Meyers, 2010). Very few studies have explored cognitive problems of women with breast cancer in East Asian countries (Inagaki et al., 2007; Lee, 2005). Due to this lack of studies on cognitive health in women with breast cancer from non-western cultures, it is unclear whether actual and perceived cognitive problems in attention and memory function occur in Korean breast cancer survivors following adjuvant chemotherapy.

Potential mechanisms underlying chemotherapy-related cognitive deficits in breast cancer survivors include 1) biological changes induced by certain types of chemotherapeutic agents administered to treat breast cancer (Vodermaier, 2009) and 2) loss of cognitive capacity as a result of intense or prolonged mental demands associated with diagnosis of breast cancer (Cimprich, 1993). Recent studies have demonstrated that cognitive deficits are associated with neurotoxic effects of some chemotherapeutic agents administered to treat early stage breast cancer. Although the biological mechanisms for neurotoxic effects of these agents on cognitive function are still not fully explored, it is generally accepted that some types of chemotherapeutic agents may negatively influence the integrity of higher levels of brain function or executive functioning including multitasking and learning (Aluise et al., 2010; Correa & Ahles, 2008; Deprez et al., 2011; Inagaki et al., 2007; Konat, Kraszpulski, James, Zhang, & Abraham, 2008; Liedke et al., 2009; Raffa & Tallarida, 2010; Tangpong et al., 2007; Wefel et al., 2010; Wigmore et al., 2010).

Women with breast cancer may also be confronted with various cognitive demands requiring the use of attention and working memory during the course of breast cancer treatment (Cimprich, 1992a; Cimprich & Ronis, 2001; Munir, Burrows, Yarker, Kalawsky, & Bains, 2010; Stark & Cimprich, 2003). Demands include participating in treatment-related decision making, learning new information about their illness and its treatment, adjusting to the physical and psychological burdens imposed by treatment for breast cancer, and coping with changes in personal and interpersonal roles at home and at work. These demands may continue to persist even after the completion of adjuvant treatment and lead to attentional fatigue which reduces effectiveness in performing intended activities, handling distressing affective states, and maintaining an individual's ability to focus and think clearly. In this regard, women treated with chemotherapy for breast cancer may be vulnerable to cognitive deficits as a result of increased cognitive demands associated with their illness.

In addition to neurotoxic effects of chemotherapy and multiple cognitive demands requiring more mental effort, the cultural context of Korean breast cancer patients needs to be considered as an important factor when examining cognitive function in breast cancer survivors from non-western countries as compared to those from western countries. Individuals within a culture are prone to attend to, remember, and interpret life experiences in culturally derived ways (Goh & Park, 2009; Hedden, Ketay, Aron, Markus, & Gabrieli, 2008; Nisbett & Masuda, 2003; Nisbett & Miyamoto, 2005). People raised within East Asian cultural contexts such as the Korean culture have a predominant tendency toward holistic processing which is favored by collectivist culture (Markus & Kitayama, 1991; Nisbett & Masuda, 2003; Nisbett & Miyamoto, 2005; Nisbett, Peng, Choi, & Norenzayan, 2001). Holistic processing is a mode of thought which emphasizes attention to the surrounding context in which objects are embedded, focuses on relationships between parts of a whole, and attributes causality to situational or contextual features in terms of interdependence. Further, individuals within East Asian cultures appear to require greater cognitive effort in performing culturally nonpreferred attention tasks (e.g., focusing on a target object and ignoring an association with its context) than in conducting culturally preferred attention tasks (e.g., perceiving the target object and its context together) (Goh & Park, 2009). This finding demonstrates that the cultural context can influence brain function engaged in attentional control, thereby affecting performance and responses (Hedden et al., 2008).

It is important to note that breast cancer survivors can have reduced attention and working memory function following the completion of adjuvant chemotherapy as they are transitioning from ‘patient’ to ‘survivor’ (Downie, Mar Fan, Houede-Tchen, Yi, & Tannock, 2006; Reid-Arndt, Hsieh, & Perry, 2010). In order to assist Korean breast cancer survivors with successfully returning to their usual life patterns, it is necessary to investigate the incidence, severity, and the associated factors related to deficits in attention and working memory immediately following treatment. Specifically, it is necessary to examine the basic characteristics of cognitive problems in Korean women treated with adjuvant chemotherapy for breast cancer and explore whether there are culture-specific cognitive burdens related to deficits in attention and working memory. Further, it is critical to investigate whether there are any predictors of cognitive deficits defined by objective performance and subjective perception of attention and working memory functioning. This study is the first step in understanding cognitive problems in Korean breast cancer survivors treated with adjuvant chemotherapy. Findings of this study can help researchers and health care professionals develop therapeutic interventions to improve cognitive health for breast cancer survivors from non-western cultures.

Statement of Purpose

The purpose of this study was twofold: 1) to examine the impact of adjuvant chemotherapy on cognitive function, especially attention and working memory, in Korean women treated for early stage breast cancer; and 2) to explore the factors associated with deficits in attention and working memory.

Significance of the Problem

Attention and working memory are important domains for effective functioning in daily living. These cognitive functions are required to perform even simple tasks such as getting to work on time, driving a car, prioritizing multiple activities, grocery shopping, performing mundane household chores, managing important financial transactions, planning or organizing family events, handling conflicts within the family, and actively participating in social conversations (Stark & Cimprich, 2003). Directed attention is responsible for actively inhibiting distracting or competing stimuli from the environment while effectively focusing on information relevant to task demands (Kaplan & Kaplan, 1989; Posner, 1995). Working memory provides the ability to temporarily maintain and manipulate information for intended purpose. This cognitive function is critical in guiding cognitive and behavioral responses that allow goal-directed activities in a real world setting (Baddeley, 2003; Knudsen, 2007; Smith & Jonides, 1999). In this regard, attention and working memory support effective functioning, which is necessary to meet changing environmental demands, to maintain coherent trains of thoughts and behaviors, and block the interference of distractions in everyday life (Awh & Jonides, 2001; Egner & Hirsch, 2005; Kahneman, 1973). Thus, attention and working memory need to be considered when developing effective interventions to improve cognitive health in people encountering stressful life situations.

Functional efficacy of directed attention and working memory may be restricted (Duncan, 1980; Posner & Petersen, 1990). When cognitive demands increase, greater cognitive effort is required to allow individuals to effectively perform intended activities. Unfortunately, attention and working memory have a limited capacity with intense or prolonged exertion of cognitive effort in stressful life situations that leads to fatigue and loss of directed attention and working memory function (Cimprich, 1993; Kaplan & Kaplan, 1989). As a result, deficits in attention and working memory capacity can compromise an individual's ability to effectively deal with numerous life challenges such as the diagnosis of life-threatening illness (Cimprich, 1993).

According to Cimprich and her colleagues' studies, breast cancer patients and survivors are known to be at high risk for developing deficits in attention and working memory capacity (Cimprich, 1992a; Cimprich & Ronis, 2003; Cimprich, So, Ronis, & Trask, 2005). Following breast cancer diagnosis, women face various cognitively demanding situations throughout the entire period of breast cancer treatment (Mitchell & Turton, 2011). Even after completion of cancer treatment, women may be confronted with extra needs for cognitive effort to deal with challenges upon their return to usual life activities which may be different from their "normal" life before cancer diagnosis (Allen, Savadatti, & Levy, 2009). During this phase of cancer survivorship, they are required to deal with affective, informational, and behavioral demands including unrelenting worries about recurrence, the burden of a new responsibility for monitoring signs of recurrence, a sense of uncertainty regarding their ability to reintegrate back to their normal life, and maintaining a balance in performing their duties at home, work, and in the community (Munir et al., 2010). Such multiple demands can lead to overuse of attention and working memory leading to a reduced cognitive capacity and, subsequently, a significant decline in daily functioning and quality of life in breast cancer survivors (Reid-Arndt, Yee, Perry, & Hsieh, 2009). In this regard, cognitive demands make women more susceptible to deficits in attention and working memory function during this transition period following treatment. Thus, it is imperative to examine cognitive function immediately following the completion of chemotherapy for breast cancer when health care professionals assist breast cancer survivors for the transition to long-term survivorship.

A growing body of research has examined chemotherapy-related cognitive deficits in women treated with chemotherapy for early stage breast cancer. These studies reported that the incidence of cognitive deficits broadly ranges from 17% to 75% in women treated with chemotherapeutic agents for early stage breast cancer. This wide range most likely reflects theoretical and methodological limitations in the research including heterogeneity in the types of chemotherapy regimens, methods of assessing cognitive function, and the length of time since chemotherapy completion (Boykoff, Moieni, & Subramanian, 2009; Marin, Sanchez, Arranz, Aunon, & Baron, 2009; Phillips

& Bernhard, 2003; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006; Tannock, Ahles, Ganz, & van Dam, 2004). This body of research suggests that chemotherapy may induce or exacerbate cognitive deficits by neural changes in specific brain regions such as a reduced density of fronto-subcortical circuitry engaged in attention and speed of information processing, hyporesponsiveness of the prefrontal cortex in performing executive functioning tasks, and recruitment of bilateral frontal brain regions to support attention and working memory function (de Ruiter et al., 2011; Deprez et al., 2011; Ferguson, McDonald, Saykin, & Ahles, 2007; Inagaki et al., 2007; Silverman et al., 2007). Taken together, breast cancer survivors are more likely to be vulnerable to deficits in attention and working memory; these cognitive deficits seem to be associated with neurotoxic effects of chemotherapeutic agents that may be compounded by overuse of cognitive effort due to increased demands during and following treatment.

The onset and development of cognitive deficits may be partially associated with physical and psychological distress including treatment-related symptoms, fatigue, anxiety, depression, sleep problems, menopausal state and comorbid condition (Bender et al., 2006; Castellon et al., 2004; Cimprich, 1992a; Debess, Riis, Pedersen, & Ewertz, 2009; Downie et al., 2006; Jansen, Cooper, Dodd, & Miaskowski, 2011; Kim, Hwang, Jon, Ham, & Seok, 2008; Mehnert et al., 2007; Myers, 2009; Reid-Arndt et al., 2010; Schagen et al., 2002; Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005; van Dam et al., 1998; Vearncombe et al., 2009). Higher levels of fatigue were significantly related to changes in neuropsychological performance in attention and working memory (Cimprich, 1992a; Mehnert et al., 2007; Reid-Arndt et al., 2010). Higher levels of psychological distress including depression and anxiety also were reliably correlated with cognitive deficits (Bender et al., 2006; Castellon et al., 2004; Debess et al., 2009; L. S. Kim et al., 2008; Reid-Arndt et al., 2010; Schagen et al., 2002; Vearncombe et al., 2009). Menopausal symptoms or menopausal states may also significantly contribute to cognitive deficits (Downie et al., 2006; Jansen et al., 2011; Shilling et al., 2005). However, other studies failed to show the meaningful relationships between cognitive deficits and these covariates (Ahles et al., 2002; Jenkins et al., 2006; Jim et al., 2009; Tchen et al., 2003). Also, some studies were conducted to examine cognitive deficits without controlling for the effects of these potential covariates on objective performance or subjective perception regarding cognitive functioning (Donovan et al., 2005; Quesnel, Savard, & Ivers, 2009; Scherwath et al., 2006; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). Accordingly, it seems that associations between covariates and cognitive deficits have not been fully explored in women treated with adjuvant chemotherapy for early stage breast cancer. Further studies are needed to define possible risk factors for the development of cognitive deficits (Marin et al., 2009).

Cultural characteristics are other possible covariates which can influence the activation of brain networks engaged in executive control. For example, in Asian countries, greater cognitive effort may be needed to perform culturally nonpreferred versus culturally preferred attention tasks (Nisbett et al., 2001). Greater use of cognitive effort can negatively affect attention and working memory task performance. Thus, it is hypothesized that breast cancer survivors from non-western cultural contexts will show a pattern of greater deficits in actual performance and perceived effectiveness of attention and working memory function, as compared to women without breast cancer.

Study Aims and Research Questions

The specific objectives of the study were to examine: 1) the incidence and severity of cognitive deficits measured by objective performance and subjective perception of attention and working memory function in Korean women treated with adjuvant chemotherapy for early stage breast cancer; and 2) the factors (demographic and general health characteristics, physical and psychological symptoms, and cultural characteristics) associated with deficits in attention and working memory in Korean women. The specific questions for investigation were addressed below:

1.1. Are there identifiable differences in the incidence and severity of deficits in cognitive performance between Korean women treated with chemotherapy for early stage breast cancer and women without breast cancer?

1.2. Is there a difference in perceived effectiveness of attention and working memory function between Korean women treated with chemotherapy for breast cancer and women without breast cancer?

2.1. What are the relationships between demographic and general health characteristics, physical and psychological symptoms, and cultural characteristics and cognitive performance and perceived effectiveness in attention and working memory function?

2.2. What are the significant predictors of cognitive performance and perceived effectiveness in attention and working memory function?

2.3. What is the relationship between self-blame tendencies and cognitive performance and perceived effectiveness in attention and working memory function in women treated with chemotherapy for breast cancer?

Theoretical Framework

A Theoretical Model of Cognitive Deficits in Attention and Working Memory

This study is based on a biobehavioral-neurocultural framework that links neurobehavioral theory of cognitive function, specifically attention and working memory, the biological effects of chemotherapy on cognitive function, and cultural influences on cognitive deficits related to the impact of breast cancer diagnosis and its treatment. According to neurobehavioral theory of attention and working memory, these basic processes are important to regulate inhibitory or mental effort for purposeful activities in everyday life. As cognitive demands increase, greater use of attention and working memory is required to assist individuals to effectively perform intended tasks. In this regard, breast cancer survivors may be susceptible to loss of attention and working memory capacity following adjuvant chemotherapy because of the various and often urgent cognitive demands experienced for the successful transition from the completion of scheduled treatment to ‘new normal’ life after treatment. Furthermore, chemotherapeutic agents administered to treat breast cancer can have neurotoxic effects on the brain affecting attention and working memory systems and may lead to reduced cognitive function or exacerbation of cognitive deficits which may already exist prior to adjuvant treatment. Thus, women are more likely to be vulnerable to cognitive deficits following chemotherapy for breast cancer.

Definition of Terms

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

Directed attention. Directed attention (attention) is the ability to effectively focus on information relevant to cognitive demands through the active process of inhibiting competing or distracting stimuli from the environment (James, 1890; Kaplan & Kaplan, 1989; Posner, 1995). The functional efficacy of attention may be restricted by a limited capacity due to continued use of mental or inhibitory effort to achieve mental clarity (Kaplan & Kaplan, 1989).

Working memory. Working memory is regarded as an ability to temporarily store and manipulate information for some purpose (Baddeley, 1986; Smith & Jonides, 1999). Short-term storage refers to a memory system which involves temporary maintenance of a limited amount of information depending on individual's capacity (Miller, 1994). The manipulation of information involves attentional control to operate on the contents stored in memory (Baddeley, 1986). Thus, working memory function is inextricably related to directed attention in allowing cognitive and behavioral responses during intended activities in the real world (Awh & Jonides, 2001; Knudsen, 2007).

Attention and working memory deficits. Deficits in attention and working memory are delineated as a loss of cognitive capacity to inhibit competing stimuli and hold relevant information (Cimprich, 1992a; Kaplan & Kaplan, 1989). Specifically, attention and working memory deficits are thought to diminish an individual's ability to maintain clarity in thinking, follow a train of thought, set goals, launch a new project, solve a problem, understand new information, or exert cognitive effort for performing executive activities, even simple daily tasks (Cimprich, 1995; Kaplan & Kaplan, 1989; Lorist, 2008; Lorist, Boksem, & Ridderinkhof, 2005; van der Linden, Frese, & Meijman, 2003).

In this study cognitive deficits were determined by actual scores and the sum of z-transformed scores on selected cognitive tests (Digit Span and Controlled Oral Word

Association tests) with lower scores indicating greater deficits in directed attention and working memory. The deficits also were represented as poor behavioral performance in terms of higher error rates and longer reaction times on the Attention Network Test. Poor behavioral performance indicates deficits in directed attention systems. Finally, cognitive deficits were defined with self-report scores on the Attention Function Index. Lower scores indicate decrease in perceived cognitive effectiveness in performing daily activities requiring attention and working memory.

Cultural characteristics. Cultural differences influence the way that an individual thinks, perceives, and understands the real world. Korean culture is characterized by an emphasis on the interdependence (inter-relationship) which is a main feature of collectivism. More specifically, neo-Confucianism and Confucian familism are suggested as main cultural characteristics which operate as “the habits of mind” in terms of cultural values, viewpoints, and behavioral guidance for Korean people (Choi, 2002; Hahm, 2003; Lee, 2000; Park, 1985). When women are confronted with uncertain situations such as having a life-threatening illness, culture substantially influences the processes of cognitive interpretation and behavioral engagement for dealing with confusion and helplessness in a culturally familiar way (Kaplan & Kaplan, 1989; Markus, Kitayama, & Heiman, 1996). However, culture does not always provide the best support for problem solving. When women deal with undesirable experiences related to life-threatening illness such as breast cancer, culturally learned responses previously acquired in their cultural context can come into conflict and cause extra cognitive burden in carrying out illness-induced demands (Ashing-Giwa et al., 2004; Cho, 2002; Im, 2000; Im, Lee, & Park, 2002). Based on literature review of Korean culture and Korean women's responses to breast cancer diagnosis and treatment, collectivistic tendency, women's perceptions about culturally prescribed role performance, and self-blame tendency were identified as potential cognitive demands leading to deficits in attention and working memory. Cultural attitude of collectivism, women's burden regarding household chores and childrearing, and the self-blame tendency were used to measure the associations between cognitive deficits and selected cultural characteristics in Korean women with and without breast cancer.

Detailed information about the biobehavioral-neurocultural framework established for this study is presented in Figure 1. Briefly, demographic characteristics include age, educational level, marital status, having children (sons or daughters), and socioeconomic status (employment status and annual household income). Breast cancer characteristics consist of information about cancer diagnosis (stage of disease and time since diagnosis) and its treatment (type of treatment and time since treatment). General health characteristics were composed of menopausal state and comorbidity. Cultural characteristics and physical and psychological symptoms were included as important factors associated with deficits in attention and working memory. Cultural characteristics are cultural attitude of collectivism, housework burden, childrearing burden, and self-blame tendency related to having a breast cancer diagnosis. Physical and psychological symptoms include fatigue, anxiety, depressed mood, sleep problem, and number and severity of symptoms. Functional outcomes were not assessed in the present study.

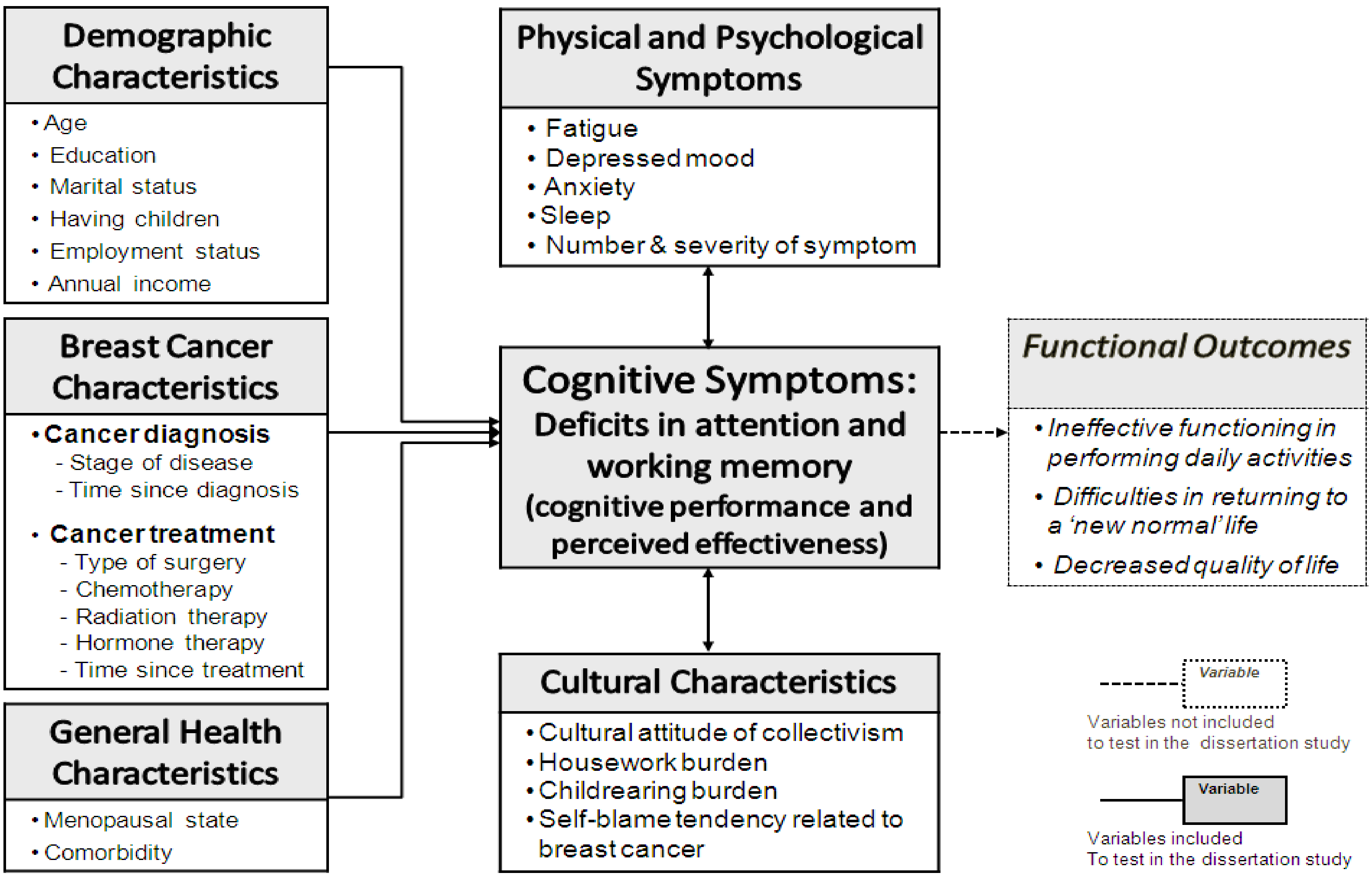

Figure 1. A Biobehavioral-Neurocultural Framework of Attention and Working Memory Deficits in Korean Women with Breast Cancer

CHAPTER II

COGNITIVE DEFICITS AND BREAST CANCER

During the past two decades there has been a growing awareness of chemotherapy-associated cognitive problems observed in individuals treated for breast cancer (Correa & Ahles, 2008; Janelsins et al., 2011; Marin et al., 2009; Morse, Rodgers, Verrill, & Kendell, 2003; Phillips & Bernhard, 2003; Stewart et al., 2006; Tannock et al., 2004; Vodermaier, 2009; Weiss, 2008). Despite the lack of a conceptual definition and theoretical consistency in measuring cognitive problems, cross-sectional studies have shown mild to moderate cognitive deficits in women treated with adjuvant chemotherapy for breast cancer (Ahles et al., 2002; Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Mehnert et al., 2007; Schagen, Das, & van Dam, 2009; van Dam et al., 1998; Wieneke & Dienst, 1995). Specifically, cognitive deficits were frequently detected in the domains of attention and working memory which are prerequisites for effectiveness in higher order executive functions such as learning, decision making, and effective interpersonal relations (Cimprich & Ronis, 2003; Mesulam, 1998; Posner, 1995; Shilling et al., 2005; Smith & Jonides, 1999). Attention and working memory deficits have also been observed in neuroimaging studies assessing cognitive deficits in breast cancer survivors. Functional and structural changes observed in specific brain regions included a reduced density of fronto-subcortical circuitry engaged in attention and information processing, hyporesponsiveness of the prefrontal cortex in performing an executive functioning task and greater activation in bilateral brain regions engaged in attention and working memory function (Cimprich et al., 2010; de Ruiter et al., 2011; Deprez et al., 2011; Ferguson, McDonald et al., 2007; Inagaki et al., 2007; Silverman et al., 2007). Together, these findings suggest that deficits in attention and working memory may exist in a certain group of women treated with chemotherapy for breast cancer.

Potential mechanisms by which chemotherapeutic agents could impair cognitive function have been proposed including direct neurotoxic damage associated with demyelination, secondary cytokine responses, increased apoptosis and DNA damage through increases in oxidative stress (Aluise et al., 2010; Azim, de Azambuja, Colozza, Bines, & Piccart, 2011; Konat et al., 2008; Liedke et al., 2009; Seigers et al., 2009; Tangpong et al., 2007; Wigmore et al., 2010). However, recently published prospective studies have failed to find evidence of cognitive deficits induced by chemotherapy (Hermelink et al., 2007; Reid-Arndt et al., 2010; Stewart et al., 2008). In a longitudinal study, cognitive decline was found in 34% of breast cancer survivors (n = 50) while more than half of the sample showed improved cognitive function four weeks after chemotherapy as compared to baseline assessment prior to chemotherapy (Shilling et al., 2005). These findings propose that it is needed to identify which cognitive domain is affected by chemotherapy and which factors are associated with cognitive deficits in order to examine the putative association between chemotherapy and cognitive deficits. In this section, a systematic review of chemotherapy-associated cognitive deficits is presented in terms of incidence, severity, neuro-cognitive domain characteristics, and effects of chemotherapeutic agents on cognitive function. Next, other potential predictors associated with cognitive deficits are reviewed.

Cognitive Deficits Following Adjuvant Chemotherapy

The majority of published studies examined the immediate or delayed effects of chemotherapy on cognitive function in women with breast cancer. In particular, acute cognitive deficits were assessed within approximately six months after completing the last cycle of chemotherapy. In order to identify cognitive deficits in breast cancer survivors receiving adjuvant chemotherapy, selected neuropsychological performance scores were compared between chemotherapy-treated breast cancer survivors and reference groups such as women without breast cancer or breast cancer survivors receiving other treatment (surgery, radiation, or hormonal therapy) without chemotherapy (Brezden et al., 2000; Jenkins et al., 2006; Schagen et al., 1999; Shilling et al., 2005; Wieneke & Dienst, 1995). Likewise, a dose-dependent impact of chemotherapy was evaluated in breast cancer survivors treated with standard adjuvant versus high-dose chemotherapy (Schagen et al., 2002; van Dam et al., 1998).

Acute cognitive deficits were found in approximately a third of breast cancer survivors within six months after the completion of adjuvant chemotherapy despite heterogeneity in types of chemotherapy regimens administered and cognitive measures used. An early investigation by Wieneke and Dienst (1995) showed that 75% of 28 early stage breast cancer survivors six months following chemotherapy regimens using 5-fluorouracil, methotrexate, and cyclophosphamide (CMF) or 5-fluorouracil, adriamycin, and cyclophosphamide (CAF) had moderate cognitive deficits on at least one neuropsychological test.

Similarly, four longitudinal studies found the existence of cognitive deficits in breast cancer patients one month following chemotherapy. In two studies published by the same research team, cognitive deficits were assessed in chemotherapy-treated breast cancer survivors four weeks after chemotherapy. When comparing neuropsychological performance scores assessed pre-chemotherapy with those measured four weeks post-chemotherapy, reduced cognitive function was reported in 20% to 34% of survivors treated with chemotherapy regimens including chemotherapeutic drugs such as 5-fluorouracil, cyclophosphamide, adriamycin or epirubicin, methotrexate, and paclitaxel or docetaxel. However, either a group of women receiving non-chemotherapy for breast cancer or a group of women without breast cancer also showed changes in cognitive function (Jenkins et al., 2006; Shilling et al., 2005). Unfortunately, these studies did not further examine a specific pattern of cognitive deficits for a subset of breast cancer patients who had pre-existing cognitive deficits found at the initial assessment point. Moreover, these studies failed to find significant predictors to explain pre- and post-chemotherapy cognitive deficits, except for commonly accepted factors such as age and education (Jenkins et al., 2006).

A recent study performed by Wefel et al (2010) is particularly important, as it confirmed neurotoxic effects of chemotherapy on cognitive function in women with early stage breast cancer. Forty two women were assessed for cognitive function before chemotherapy, during chemotherapy, and approximately two months and one year after the completion of chemotherapeutic regimens including 5-fluorouracil, adriamycin, and cyclophosphamide (FAC) with or without paclitaxel. Wefel et al (2010) reported that 24 participants (65%) had acute cognitive deficits during and shortly after chemotherapy. Importantly, all participants (n = 9) identified as having pre-chemotherapy cognitive deficits showed post-chemotherapy cognitive deficits as well. Further, approximately half of women who had unimpaired cognitive function prior to chemotherapy were classified as a group having post-chemotherapy cognitive deficits. These findings suggest that chemotherapy may not only induce the onset of cognitive deficits following chemotherapy but also increase the likelihood of failure to recover from pre-chemotherapy cognitive deficits (Wefel et al., 2010).

Similar incidence rates of cognitive deficits have been reported in other studies (Brezden et al., 2000; Schagen et al., 1999; van Dam et al., 1998). Van Dam and colleagues (1998) reported cognitive deficits within two years following treatment in 32% of 34 patients treated with a high-dose chemotherapy regimen including cyclophosphamide, thiotepa, and carboplatin and 17% of 36 patients treated with standard-dose 5-fluorouracil, epirubicin, and cyclophosphamide (CEF) regimen, while only 9% of 34 women treated without chemotherapy reported cognitive deficits. In another study performed by Schagen et al (1999), cognitive deficits were observed in 28% of 39 breast cancer survivors receiving standard-dose CMF chemotherapy as compared with 12% of 34 breast cancer survivors treated with surgery only approximately two years after surgery. A similar pattern of incidence in cognitive deficits was reported in a study performed by Brezden et al (2000). Approximately 48% of 31 breast cancer patients currently receiving the chemotherapeutic regimen of CMF or CEF and 50% of 40 participants treated with these same chemotherapeutic regimens had moderate or severe cognitive deficits as compared with 11.1% of 36 healthy controls. These findings suggest that long-term cognitive deficits in breast cancer survivors are likely to persist after chemotherapy when compared with other breast cancer survivors treated without chemotherapy and healthy women without breast cancer.

Perceived cognitive deficits were also reported in the short-term (four weeks) and long-term (1 to 10 years) in individuals following chemotherapy for breast cancer (Debess et al., 2009; Hermelink et al., 2007; Jansen et al., 2011; Jenkins et al., 2006; Quesnel et al., 2009). Four longitudinal studies showed that women treated with adjuvant chemotherapy experienced cognitive problems during or in the short-term after the completion of chemotherapy. In a study performed by Jenkins et al (2006), perceived cognitive problems in attention and executive function were assessed using the Cognitive Failures Questionnaire (CFQ) in 85 breast cancer patients scheduled for chemotherapy, 43 breast cancer patients scheduled for other adjuvant treatment (radiation therapy or hormonal therapy), and 49 healthy controls. Scores of the CFQ in chemotherapy-scheduled patients significantly increased between the initial assessment (prior to chemotherapy) and the second assessment (four weeks after chemotherapy), indicating that breast cancer patients experienced more cognitive problems during chemotherapy. In contrast, healthy women showed an unchanged pattern of perceived cognitive function across the entire assessment period (Jenkins, Atkins, & Fallowfield, 2007). In a study performed by Quesnel et al (2009), perceived cognitive function assessed by the CFQ was significantly reduced in 41 chemotherapy-treated breast cancer survivors three months after chemotherapy, as compared to their scores prior to chemotherapy with AT, ACT, or CEF regimens.

Hermelink et al (2007) reported similar findings from a study conducted in 101 women with early stage breast cancer. Perceived attention deficits experienced in daily life were assessed with two self-report measures, the Questionnaire of Experienced Attention Deficits and the Cognitive Function Scale of the European Organization for

Research and Treatment of Cancer Quality-of-life questionnaire, prior to neoadjuvant chemotherapy and immediately before the last cycle of neoadjuvant chemotherapy with combined epirubicin, paclitaxel, and cylophosphamide. Perceived cognitive problems significantly increased during chemotherapy (Hermelink et al., 2007).

In a recently published study performed by Jansen et al (2011), perceived effectiveness in attention and working memory function, which was measured by the Attentional Function Index (AFI), decreased immediately after completion of the AC or ACT chemotherapeutic regimen for breast cancer as compared with AFI scores prior to chemotherapy. After that, the AFI scores assessed six months after chemotherapy returned to the level of the baseline scores measured prior to chemotherapy (Jansen et al., 2011). However, when considering that breast cancer patients may already be vulnerable to cognitive deficits even prior to any treatment, improved AFI scores six months post-chemotherapy may not reflect recovery to optimal level of functioning (Cimprich, 1999; Cimprich et al., 2005). A recently published study supported this fact that women treated with surgery for breast cancer experienced lower effectiveness in cognitive function prior to chemotherapy. Debess et al (2009) showed that women receiving surgery for breast cancer reported lower scores on perceived attention and memory function prior to the start of any adjuvant treatment as compared to healthy controls. Thus, perceived deficits in attention and working memory may persist in women during and following chemotherapy for breast cancer.

Taken together, cognitive deficits have been reported in cross-sectional as well as prospective studies conducted in women following chemotherapy for early stage breast cancer. Overall, a review of these studies found acute cognitive deficits in 20% to 75% of women within six months after adjuvant chemotherapy for breast cancer. Similarly, perceived cognitive deficits were reported in chemotherapy-treated breast cancer survivors. However, these findings need to be interpreted with caution due to methodological heterogeneity such as varying types of chemotherapy administered, cognitive measures used, statistical definition for cognitive deficits, and types of control groups. Nevertheless, chemotherapy may be associated with cognitive deficits, decrease the likelihood of full recovery from pre-chemotherapy cognitive deficits, and lead to long-term cognitive deficits in women with breast cancer.

Characteristics of Cognitive Deficits

The nature of cognitive deficits has been described in an inconsistent manner up to date. In order to determine the neuro-cognitive characteristics of cognitive deficits following chemotherapy, cognitive deficits were reviewed in terms of severity and domain-specific characteristics.

Severity of Cognitive Deficits

With regard to the severity of cognitive deficits in chemotherapy-treated breast cancer survivors, two meta-analysis studies were conducted to determine the severity of chemotherapy-associated cognitive deficits defined by effect size of general or domain-specific deficits (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Stewart et al., 2006). In a study performed by Falleti et al (2005), five cross-sectional studies were included to evaluate the effect size of cognitive deficits measured with neuropsychological tests for attention, memory, motor function, executive function, spatial ability, and language. Across these studies, 87.3% of all participants were treated with various chemotherapeutic regimens with 5-fluorouracil as a part of adjuvant chemotherapy. Participants were assessed approximately 3 years following adjuvant chemotherapy, ranging from six months to 10 years post-chemotherapy. Cohen's *d* values for six domains of cognitive deficits were reported ranging from -0.03 and -0.51 of a standard deviation below matched controls, specifically, motor function (d = -0.51), spatial ability (d = -0.48), language (d = -0.41), memory (d = -0.26), executive function (d = -0.18), and attention (d = -0.03). Of these six domains analyzed, three most affected domains were included to examine the general cognitive deficits. The effects sizes of overall deficits including memory, motor function, and executive function ranged from -0.07 to -0.50. The negative effect size indicates poorer cognitive function as compared to control groups. These findings suggest that the impact of adjuvant chemotherapy on cognitive function is mild to moderate and can persist even 10 years following treatment for breast cancer.

In contrast, cognitive improvement was also reported in only one longitudinal study which was included in the meta-analysis study. Effect sizes ranged from 0.11 to 1.09, indicating that cognitive improvement occurred from the beginning of chemotherapy to short-term and even longer term of one year following chemotherapy for breast cancer (Falleti et al., 2005). However, the longitudinal study did not include other groups for comparison of changes in cognitive function over time. Thus, whether chemotherapy affects cognitive function over time needs to be carefully interpreted.

Similar findings were reported in the other meta-analysis study in which six cross-sectional and one prospective study were analyzed to determine the association between adjuvant chemotherapy for breast cancer and cognitive deficits (Stewart et al., 2006). Hedge's *d* values for domain-specific cognitive deficits ranged from -0.13 to -0.37. These results suggest that women treated with chemotherapy for breast cancer had poorer cognitive function as compared to control groups, including age- and education-matched control groups. The average overall effect size was -0.26 which was in the small to moderate range. The largest differences were found in language (*d* = -0.37), and short-term memory (*d* = -0.31).

These two meta-analysis studies commonly showed the mild to moderate impact of chemotherapy for breast cancer on general cognitive function. Specifically, women treated with adjuvant chemotherapy for breast cancer had poorer cognitive function than control groups, and subtle but diffuse changes in cognitive function were revealed. However, these studies introduced differing cognitive domains with impaired function probably due to heterogeneous methods used to measure cognitive function. For example, one study showed that chemotherapy-treated breast cancer survivors had poorer scores in motor function, spatial ability, and language (Falleti et al., 2005), while another study reported poorer scores in language and short-term memory (Stewart et al., 2006). Domain-specific deficit effect size seems to be determined depending on the sensitivity of each neuropsychological measure administered for assessing a certain cognitive domain. In this regard, domain-specific effect sizes of cognitive deficits should be interpreted with caution.

Domain-Specific Cognitive Deficits

Domain-specific cognitive deficits were reviewed in 22 studies which examined each domain of cognitive function in women treated with chemotherapy for early stage breast cancer (see Table 1). Specifically, nine cross sectional studies following adjuvant chemotherapy and 13 longitudinal studies including post-chemotherapy assessment were included. Overall, deficits in attention and working memory function (short-term storage and manipulation) were observed in both cross-sectional and longitudinal studies. Specifically, cognitive deficits following chemotherapy for breast cancer were reported in the domains of selective attention (47%), speed of information processing/psychomotor function (43%), verbal, visual, or spatial memory (40%, 53%, 38% respectively), and information manipulation including learning, verbal ability, and other executive functions (38%, 17%, 33% respectively). Recent neuroimaging studies reported structural and functional changes in the brain associated with chemotherapy, which are consistent with domain-specific cognitive deficits presented in Table 1. In a study performed by Inagaki et al (2007), voxel-based morphometry was used to evaluate the impact of adjuvant chemotherapy on regional volume in the brain. This method allows the examination of focal neuroanatomical volume differences in the brain among participants. Breast cancer survivors were scanned at about one year or three years following the initial surgery and compared with age-matched healthy women without breast cancer. Approximately half of all survivors were treated with adjuvant chemotherapy and others were treated only with local therapy. Chemotherapy-treated survivors (n = 51) at a year after surgery had reduced gray and white matter, specifically in the right prefrontal and parahippocampal gyrus, bilateral middle frontal gyrus, left parahippocampal gyrus, left precuneous, and right anterior cingulate gyrus, when compared with breast cancer survivors treated with local therapy (n = 54) and healthy women (n = 55). Reductions in these regional volumes were significantly correlated with poor performance on attention and visual working memory tasks (Inagaki et al., 2007). No significant differences in regional volumes were found at three years following chemotherapy.

Table 1

Domain-Specific Cognitive Deficits in Women with Breast Cancer

Domains	Attention		Working memory					
	Selective attention	Speed of information	Short-term storage			Data manipulation		
			Verbal	Visual	Spatial	Learning	Verbal ability	Complex performance
Ahles et al (2002)[C]	○	◉	○	○	○	○	○	
Bender et al (2000)[L]		○	◉	◉				○
Castellon et al (2004)[C]	○	○	○	◉	◉	○	◉	
Cimprich & Ronis (2001)[L]	◉							
Debess et al (2010)[L]						○		○
Donovan et al (2005)[C]	○		○	○			○	○
Hermelink et al (2007)[L]	◉	◉	◉					◉
Jansen et al (2011)[L]	◉		○	◉	◉		○	○
Jenkins et al (2006)[L]		○	◉	◉				○
Jim et al (2009)[C]	○		◉	◉				◉
Mehlsen et al (2009)[L]	○	○	○	○	○		○	○
Mehnert et al (2007)[C]	○		○	○				○
Noal et al (2011)[L]			○					○
Quesnel et al (2009)[L]	○	○	◉	○			◉	○
Reid-Arndt et al (2010)[L]	○	○	○				○	
Schagen et al (1999)[C]	◉	◉	○	◉			◉	◉
Scherwath et al (2006)[C]	◉		○	○				○
Stewart et al (2008)[L]		○	○	○	○	○	○	◉
Van Dam et al (1998)[C]	◉	◉	○	◉	○		○	○
Vearncombe et al (2009)[L]	○	○	◉	○		○		○
Wefel et al (2004)[L]	◉	◉	◉	◉	○	◉		◉
Wineke & Dienst (1995)[C]	◉	◉	◉	◉	◉		◉	◉
	8/17 (47%)	6/14 (43%)	8/20 (40%)	9/17 (53%)	3/8 (38%)	1/6 (17%)	4/11 (36%)	6/18 (33%)

Note. ○ indicates specific domains measured; ◉ indicates specific domain which showed reduced neuropsychological performance; #/# = the number of articles which showed significant findings for each domain/the number of articles which assess each domain; ( ) = percents of deficits in each cognitive domain assessed.

[C] indicates cross sectional study. [L] indicates longitudinal study.

Furthermore, Deprez et al (2011) examined the integrity of cerebral white matter in breast cancer survivors (n = 17) who received the CEF regimen with or without taxol within six months before testing with magnetic resonance diffusion tensor imaging (DTI). DTI is a method which can show connections between brain regions through producing brain tissue images weighted with the local microstructural characteristics of water diffusion. Healthy women (n = 18) and breast cancer survivors treated with only local treatment (n = 10) were recruited as comparison groups. Chemotherapy-treated survivors had decreased white matter integrity in frontal and temporal white matter tracts as compared to the two comparison groups. The decreased white matter integrity was significantly associated with neuropsychological performance on attention and speed of information/psychomotor function (Deprez et al., 2011).

Similarly, McDonald et al (2010) reported altered gray matter density approximately one month following chemotherapy as compared with that prior to any adjuvant treatment. Voxel-based morphometry was used to compare changes in gray matter density between chemotherapy-scheduled breast cancer patients (n = 17) and two comparison groups, nonchemotherapy-treated breast cancer patients (n = 12) and demographically matched healthy women (n = 18) over time. Chemotherapy-treated breast cancer survivors showed decreased gray matter density in bilateral frontal, temporal, and cerebellar regions and right thalamus, while the other two comparison groups showed insignificant changes in gray matter density over time. Further, at one year following chemotherapy some gray matter changes did not return to the level prior to chemotherapy (McDonald, Conroy, Ahles, West, & Saykin, 2010). Thus, these aforementioned findings suggest that chemotherapy can affect cortical-subcortical circuitry engaged in performing cognitive tests requiring attention and working memory.

Other studies using functional magnetic resonance imaging (fMRI) showed the associations between alterations in brain activation and chemotherapy. Saykin et al (2006) examined regional brain activation patterns during a verbal working memory task in women scheduled for chemotherapy for breast cancer (n = 15) prior to and one month after chemotherapy. Both brain activation patterns and associated behavioral data were compared with those in age and education-matched comparison groups (local therapy-treated breast cancer patients, n = 7; healthy women, n = 7). Interestingly, chemotherapy-treated women showed greater activation in bilateral parietal and medial frontal regions following treatment, while two comparison groups exhibited increased activation in the bilateral anterior frontal regions at the similar interval. The findings suggest that less activation in frontal regions can be an indicator of deficits in brain circuitry of verbal working memory (Saykin et al., 2006).

A similar finding was reported in two other fMRI studies. A study was conducted to compare neurocogntive responses between twins, one twin without breast cancer and the other twin with breast cancer approximately two years following chemotherapy. This study showed consistent relationships among self-report, neurocognitive responses, and functional changes evaluated with imaging techniques in the twin experiencing cognitive difficulties associated with chemotherapy for breast cancer. Specifically, the chemotherapy-treated twin showed increased recruitment of verbal working memory brain regions, such as bifrontal and biparietal areas, in response to increasing demand on a verbal working memory test, when compared with her healthy twin (Ferguson, McDonald et al., 2007). The other study performed by de Ruiter et al (2011) showed decreased activation in brain regions relating to active manipulation of working memory and visuospatial attention in women approximately 10 years following high-dose chemotherapy for breast cancer. The chemotherapy-treated group (n = 19) had significantly lower accuracy scores on executive function tests and decreased activation in left dorsolateral prefrontal cortex and bilateral posterior parietal cortex than the healthy control group (n = 15). These findings suggest that chemotherapy may contribute to hyporesponsiveness in these brain regions reflected in impaired attention and working memory function (de Ruiter et al., 2011).

Summary

Domain-specific deficits may be overlooked in women treated with chemotherapy for breast cancer due to a small effect size secondary to heterogeneous methods used to assess each cognitive domain. Nevertheless, chemotherapy-associated cognitive deficits showed a tendency toward domain-specific problems, specifically deficits in attention and working memory. Deficits in attention and working memory appear to be consistently accompanied by altered brain structure and function, which may lead to impaired behavioral responses in executive functioning and other aspects of daily life.

Impacts of Chemotherapeutic Agents on Cognitive Function

Adjuvant chemotherapy contributes to an increase in the survival rate of breast cancer patients; however, this treatment has been associated with neurological complications observed in chemotherapy-treated cancer survivors (Weiss, 2008). Neurological manifestations of chemotherapy-associated neurotoxicity in the central nervous system (CNS) include encephalopathy, cerebellar dysfunction, seizures, retinopathy, cerebral venous thrombosis, extrapyramidal reactons, psychiatric symptoms and cognitive deficits (Lachkar, Bota, Nouvet, & Thiberville, 2006; Minisini, Pauletto, Andreetta, Bergonzi, & Fasola, 2008; Nieto et al., 1999; Ziske et al., 2002). Post-chemotherapy cognitive deficits have been investigated in individuals receiving a specific group of chemotherapeutic agents such as 5-fluouracil, doxorubicin, cyclophospahmide, methotrexate, and paclitaxel (Bender et al., 2006; Brezden et al., 2000; Deprez et al., 2011; Jenkins et al., 2006; Kreukels et al., 2005; Nagar, 2010; Schagen et al., 1999; Shilling et al., 2005; van Dam et al., 1998; Wefel et al., 2004; Wieneke & Dienst, 1995). Also, post-chemotherapy cognitive deficits in breast cancer survivors have been explored with prelinical models in order to examine whether there was the potential detrimental impact of chemotherapeutic agents on brain structure and function. Overall, preclinical research suggests chemotherapy-induced CNS injury as a possible candidate mechanism underlying cognitive deficits in animals receiving 5-fluouracil, doxorubicin, cyclophosphamide, methotraxate, or paclitaxol (Aluise et al., 2010; Azim et al., 2011; Han et al., 2008; Jang et al., 2008; Joshi et al., 2010; Konat et al., 2008; Liedke et al., 2009; Seigers & Fardell, 2011; Seigers et al., 2009; Tangpong et al., 2007; Wigmore et al., 2010). These studies indicated that chemotherapy was associated with decreased neurogenesis, increased apoptosis, neurotoxic damages associated with demyelination, DNA damage secondary to oxidative stress and cytokine responses, white matter injury, and reduced brain blood flow and metabolism. Although continued research is still needed to reduce the research gaps between animal and human models, the proposed potential mechanisms raise the possibility of neurotoxic effects of chemotherapy leading to reduced cognitive function observed.

CHAPTER III

POTENTIAL COVARIATES OF COGNITIVE FUNCTION

It is important to investigate the effect of physical symptoms and psychological distress on cognitive function in women with breast cancer because chemotherapy is not the only predictor to fully explain the phenomenon of cognitive deficits. Studies by Cimprich et al (2005) provided significant evidence that all cognitive deficits cannot be explained as neurotoxic effects of chemotherapy for breast cancer because cognitive deficits were observed even before any treatment (Cimprich et al., 2010; Cimprich et al., 2005). Many studies investigating cognitive difficulties in women with breast cancer have evaluated the possible correlation between cognitive deficits and physical symptoms (fatigue, treatment-induced symptoms), psychological distress (anxiety and depressed mood), and individual characteristics (age, education, menopause status, and presence of comorbidity) following adjuvant chemotherapy (Bender et al., 2006; Castellon et al., 2004; Cimprich, 1992a; Debess et al., 2009; Downie et al., 2006; Jansen et al., 2011; L. S. Kim et al., 2008; Mehnert et al., 2007; Myers, 2009; Reid-Arndt et al., 2010; Schagen et al., 2002; Shilling et al., 2005; van Dam et al., 1998; Vearncombe et al., 2009). Some studies have reported the detrimental effects of physical symptoms and psychological distress on cognitive function defined by neuropsychological tasks or self-report measures of functioning (Bender et al., 2006; Castellon et al., 2004; L. S. Kim et al., 2008; Mehnert et al., 2007; Reid-Arndt et al., 2010; Schagen et al., 2002; van Dam et al., 1998; Vearncombe et al., 2009), while others failed to find any significant association of covariates or did not examine the association in chemotherapy-treated breast cancer patients and survivors (Jenkins et al., 2006; Jim et al., 2009; Noal et al., 2011; Scherwath et al., 2006; Stewart et al., 2008; Wefel et al., 2010; Wieneke & Dienst, 1995).

Methodological limitations are likely to contribute to the variation of findings. One limitation is that some of the studies listed above did not specifically explore the impact of physical symptoms and psychological distress on domain-specific cognitive deficits. For example, when examining the association between fatigue and general cognitive function, a significant association was not found in women with breast cancer. However, when investigating the effect of fatigue on domain-specific cognitive function, it was found that greater fatigue was significantly associated with impairment in working memory in women treated with chemotherapy for breast cancer (Mehnert et al., 2007). This finding provides the insight that physical symptoms and psychological distress can selectively influence deficits in specific cognitive functions that cannot be observed when assessing general cognitive deficits. Another limitation is that most of the studies selected only a few of the aforementioned factors (treatment-induced symptoms, psychological distress, age, education, menopause status, and presence of comorbidity). Fatigue, anxiety, and depression have been frequently studied to determine the associations with cognitive deficits, while few studies have examined treatment-related symptom distress in women treated for breast cancer (Bender et al., 2006; Castellon et al., 2004; Cimprich, 1992a, 1993; Debess et al., 2009; L. S. Kim et al., 2008; Mehnert et al., 2007; Reid-Arndt et al., 2010; Schagen et al., 2002; Vearncombe et al., 2009). Further, there were no studies published to explore the impact of sleep problems on neuropsychological performance following adjuvant chemotherapy for breast cancer. Due to insufficient investigation of the effects of potential covariates on cognitive deficits, inconsistent findings of chemotherapy-associated cognitive deficits are more likely to be reported. To elucidate cognitive deficits in chemotherapy-treated breast cancer patients and survivors, the potential covariates of cognitive deficits need to be included in further research. Thus, in this section of effects of physical symptoms and psychological distress, fatigue, anxiety and depression, symptom distress, sleep disturbance, and demographic and health-related characteristics on cognitive function will be reviewed.

Fatigue

Fatigue has been the most frequently measured factor potentially influencing cognitive deficits in women with breast cancer. However, only a few studies explicitly reported an association between fatigue and cognitive performance in women treated for breast cancer. Specifically, three studies examined the association between cognitive deficits and perceived fatigue (Mehnert et al., 2007; Reid-Arndt et al., 2010; Vearncombe et al., 2009). First, Mehnert et al (2007) assessed cognitive function in 47 breast cancer survivors treated with standard-dose (n = 23) or high-dose chemotherapy (n = 24) and 29 early stage breast cancer patients receiving radiation therapy. They found that working memory performance was significantly correlated with general fatigue and mental fatigue in the group of women receiving standard-dose chemotherapy for breast cancer (Mehnert et al., 2007).

In a study performed by Vearncombe et al (2009), a significant association between fatigue and cognitive test performance was found in 136 women receiving chemotherapy for breast cancer at two time points: at baseline assessment (after surgery but prior to starting adjuvant chemotherapy) and one month following treatment. Fatigue measured by the Functional Assessment of Chronic Illness Therapy-Fatigue scale was significantly correlated with changes in cognitive function, especially attention and executive function. In addition, they found a significant relationship between fatigue and scores on the Controlled Oral Word Association Test which is used to assess frontal cortex-oriented cognitive function such as working memory (Lezak, 2004). This result indicated that greater fatigue can be significantly correlated with deficits in attention and working memory (Vearncombe et al., 2009).

The final study by Reid-Arndt et al (2010) showed consistent findings that fatigue continued to negatively affect cognitive performance requiring directed attention, short-term memory, and even long-term memory function over time. Fatigue were assessed by the fatigue subscale of the Profile of Mood States-Short Form (POMS) and cognitive function was assessed using six neuropsychological tests in chemotherapy-treated breast cancer survivors at six months (n = 39) and one year (n = 33) following treatment. Scores on POMS fatigue subscale were significantly correlated with the Stroop test performance requiring response inhibition in breast cancer survivors at six months after chemotherapy. Furthermore, significant negative correlations were found between fatigue scores and neuropsychological test performance requiring short-term (WMS-III logical memory test) and long-term memory (WMS-III logical memory test and Rey auditory verbal learning test) for recalling verbal information at one year post-chemotherapy (Reid-Arndt et al., 2010). Accordingly, these three studies commonly suggest that cognitive performance in attention and working memory decreased with increased fatigue in chemotherapy-treated breast cancer survivors.

A similar finding was reported in a meta-analysis study of cognitive deficits in people with chronic fatigue syndrome. Although there are no studies exploring similarities and differences between chronic fatigue syndrome and chemotherapy-associated fatigue, it is clear that perceived fatigue can be significantly related to the deficits in performing tasks requiring attention and working memory. Individuals with chronic fatigue syndrome showed significant decrease in attention, memory, and executive function as compared to healthy controls. In addition, they had more difficulties in performing even simple neuropsychological tasks requiring directed attention (Cockshell & Mathias, 2010).

Taken together, aforementioned studies reported an important association between fatigue and domain-specific cognitive deficits. Although there are some methodological limitations including a small sample size and sensitivity of tests used to measure domain-specific cognitive function, it is evident that greater fatigue was significantly related to decreased performance in attention and memory and, thus, people are more likely to have trouble in performing daily activities and occupational tasks requiring attention and working memory effort as they become fatigued.

Depression and Anxiety

Depression and anxiety have been suggested as forms of psychological distress which may affect objective performance and perceived effectiveness in cognitive functioning in chemotherapy-treated breast cancer survivors (Bender et al., 2006; Castellon et al., 2004; Reid-Arndt et al., 2010; Schagen et al., 2002; van Dam et al., 1998; Vearncombe et al., 2009). Previous studies found a significant association between depressed mood and cognitive function in women treated with adjuvant chemotherapy for breast cancer. A study performed by Schagen et al (2002) showed the impact of psychological distress on cognitive deficits approximately 4 years following chemotherapy. Depressed mood was significantly related to cognitive impairment in women treated with CTC (cyclophosphamide, thiotepa, and carboplatin) or FEC (5-fluorouracil, epirubicin, and cyclophosphamide) chemotherapy while anxiety was not found to be a significant predictor. The impact of psychological distress on domain-specific cognitive function was not reported in this study (Schagen et al., 2002).

Similarly, two other studies showed the effect of depressed mood on cognitive function. In a study performed by Bender et al (2006), depressed mood measured by the Beck Depression Inventory (BDI), was significantly correlated with verbal working memory defined by scores on the Four Word Short Term Memory Test, indicating that depressed breast cancer participants have a decreased ability to immediately retrieve verbal information (Bender et al., 2006). Another study also showed a continued impact of depression measured by the BDI on cognitive test performance requiring response inhibition (Stroop test) and immediate retrieval of verbal information (WMS-III logical memory test) in women treated with chemotherapy for breast cancer (Reid-Arndt et al., 2010).

In contrast to the above findings, a study by Vearncombe et al (2009) found that both anxiety and depression scores were important factors of cognitive decline over the treatment period. Anxiety and depression were measured by the Hospital Anxiety and Depression Scale. Increased level of anxiety during chemotherapy was found to be an important predictor for decline in general cognitive function. However, they did not report which cognitive domain was specifically affected by anxiety. Depression scores were significantly associated with changes in scores on a working memory test. Overall findings suggest that psychological distress is significantly correlated with chemotherapy-associated cognitive deficits.

The effect of psychological distress on attention and working memory was consistently reported in a meta-analysis of severity of depressed mood and cognitive performance in individuals with major or minor depression diagnosed according to the DSM-III/DSM-V (McDermott & Ebmeier, 2009). Although breast cancer patients and survivors were not the target sample in this study, similar findings were reported; greater depressed mood was associated with lower cognitive test performance in verbal memory (short-term and long-term), attention, and working memory. A study using Positron-Emission Tomography (PET scan) highlighted the fact that depressed mood in breast cancer patients can negatively impact attention. The severity of depressed mood was measured by the BDI. During a PET scan, attention capacity was assessed by the Sustained Attention to Response Task (SART) in 12 patients with clinically diagnosed depressive symptoms and 12 patients without clinically depressed mood. Depressed breast cancer patients showed lower behavioral performance on the SART than patients without depression. Higher level of depressed mood was significantly correlated with worse behavioral performance on the attention task and with a reduced glucose metabolism in bilateral dorsolateral prefrontal cortices (L. S. Kim et al., 2008). These results suggest that depressed mood in breast cancer patients might be associated with deficits in prefrontal-dependent cognitive function.

Consistently, psychological distress has been significantly correlated with self-report of cognitive problems in women treated with chemotherapy (Bender et al., 2006;

Castellon et al., 2004; Reid-Arndt et al., 2010; van Dam et al., 1998). Furthermore, the impact of psychological distress on perceived cognitive function has been reported even prior to the start of any adjuvant treatment (Cimprich, 1999; Cimprich et al., 2005; Debess et al., 2009).

Taken together, higher level of psychological distress has been associated with poorer cognitive test performance and lower effectiveness in attention and working memory in women with breast cancer. However, most studies failed to show that psychological distress was simultaneously correlated with both actual performance and perceived cognitive function. In order to explore the true effects of psychological distress on actual performance on tasks and perceived cognitive function, it is necessary to select sensitive measures that are specifically designed to assess targeted domains of cognitive function.

Sleep Difficulty

Sleep difficulty has been reported as a common problem in breast cancer patients and survivors across countries and ethnic groups (Bower, 2008; Kuo, Chiu, Liao, & Hwang, 2006). The incidence of subjective sleep disturbance ranged from 20% to 70% in western women treated for breast cancer (Enderlin et al., 2010; Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002; Savard, Simard, Blanchet, Ivers, & Morin, 2001). So far, no studies have been published identifying the effect of sleep difficulty on cognitive function over the period of breast cancer diagnosis and its treatment. Recently three published studies in noncancer populations described neurocognitive consequences of sleep problems as follows: 1) insufficient sleep causes slowing of response speed in performing tasks of attention (simple attention, sustained attention, and complex attention) and working memory; 2) insufficient sleep can lead to an increase in the number and duration of attentional lapses even in performing simple tasks; 3) insufficient sleep is associated with reduced activation in a network of brain regions (e.g., frontoparietal cortices) for attention and working memory function; and 4) chronic sleep difficulty can lead to cumulative deficits in cognitive functions even in healthy adults (Goel, Rao, Durmer, & Dinges, 2009; Killgore, 2010; Lim & Dinges, 2010). Taken together, there is a general agreement that sleep difficulty can negatively influence effective functioning in domains of attention and working memory. However, little is known about the negative consequences of sleep difficulty on these domains in women treated with chemotherapy for breast cancer. Thus, further research is needed to explore whether cognitive deficits are negatively influenced by sleep difficulty following chemotherapy.

Symptom Distress

Treatment-related symptom distress can negatively influence daily functioning and quality of life in women with breast cancer (Janz et al., 2007; Kim 2009; Park et al., 2009). Only a few studies, however, have been published to examine the association between symptom distress and cognitive deficits in women treated for breast cancer. Specifically, a higher number of symptoms was associated with lower effectiveness in performing tasks requiring attention and working memory (Cimprich, 1999). Also, greater symptom distress was significantly correlated with poorer performance and lower effectiveness in attention and working memory function (Cimprich et al., 2005). Until now, there are no published studies to examine the effect of symptom distress on cognitive deficits following chemotherapy for breast cancer. However, when considering the above findings, it is likely that symptom distress may play an important role in cognitive deficits following adjuvant chemotherapy.

Individual Characteristics

Age and education are frequently reported predictors of cognitive function in women with breast cancer (Ahles et al., 2002; Cimprich & Ronis, 2001; Cimprich et al., 2005; Schagen et al., 2002). Aging is generally associated with a loss of cognitive capacity and education has been correlated with better performance for attention and working memory (Lezak, 2004). Numerous studies have showed that the overall performance on cognitive tests was negatively correlated with getting older and lower educational level. Accordingly, age and education need to be considered as potential covariates in any study of cognitive function. Two health-related factors including the presence of other health problems and menopause status are suggested as potential covariates of cognitive deficits. Presence of comorbidity was found to be significantly associated with lower scores on tasks of attention and working memory but not correlated with scores on the subjective measure of cognitive function (Cimprich et al., 2005). Menopausal status (pre- versus post-menopause) was associated with scores on objective measures of attention and working memory (Cimprich et al., 2005), with greater menopausal symptoms being significantly associated with cognitive deficits in women treated for breast cancer (Downie et al., 2006; Jansen et al., 2011; Shilling et al., 2005).

Summary

Cognitive deficits in women treated for breast cancer cannot be solely explained by adjuvant chemotherapy. Attention and working memory have been known to be affected by physical symptoms, psychological distress, and individual characteristics.

Specifically, effects of fatigue, anxiety and depression, age, years of education, and menopausal status on attention and working memory function were investigated in chemotherapy-treated breast cancer survivors and have found to be significant covariates. The effects of symptom distress, sleep difficulty, and presence of comorbidity were not examined following chemotherapy for breast cancer. To elucidate cognitive deficits in chemotherapy-treated breast cancer patients and survivors, the potential covariates of cognitive deficits need to be included in further research.

CHAPTER IV

KOREAN CULTURE AND BREAST CANCER

Culture is a coherent, familiar, and shared cognitive framework that helps individuals make sense of surroundings and deal with uncertain situations (Kaplan & Kaplan, 1989; Markus & Kitayama, 1991). Generally, people are likely to understand their worlds through their own ‘cultural window’, choose strategies learned under the cultural predispositions, and cope with various difficulties in culturally preferred ways (Kaplan, & Kaplan, 1989). When people are confronted with stressful situations, culture substantially influences overall cognitive representation as well as processes that hold in mental function including attention, memory, and executive control (Hedden et al., 2008; Kitayama, Mesquita, & Karasawa, 2006; Markus et al., 1996; Nisbett et al., 2001). Specifically, people raised in collectivist culture predominantly show a tendency of holistic thinking as compared with those in individualistic culture which is manifested as analytic thinking (Markus & Kitayama, 1991; Nisbett & Masuda, 2003; Nisbett & Miyamoto, 2005; Nisbett et al., 2001). Holistic thinking is a mode of thought which focuses on the relationship between an object and the surrounding context, emphasizes the importance of harmony with nature, and is predominantly associated with interdependence in defining a self as a part of a whole. In this regard, East Asian people tend more or less toward the typical characteristics of collectivism and the associated preferences in cognitive and social processing (Ketay, Aron, & Hedden, 2009).

A generalization from existing literature regarding cultural influences on cognition suggest that cultural ideas and practices encourage the predominance of a culturally preferred way of thinking, holistic processing favored by collectivism versus analytic processing favored by individualism (Goh & Park, 2009; Ketay et al., 2009). A study performed by Hedden et al (2008) showed the impact of cultural differences on attentional system between East Asian and American young adults. Participants appeared to exert greater attentional effort in performing culturally nonpreferred attentional tasks than culturally preferred attentional tasks. This finding related to a greater contextual relationship-focused bias in East Asians and a more object-focused bias in Westerners indicated that culture-driven bias can modulate cognitive processes requiring attentional effort (Hedden et al., 2008). Furthermore, Goh et al (2007) suggested that older adults were likely to be more susceptible to their cultural bias; especially, old East Asians showed a maintained bias for contextual relationship-focused bias than young East Asians. That is, cultural effects get stronger in age as cultural experience increases (Goh et al., 2007). Accordingly, considering that cultural influences on attentional effort occur in individuals with different cultural contexts in different ways, and a majority of Korean breast cancer patients are middle-aged women, women with breast cancer may show greater cognitive effort in performing culturally incompatible tasks requiring attentional control.

Despite such growing research on cultural effects on cognitive function, to date there have been no published studies to determine whether Korean culture affects cognitive function, especially attention and working memory, in Korean women with breast cancer. Further, there is lack of information on identifying which characteristics in

Korean culture act as cognitive demand which may lead to deficits in attention and working memory following breast cancer diagnosis and its treatment. Only a few studies that have focused on Korean women's responses to their cancer diagnosis and treatment implied that potential cognitive demands seem to be associated with Confucian beliefs and practices focusing on interdependence and connectedness, self-restraint in sustaining interpersonal harmony, and gender-divided cultural expectations for women's role performance such as child-rearing and housework tasks (Ashing-Giwa et al., 2004; Im et al., 2002). In particular, the aforementioned cultural characteristics may come into conflict with illness-induced demands and hinder effective functioning in their everyday lives when Korean women need to take on a new role of caring for themselves and meeting their obligation related to cancer diagnosis and treatment.

It is important to understand Korean women's responses related to breast cancer and its treatment because this understanding will allow for the identification of cultural characteristics linked to cognitive burdens affecting cognitive health and quality of life in Korean women with breast cancer. As such, culture-specific representation and individual responses related to breast cancer will be reviewed below.

Influences of Korean Culture on Representation of Breast Cancer

Meanings of the Female Breast

The interpretive understandings, which a certain culture holds, generate individuals' perceptions and reactions to their everyday lives (Strauss & Quinn, 1994). In this sense, culturally accepted meaning, values, and behaviors offer a context in which individuals make sense of objects or events including women's health and illness (Suh, 2006). Perceptions of Korean women's health and illness are shaped by their understanding of Neo-Confucianism (Lee, 1996). In particular, the meaning of women's health seems to be restricted to their reproductive function, a main role of women in traditional society. Similarly, their illness is understood as a part of life predestined by the Creator of the universe (Ashing-Giwa et al., 2004; Park, 2003). Thus, this metaphysical understanding regarding women's health and illness may crucially influence women's perceptions concerning the female breast, breast cancer, and breast cancer-related issues.

In Korean culture, the female breast is a symbol of maternity rather than feminity (Jun, 1994; Kim, 1998; Lee, Tripp-Reimer, Miller, Sadler, & Lee, 2007; Suh, 2006). Korean women have considered the female breast as the conceptual icon of mothering, motherhood, breast feeding, and the relationship between mother and baby (Lee et al., 2007; Suh, 2006). Moreover, on the basis of their child rearing experience, they believe that the female breast works as a mediator between a woman and her loved family members, indicating that the cognitive meaning of the female breast tightly corresponds with aspects of Korean culture, such as Neo-Confucianism and familism, which emphasizes both women's reproductive and productive functions (Im, 2000; Suh, 2006; Suh, 2008).

The culture-specific meaning of the female breast is consistent with the literal meaning of Korean terms for the breast. One of the Korean terms is *you-bang*, which means "room for mother's milk." The other term for breast is *ab-ga-sum*, which means the frontal part of the chest in the female body. *Ab-ga-sum* is an indirect and modest label in the Confucian manner, which includes social taboos regarding using the word breast to express feminity (Suh, 2006). More specifically, feminine beauty regarding the breasts is not openly discussed in the aesthetic perspective because Koreans are still aware that to openly talk about their breasts is a shameful behavior (Lee et al., 2007; Suh, 2006).

Although a purely aesthetic meaning of the female breast has not been openly shaped owing to the asceticism of Confucianism, the female breast is indistinctively defined as a sort of something including good meanings (such as generosity, good luck, and good things from the Creator of the universe). In addition, it is reported that culture-specific aesthetics related to the female breast were shaped by the influence of collectivism which emphasizes relational harmony (Y. I. Kim, 1998; Lee, 2001; Suh, 2006). For example, Korean women make much account of balance in size (Suh, 2006). That is, their preference of their breasts is not for size itself but the proportional size of breasts to their bodies. Accordingly, it is possible that aesthetic perspective about female breast is thought to be consistent with collectivistic values such as relational harmony.

Meanings of Breast Cancer and its Treatment

Meanings of breast cancer diagnosis and treatment in Korean women with breast cancer seem to be somewhat biased by myth and collectivistic influences. In particular, cancer etiology-related myth still remains among breast cancer survivors in even modern Korean society. Etiological myths about breast cancer were reported in Korean survivors, especially older and less educated women (Ashing-Giwa et al., 2004). They mentioned that main etiologies of breast cancer were fate, divine punishment, and psychological distress (Ashing-Giwa et al., 2004; Im et al., 2002; Jung, 1991; Park, 2003; Shin, 1995; Suh, 2008). In the fatalistic perspective, breast cancer patients were prone to accept their cancer diagnosis as a “given” terrible fate because they believed that having cancer was part of a providential plan. In addition, divine punishment was perceived as a potential cause of breast cancer. Some Korean breast cancer survivors considered their illness as the outcome offered in reliance on God's judgment about their slips and blunders. The last etiological myth was psychological distress. Korean survivors reported breast cancer may occur as a consequence of worries, anger, or emotional conflicts. Especially, they pointed out emotional disturbance caused by relational conflicts with husbands or in-laws, indicating that a main exogenous stressor from which breast cancer arises is familial conflict with the family of her husband.

Responses Regarding Breast Cancer and Its Treatment

Korean women tend to have greater self-blame tendency in relation to having breast cancer diagnosis. Blaming oneself is particularly considered as a potential cognitive burden which can interfere with successful adjustment following cancer diagnosis and treatment. Self-blame is involved in a way that women used to explain the cause of breast cancer (Bennett, Compas, Beckjord, & Glinder, 2005). Korean women with breast cancer addressed cause of their illness as a consequence of their past 'bad' behaviors such as the failure of managing relational conflicts. For example, they reported that breast cancer was caused by the failure of ignoring psychological stress in relation to conflicts with their mother-in-law or their husband (Ashing-Giwa et al., 2004; Im et al., 2002; Y. I. Kim, 1998). In addition to blaming their past behaviors, they mentioned that their illness was attributed to their personality or character. Specifically, women treated for breast cancer reported that they got sick because of being too patient during stressful relationship with their husband, children, or patents-in law. In general, Korean women were likely to hold a feeling of being a victim because being patient is required to them when they experienced interpersonal conflicts. Accordingly, women with breast cancer regarded their disease as a consequence of too much stress and pressure accumulated inside their mind (Ashing-Giwa et al., 2004; Im et al., 2002; Y. I. Kim, 1998; Park, 2003; Shin, 1995).

Self-blame is known to be correlated with psychological distress, especially depression (Bennett, Goldstein, Friedlander, Hickie, & Lloyd, 2007; Bennett et al., 2005). It has been reported that Korean breast cancer patients experienced negative emotions such as worries, concerns, helplessness, loneliness, or fear and these emotions can interfere with their positive coping behaviors during the whole treatment period of breast cancer (Hur & Kim, 1999; Jun, 1994; Kim, Jun, & Lee, 2006; Park, 2003). Of these emotional responses, anger may be a culturally specific response observed in Korean women treated for breast cancer. Park (2003) addressed that anger was a negative emotional response formed through interpersonal relationships. However, ironically, a sense of powerlessness in anger expression was also reported simultaneously owing to a cultural habit of self restraint (Park, 2003; Youn & Tae, 2004). That is, their anger seems to be toward the inside of their minds and can be hidden in terms of internalization. The suppression of anger indicates that cognitive effort should be required in order to maintain a constant inhibition of negative emotional expression. Thus, it is possible that self-blame tendency can be a potential cognitive demand, is closely linked with suppression of anger expression, and thus may be a negative impact on coping with transitional life events related to breast cancer.

Culture-Specific Cognitive Burdens Related to Breast Cancer

Overall Influences of Korean Culture on Women's Lives

Traditional values of Korean culture remain in various areas of Korean society influencing all aspects of living from personal perception/behavior to social ethics/ideological basis (Cha, 2001; Lee, 2007; Lee, 2000). The traditional values have been deeply linked with collectivism and familism prioritized in Confucianism over a period of 500 years and have provided an orthodox principle as the overall guideline of consciousness and behaviors in Korea (Choi, 2002; Kim & Cho, 1991; Shin, 1998a, 1998b; Suh, 2003). Recently, the extent to which these values influence Koreans' beliefs and attitudes has been changing over time. Since the restoration of independence in 1945, the influences of traditional culture were weakened due to socio-cultural changes including the acceptance of democracy and capitalism, rapid industrialization, the wide spread of mass media, and the influx of new culture from western countries (Go, 1996). Especially, Korean values have changed from collectivistic to individualistic, authoritarian to egalitarian, conservative to progressive, fatalistic to instrumental, and idealistic to materialistic views (Im, 2003; G. N. Kim, 1998). Furthermore, an individual's propensity toward traditional values is likely to vary in accordance with westernization such as years of education and experiences in individualistic culture. It is reported that age, years of education, and experience related to individualistic culture are significantly associated with personal preferences toward traditional values. Increasing age or years of education is associated with cultural value. That is, as individuals are getting older or their years of education decreased, they are likely to show a greater tendency to prefer traditional (collectivistic) values than individualistic values (Kim, Shin, & Choi, 2003; H. O. Kim, 2002). Therefore, either young or highly educated people are likely to have stronger individualistic tendencies whereas old or less educated people seem to have higher collectivistic characteristics.

Interestingly, changes in traditional values may not noticeably affect cultural and social expectations about gender-divided role performance related to child-rearing and housework tasks. Korean society continues to emphasize the women's responsibility to care for her family members as a mother, daughter-in-law, and wife rather than one of independent individuals (Moon, 2000). Due to the traditional values toward gender-divided roles and obligations between women and men, primary roles of a woman, especially a married woman, continue to be predominantly confined within domestic settings and occupied with caring for her husband's families and household chores for them. If a woman becomes ill, she will still regard herself as a primary person to take care of her family. These culturally biased values and beliefs can make ill women feel guilty about their reduced ability to perform the roles for their husband or children. At the same time, women usually take care of other female family members such as their daughter, daughter-in-law, or mother (Hahm, 2003). Thus, it is meaningful to note that culturally learned responses and expectations about women's role performance for their family may raise psychological, cognitive, and behavioral burden for both a sick woman as well as other women who have to care for an ill female family member.

In addition to the above-mentioned cultural effect on women's lives, women's roles were expanded since 1960 (Johnsrud, 1995; S. H. Lee, 1997; Moon, 2000). The rapid economic development increased opportunities of education and employment to women (Cho, 1986; D. W. Lee, 1997). According to the Korean Statistical Information Service, the rate of women's labor force participation has increased over time;

specifically, 54.8% of women over 15 years of age were employed and 96.2% of working women over 30 years were married in 2007 (Korean Statistical Information Service, 2008). Regardless of increases in the rate of employed women, social expectation on women's role performance has not moved far from traditional roles (Chang, 1999; Hahm, 2003; Kim & Han, 1996; D. W. Lee, 1997; S. H. Lee, 1997; Moon, 2000). Thus, dual burdens for work and at home seem to be imposed on Korean women.

Historically, Korean women played their traditional roles without confusion about their responsibilities in the past because their lives were completely limited to the domestic settings. However, modern women face dual obligations and duties; they are engaged as financial assistants as well as family caregivers at the same time (Chang, 1999). In particular, married women having a part-time or full-time job are expected to carry out their roles at home as a wife, mother, or daughter-in-law no matter what duties they have at work (Chang, 1999; Moon, 1995). The typical example is the quantity of hours spent for family care and home management between women and men. The mean hours of women's housework performance ranged from 3 hours and 31 minutes to 9 hours and 12 minutes per weekday (M. J. Kim, 2002; Lu & Lee, 2004; Park, Oh, & Suh, 2000). Even working women who work about 46 hours per week spent an average of 30 hours a week on domestic tasks. In contrast, the mean hours of men's housework performance were 2 hours and 30 minutes a week when the men work 55 hours a week. Specifically, married men spent about a half of their time on coaching children's studies and only 12 minutes (8.8%) for providing meals and doing laundry and housework performance (Lu & Lee, 2004). According to the literature review addressed above, the initiation of social involvement of Korean women was driven not by their own desires but by social demands (Moon, 1995). As a result, women are expected to do dual roles in work places and at home and the unchanged, expanded social expectations may increase burdens in women's lives. These findings suggest the possibility that women with breast cancer may suffer from burden caused by expectation of dual roles.

Women's Response to Child-Rearing

Korean women have addressed challenges related to child rearing and housework performance (Chang, 1999; S. H. Lee, 1997; Song & Kim, 2003). On evaluating the perceived burden related to role performance, unemployed women experienced more physical, psychological, and financial burdens relative to elder care while employed women were more likely to feel guilty about their alleged incapacity to meet the needs of their family members, in particular, their children (Chang, 1999; S. H. Lee, 1997; Song & Kim, 2003). If women have life-threatening illness such as cancer, they experience greater physical difficulties and self-blame in relation to taking care of their children (Im et al., 2002; Jun, 1994; Kim, Kim, Yoo, Yong, & Song, 2003; Park, 2003; Youn & Tae, 2004). Specifically, women with breast cancer appear to experience guilt and worthlessness because of their perceived functional losses and associated difficulties with role performance (Im et al., 2002; Jun, 1994; Park, 2003; Youn & Tae, 2004).

Likewise, women treated for other cancer experienced sadness and concern for their inability to care for their children because of pressures associated with the cultural expectation that women have the primary responsibility for all child-rearing affairs ranging from children's education and their marriage to the life of the children even after they are married (Cho, 2002; Kim, Ko, & Jun, 2011). Specifically, Korean women treated for lymphoma reported that they had physical difficulties in performing their primary roles such as taking care of themselves as well as their children. In addition to burden related to physical weakness, the perceived inability to do daily activities for their family made the women to suffer severe feelings of defeat.

Similarly, a recently published qualitative study performed by Kim et al (2011) showed the impact of breast cancer diagnosis and its treatment on women's parenting. Seven Korean women treated with chemotherapy for early stage breast cancer were interviewed. Participants were middle-aged married women who lived with their school-aged or adolescent children. They reported that they struggled with the challenge of continuing to care for their children since cancer diagnosis. In addition, they felt pressure to protect their children against social stigma of cancer due to a cultural expectation that a mother has all child-related responsibilities. Furthermore, they reported that focusing on themselves being sick was in a conflict with caring for their children. Owing to the lack of preparation in re-prioritizing to focus on self foremost, they seemed to lose the balance between self as a breast cancer survivor and self as a parent taking care of her children. The failure in balancing may act as an additional psychological burden to women with breast cancer (Kim et al., 2011).

Familial Support for Women's Role Performance

Of various burdens in Korean women with breast cancer, behavioral burdens are thought to be associated with the amount of actual support from their family members (familial support) rather than other social support. Considering the characteristics of collectivistic Korean culture emphasizing relatively strict boundaries between in-group (such as family) and out-group, it is not surprised (Cho & Lee, 2007; Nisbett & Masuda, 2003). However, sufficient support might have not been continuously provided to women with breast cancer during the whole treatment period. A study to investigate the patterns of familial support in Korean breast cancer patients showed that scores on familial support was the highest immediately after surgery for breast cancer and, then, decreased for periods of adjuvant therapy (Park, 2004). Women may re-face behavioral challenges from their role performance for their family before completely recovering physical health from the entire cancer treatment received. Two other studies suggested the additional importance of familial support in that actual support from family members, especially patient's husband, assisted women with breast cancer to obtain emotional comfort and strong will to live and helped them to have a new understanding of the meaning of life, which can work as supportive sources to return to 'new normal' life after treatment (Jo & Son, 2004; Kim, 2011).

The other salient feature of familial support is a mutually supportive relationship between mother and daughters when a mother has breast cancer. In general, relationships between Korean parents and their children are specifically delineated depending on the gender of parents and their children; more supportive relationship is observed in mother-daughter relations while more controlling relationship is shown in father-son relations (Lee, Lee, & Kim, 2008). Although there is no published study to explore the changing pattern of relationship between mother with cancer and her daughters, five qualitative studies conducted to investigate Korean women's experiences regarding breast cancer diagnosis and treatment commonly showed that their daughters tended to act as a supportive system in terms of mature attitudes, responsibilities for their own duties, and tangible assistance in performing household chores (Cho, 2002; Im et al., 2002; Kim et al., 2011; Kim, 2011; Shin, 1995). Taken together, Korean women with breast cancer received practical support from their family members but familial support is not sufficiently continued over the entire treatment period. Building up more supportive relationship between women with breast cancer and their daughters is suggested as a noticeable, culture-specific feature.

Summary

Cultural values from collectivism and familism based on Confucianism have influenced all aspects of life in Korean women. In general, the effects of collectivism on cognitive function and processes are frequently reported: 1) collectivism influences Koreans to habitually perceive, concentrate, and memorize everything within dialectical, context-dependent, and relationship-based cognitive framework; 2) collectivism influences Koreans to automatically respond to other-focused emotions rather than self-focused emotions, socially engaged emotions rather than socially disengaged emotions, and negative emotions rather than positive emotions; and 3) collectivism influences Koreans to choose conciliatory attitudes and behaviors rather than direct confrontation in conflict situations, which is referred to as the best way to maintain social harmony. Korean familism, which was formed on the basis of neo-Confucianism, seems to restrict women's life within a domestic area and enforced women's obedience, submission, or sacrifice under the patriarchal authority. Besides, social expectations about women's performing traditional roles still increase burdens about role performance in domestic life although social changes have given rise to alterations of traditional values.

The cognitive representation of female breast, breast cancer, and its treatment are influenced by Korean culture. The meaning of female breast is more likely to be addressed toward maternity than feminity, which emphasizes women's reproductive as well as productive functions. In a similar vein, cancer etiology is thought to be explained within interpersonal relationships. Fate, divine punishment, and psychological distress were suggested as etiological myths about breast cancer in Korean women. Korean women's responses regarding breast cancer diagnosis and its treatment may provide hints to explore culturally specific burdens which can interact with their returning to 'new normal' life following treatment. Three possible cultural characteristics are suggested as cognitive demands: 1); greater cultural influence of collectivism; 2) perceived burdens in performing housework tasks and taking care of children; and 3) self-blame tendency toward having breast cancer diagnosis.

CHAPTER V

THEORETICAL FRAMEWORK

A review of literature examining cognitive deficits in women with breast cancer suggests that women with breast cancer experience deficits in directed attention and working memory function. These functional deficits are known to be significantly associated with reduced performance in daily activities and poorer quality of life (Cimprich, 1995; Kaplan & Kaplan, 1989; Reid-Arndt et al., 2010). However, most studies that have examined the impact of cognitive deficits on a woman's ability to function have failed to use a theoretical framework to precisely delineate cognitive deficits. Further, this lack of a theoretical framework can lead to a vague definition of cognitive deficits and difficulty in selection of theoretically relevant methods to assess cognitive function. Owing to this research gap, many studies have failed to yield consistency between neuropsychological performance and perceived effectiveness in cognitive functioning in women with breast cancer. For this reason, an appropriate theoretical basis is needed to precisely describe cognitive deficits in terms of theoretical consistency in selecting both neuropsychological tests and self-reports. Thus, this chapter focuses on a theoretical review of function of directed attention and working memory to elucidate the phenomenon of cognitive deficits in breast cancer and subsequent behavioral responses.

Directed Attention and Working Memory

Definition of Directed Attention

Directed attention is defined as the cognitive capacity to actively inhibit competing, distracting, or irrelevant stimuli from the environment in order to effectively focus on information relevant to task demands (James, 1890; Kaplan & Kaplan, 1989; Posner, 1995). Directed attention has also been described as voluntary, effortful, or controlled attention because, when individuals initiate any goal-directed activities, voluntarily driven concentration is supported by attentional networks in the brain. On the other hand, there is a contrasting form of selective attention, involuntary attention, which is manifested as an effortless and spontaneous process (James, 1890; Kaplan & Kaplan, 1989). Involuntary attention can be easily captured by environmental stimuli of interest including salient, moving, dangerous, or mysterious things, such as fires, loud sounds, nature and pets, unexpected happenings, or life-threatening events. These stimuli are likely to be associated with an individual's interest or preference and may act as strong distractors when performing goal-directed tasks (Cimprich, 1993; Kaplan & Kaplan, 1989; Sarter, Gehring, & Kozak, 2006).

Posner and his colleague propose that there are distinct neural systems that support attention (Posner & Petersen, 1990). These neural attention systems are well described from neuroimaging studies (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). The attention system is thought to consist of three anatomically separate but interconnected networks which carry out functions of alerting, orienting, and executive control. First, the alerting system maintains cognitive vigilance for monitoring particular information such as warning signals. This system is associated with the thalamic, frontal, and parietal regions of the brain, especially the right hemisphere, and the activation of the specific brain regions is thought to be linked with cortical distribution of the norepinephrine system in the brain (Fan et al., 2009; J. Fan et al., 2005; Posner & Petersen, 1990). Second, the orienting system selects sensory information for improving the detection of stimuli relevant to the goal in a given situation. The orienting system is associated with the superior parietal lobe, the temporal parietal junction, and the superior colliculus and is labeled as the posterior attentional system (Fan et al., 2009; J. Fan et al., 2005; Posner & Petersen, 1990). The activation of the orienting system is closely related to the acetylcholine system of the brain (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000). Third, the executive control system resolves conflicts occurring between incompatible responses (Fan et al., 2009; Posner & Petersen, 1990). The executive control system is important in order to meet changing environmental demands in everyday life. Through this control system, the selective inhibition of task-irrelevant information contributes to effective goal-directed activities (Egner & Hirsch, 2005). The anterior cingulate cortex (ACC) and the lateral prefrontal cortex (PFC) are engaged in this system, and the activation of these specific brain areas are closely related to the dopamine system of the brain (J. Fan et al., 2005). Due to the anatomical locations of the ACC and the PFC, this system is named as the anterior attentional system. This system is closely related to the capacity to direct attention.

Although directed attention is important in order to control thoughts and behaviors, its functional efficiency may be restricted by a limited capacity due to need for mental or inhibitory effort (Kaplan & Kaplan, 1989). It is widely accepted that an individual’s attentional capacity is limited and that attentional performance can diminish as evidenced by inaccurate and/or slowed reaction during goal-directed activities with overuse of cognitive processes regarding mental effort (Duncan, 1980; Kahneman, 1973). Accordingly, it can be hypothesized that individuals with breast cancer can experience deficits in directed attention and subsequent altered behavioral responses secondary to demands associated with life-threatening illness such as breast cancer.

Definition of Working Memory

Working memory is a brain system that allows individuals to temporarily maintain and manipulate information in order to engage in goal-directed activities (Baddeley, 1986; Smith & Jonides, 1999). According to the traditional perspective based on Baddeley's model, working memory comprises three components including two storages (visuo-spatial sketchpad and articulatory loop) and a central executive system. The visuo-spatial sketchpad is a storage system which maintains visuo-spatial stimuli from the internal/external environments. The articulatory loop works as another storage system associated with phonological coding and rehearsal processes. The rehearsal processes are thought to keep information accessible for renewing or forming memory. The central executive system is suggested as the last component of working memory and coordinates with other working memory systems. The central executive system is assumed to inhibit distraction so that information can be manipulated in the service of complex cognitive processes (Baddeley, 1986, 2003).

Similarly, Smith and Jonides' theoretical perspective of working memory (1999) is one which consists of two components: short-term storage and a set of executive processes. Short-term storage is referred to as a memory system which involves temporary maintenance of a limited amount of information. Different kinds of information (verbal, visual, spatial stimuli) lead to involvement of different regions of the brain. Executive processes operate the contents stored in memory and support selective attention and task management. The ACC and dorsolateral PFC were deemed to be engaged in these executive processes (Smith & Jonides, 1999).

Working memory function is known to be restricted due to a limited capacity of working memory. The working memory capacity is regarded as the number of items which can be maintained during the performance of working memory tasks (Miller, 1994). In general, a person maintains limited information at one time, ranging from 4±1 to 7±2 items (Kaplan & Kaplan, 1989; Cowan, 2001). The limited working memory function is presumed to affect the ability to control selective attention during complex cognitive tasks (Awh, Vogel, & Oh, 2006; Baddeley, 2003; Knudsen, 2007; LaBar, Gitelman, Parrish, & Mesulam, 1999).

The Functional Association between Attention and Working Memory

Directed attention and working memory are critical to regulating cognitive inhibitory effort in purposeful activities (Cohen, Aston-Jones, & Gilzenrat, 2004; Miller, 2000; Posner, 1995; Smith & Jonides, 1999; St. Clair-Thompson, 2007); Purposeful activities include listening, learning, problem solving, planning, and organizing in daily activities at home and occupational tasks for work (Kahneman, 1973; Sarter et al., 2006). In order to perform these purposeful activities, directed attention and working memory allow an individual to focus on purposeful activities while blocking distracting stimuli (Kaplan & Kaplan, 1989; Knudsen, 2007; Smith & Jonides, 1999).

Directed attention and working memory are inextricably related with cognitive and behavioral responses during goal-directed activities in the real world (Knudsen, 2007). Specifically, both directed attention and working memory are thought to contribute to the efficiency of information processing (Smith & Jonides, 1999). Importantly, mental representations of information from internal or external environments can be generated into coherent trains of thoughts and behaviors through the mediation of working memory (Campbell, 2005; Lepsien & Nobre, 2006). Likewise, these processes can be protected against the interference effects from distractors through control by directed attention (Awh et al., 2006; Egner & Hirsch, 2005).

Cognitive Demands

Cognitive demands invoked in stressful and incompatible situations can act as cognitive burdens in women's lives (Cimprich, 1992b; Stark & Cimprich, 2003). Of the high risk conditions with these demands, life-threatening illness such as cancer is an exemplary situation (Stark & Cimprich, 2003). Previous studies revealed that women with breast cancer encountered challenging situations in which cognitive demands may increase during cancer diagnosis, treatment, and long-term survivorship (Cowley, Heyman, Stanton, & Milner, 2000; Ganz, 2000). For example, women with breast cancer often need to participate in treatment decision-making processes with insufficient or overabundant information under time pressure. These women reported that their mental burdens during cancer diagnosis and treatment negatively impact the necessary coping behaviors for achieving a "new normal" life.

Cognitive demands have been categorized as physical, informational, affective, and behavioral requirements for use of directed attention in a situation (Cimprich, 1992b; Kaplan & Kaplan, 1989; Stark & Cimprich, 2003). First, physical demands are factors perceived in the external environment which not only hinder the acquisition of desired environmental information but undermine necessary actions. Typical examples include crowded areas, places without privacy, or complex buildings without sufficient landmarks for ease of way finding (Kaplan & Kaplan, 1989). In addition, physical demands include symptom distress and physical problems such as hearing loss, visual weakness, pain or limited mobility (Jansen & Keller, 1998).

Second, informational demands are factors which need cognitive effort for perception and interpretation of information relevant to purposeful activities. For example, unfamiliar, conflicting, difficult or unclear information may require the use of attention and working memory in order to make sense of what is happening to a person (Cimprich, 1992b; Kaplan & Kaplan, 1989; Stark & Cimprich, 2003). Women diagnosed with breast cancer are often exposed to situations with high informational demands in order to help themselves deal with treatment for their illness. They have to learn new medical terminology and procedures related to their illness and treatment and new coping behaviors for self-care. This informational overload can serve as a threatening source of distraction, which requires greater cognitive effort to function in women with newly diagnosed breast cancer (Cimprich, 1992a; Ganz, 2000).

Third, affective demands include emotional factors, which must be inhibited to maintain normal functioning, such as worries, concerns, helplessness, loneliness, fears, or preoccupations (Jansen & Keller, 1998). Affective demands can interfere with one's ability to carry out daily activities or to achieve short- or long-term goals (Kaplan & Kaplan, 1989). Especially, intense affective demands may emerge during a critical period of transition from a patient with a newly diagnosed breast cancer and to long-term breast cancer survivor. Emotional fluctuations require greater effort for women to engage in their necessary life activities for coping with the transitional life events related to their breast cancer (Eysenck, Derakshan, Santos, & Calvo, 2007; Ganz, 2000).

Last, behavioral demands are factors which lead to an increase in cognitive effort when behavioral responses required in a given situation are incompatible, unfamiliar, or coerced, relative to one's inclination or preference (Cimprich, 1992a; Jansen & Keller, 1998; Stark & Cimprich, 2003). Women with breast cancer may encounter new behavioral challenges in order to deal with requirements in daily activities such as childrearing, housework tasks, or paid employment (Ganz, 2000). Furthermore, these women may have greater difficulty in dealing with behavioral difficulties or expectations related to role performance (Bettencourt, Schlegel, Talley, & Molix, 2007).

Functional Consequences of Cognitive Deficits

Cognitive demands require use of cognitive effort for effective cognitive functioning (Sarter et al., 2006). Simultaneously, exhausting cognitive capacity with unavoidable demands can reduce the effectiveness in cognitive effort, leading to compromise of information processing, affective responses, and behavior (Campbell, 2005; Lorist, 2008; Persson, Welsh, Jonides, & Reuter-Lorenz, 2007). An increasing number of studies have shown that cognitive deficits are associated with functional impairment and poor health-related quality of life in cancer patients and survivors (Azim et al., 2011; Biegler, Chaoul, & Cohen, 2009; Boykoff et al., 2009). Specifically, cognitive deficits involving attention and working memory are thought to reduce an individual's ability to think clearly, follow a train of thought, problem solve, and exert cognitive effort for performing goal-directed activities (Cimprich, 1995; Kaplan & Kaplan, 1989; Lorist et al., 2005; van der Linden et al., 2003). In various studies conducted to evaluate perceived cognitive difficulties in women treated for breast cancer, functional difficulties associated with attention and memory were assessed with subjective measures (Ahles et al., 2002; Cimprich, 1992a; Cimprich et al., 2005; Shilling & Jenkins, 2007; van Dam et al., 1998). These studies found that women complained about loss of ability to concentrate, set goals, launch a new project, understand new information, or carry out even simple daily work.

Likewise, alterations in attention and working memory are presumed to be associated with impaired modulation of affect and emotion. With loss of attention, people are likely to experience reduced tolerance of frustration, irritability, impatience, and impulsiveness in controlling emotional responses during interpersonal interactions (Berto, 2005; Cimprich, 1995; Hartig, Evans, Jamner, Davis, & Gärling, 2003; Kuo & Sullivan, 2001; Ulrich et al., 1991).

Lapse of attention and working memory can diminish behavioral effectiveness when performing tasks of everyday life (Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009; Kaplan & Kaplan, 1989). Specifically, behavioral consequences can include functional difficulties in vocational adjustment or persistence, driving safely, medication adherence, and financial management such as organizing household finances, managing daily monetary transactions, or shopping. Similarly, cognitive deficits in attention and working memory in cancer patients can have a strong negative impact on their capability to maintain work, to perform family roles, self-care, or even simple activities of daily living (Cimprich, 1995; Hafner, 2009; Rhodes, Watson, & Hanson, 1998). Accordingly, individuals can experience deficits in attention and working memory and corresponding behavioral difficulties when they have cognitive deficits associated with continuous use in response to the demands of life-threatening illness.

Summary

Women with breast cancer are predisposed to directed attention and working memory deficits during the entire trajectory of breast cancer treatment. Directed attention and working memory are not only important in performing purposeful activities but also functionally associated with effective cognitive, affective, and behavioral responses in everyday life. With breast cancer diagnosis, women may encounter challenging situations in which cognitive demands increase in terms of physical, informational, affective, and behavioral requirements for the use of directed attention and working memory. As a result, overuse of attention and working memory may lead to a negative impact on all functional aspects of daily activities and quality of life in women with breast cancer.

CHAPTER VI

METHODS

This study was designed to examine the impact of chemotherapy on cognitive function in a selected group of Korean women with or without breast cancer. This chapter describes the research design, the sample selection and setting, measures, data collection procedures, and data analysis procedures.

Research Design

A comparative cross-sectional design was used to explore whether there was a difference in cognitive function as assessed by standard cognitive tests and a self-report of attention and working memory between Korean women with breast cancer and healthy controls. Cognitive testing was conducted in breast cancer survivors within approximately four months following adjuvant chemotherapy. In healthy controls testing was done within six months following routine negative screening mammography.

Sample and Setting

The sample consisted of 64 female participants; 32 women treated with adjuvant chemotherapy for localized breast cancer (stage 0 – IIIa) and 32 healthy controls. Specifically, the breast cancer group was selected from the population of patients undergoing adjuvant chemotherapy for localized breast cancer at the Chungnam National University Hospital Cancer Center (CNUHCC) Breast Cancer Treatment Clinic. The initial recruitment for the healthy control group was conducted through referrals from clinic staff in the CNUHCC Breast Cancer Detection Clinic and then followed snowball sampling. Women in the healthy control group were enrolled as a comparison group for elucidating the effect of cancer diagnosis and its treatment on cognitive function.

The eligibility criteria for all subjects were as follows: 1) age 25 years or older; 2) sufficient mastery of Korean language to complete standard cognitive tests and questionnaires; and 3) a total score of at least 25 (> 24) on the Korean version of the Mini-Mental State Examination. Specific eligibility criteria for women treated for breast cancer were: 1) having a new diagnosis of early stage breast cancer ranging from Stage 0 to IIIa; and 2) receiving adjuvant chemotherapy involving intravenous administration of a combination of at least two cytotoxic agents such as cyclophosphamide (cytoxan®, endoxan®), doxorubicin (adriamycin®) or epirubicin, 5-fluorouracil, and paclitaxel (genexol®) or docetaxel (taxotere®, monotaxel®). Specific criteria for healthy women without breast cancer included a negative mammogram within six months prior to study testing.

Subjects were excluded for pre-existing conditions that could affect the ability to perform cognitive measures. Exclusion criteria included: 1) secondary diagnosis of mental, psychiatric, or learning disorder; 2) history of traumatic head injury; 3) history of alcohol or drug abuse; 4) uncorrected hearing and vision problems; 5) secondary diagnosis of debilitating medical disorder such as progressive muscular paralysis, advanced cardiac, respiratory, or renal disease; 6) currently taking psychoactive medication including antidepressant, barbiturates, or amphetamines; and 7) insufficient language skills to preclude performing cognitive tests.

During the recruitment period, a total of 43 women treated for early stage breast cancer met the eligibility criteria for this study. Of these, 32 women (74%) agreed to participate in the study. Of the 11 women who did not participate in the study, one woman lived at a distance from the cancer center, two women refused to perform the computerized cognitive test due to lack of confidence in using a computer, and one woman denied screening to ensure intact cognitive function with the Mini-Mental State Examination. Other women were unwilling to participate as follows: lack of availability or too busy to participate. No distinguishing characteristics between participants and non-participants were found in terms of stage of disease, types of surgery, and time since breast cancer diagnosis.

Measures

Cognitive Measures

Cognitive function was assessed by selected measures theoretically congruent and sensitive to attention and working memory function. A Korean version of the Mini-Mental state Examination was used for screening the presence of cognitive impairment. Selected cognitive tests consisted of a Korean version of the Digit Span Forward and Backward and a Korean version of the Controlled Oral Word Association Test, and the Attention Network Test. A self-report measure, the Attentional Function Index (AFI), was used to assess perception of effectiveness in cognitive functioning. This measure was translated through this study.

Korean version of the Mini-Mental State Examination. The Korean version of the Mini-mental State Examination (K-MMSE) was used as a screening measure to ensure intact cognitive function. The K-MMSE is a standard screening test that assesses cognitive domains including orientation, memory, attention, and language use and construction (Kang, Na, & Han, 1997; Park & Kwon, 1990). Total scores range from 0 to 30 and the score of 25 or higher is conventionally used to indicate absence of serious cognitive impairment (Folstein, Folstein, McHugh, & Fanjiang 2001).

Digit Span Forward and Backward. The digit span test is a commonly used cognitive test to evaluate directed attention and working memory across countries (Lezak, 2004). This test involves having individuals immediately recall a string of digits read by the examiner. The digit span test consists of two parts: Digit Span Forward (DSF) and Digit Span Backward (DSB). For the DSF performance, individuals are required to recite a series of digits in the same order read by the examiner. The DSF is scored as the total number of digits recalled correctly prior to two failed trials. Healthy adults can usually repeat 6 or more digits without difficulty. A span of 5 is suggested as being marginal and a span of 4 is indicated as definitely borderline (Lezak, 2004). The DSF requires less cognitive demand for the short-term storage and immediate recall of the digit sequences. The DSB involves high cognitive demand requiring sustained attention and working memory for maintaining, manipulating, and recalling a string of digits in reverse order. Depending on years of education, a span of 4 or 5 on DSB is suggested as a normal limit and a span of 3 is indicated as borderline defective (Lezak, 2004). The digit span test has been used as a sensitive measure to detect cognitive deficits among women treated for breast cancer in western countries (Cimprich, 1993, 1998; Donovan et al., 2005; Hermelink et al., 2007; Schagen et al., 2002; van Dam et al., 1998; Wefel et al., 2004). The translated instruction of the digit span test was used in Korean women in this study (see Appendix A1). The test-retest coefficients of the digit span test ranged from 0.66 to

0.89, depending on age (Lezak, 2004). Thus, it was ascertained that the digit span test is a sensitive, valid, and reliable test to detect cognitive deficits in Korean women treated for breast cancer.

Korean version of the Controlled Oral Word Association Test. The Controlled Oral Word Association (COWA) test was developed to measure verbal fluency requiring attention and working memory function (Benton & Hamsher, 1989; Lezak, 2004; Royall et al., 2002). Neurologically, the COWA test is known to be sensitive in measuring attention and working memory dysfunction in individuals with frontal or temporal lobe damage (Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001; McDonald et al., 2006). Likewise, this test has been administered in clinical studies to assess frontal lobe function in Korean patients with obsessive compulsive disorder or schizophrenia (Ahn et al., 2000; Kim, 2005).

The COWA test consists of two parts: phonemic letter fluency (COWA part A) and semantic category fluency (COWA part B) (Ruff, Light, Parker, & Levin, 1996; Tombaugh, Kozak, & Rees, 1999). In the Korean version of the COWA test, three target letters ('ㄱ, gierk'; 'ㅅ, seeot'; and 'ㅇ, eeung') were used to assess the part A and two categories of 'animals' and 'supermarket items' were asked to measure the part B (see Appendix A2). In the part A, a participant was asked to verbally generate as many words beginning with each designated letter as possible in a given time. One-minute trial per each letter was given to the participant. In general, healthy adults can produce at least 28 phonemic words without any repetition and inappropriate words. Thus, '28' words is used as a cut-off score of borderline and '25' or less is suggested as a criteria of 'deficient' (Ruff et al., 1996). In the part B, a subject was requested to verbally generate as many words appropriate to the target category (animals and supermarket items) as possible in one minute. Normative data were specified on the basis of gender, age, and educational level and '30' words were used as a cut-off score of borderline for the part B in this study (Tombaugh et al., 1999). The satisfactory levels of validity and reliability of the Korean version of the COWA test were determined in 451 Korean healthy people ranging in age from 55 to 80 years (Kang, Chin, Na, Lee, & Park, 2000).

Attention Network Test. The Attention Network Test (ANT) is an easily and quickly administered computerized measure for assessing performance of three theoretically separate attention networks (alerting, orienting, and executive control) (Fan, McCandliss, Sommer, Raz, & Posner, 2002). The alerting attention system was assessed by subtracting scores of trials with alerting cues from those of trials without any cues. The orienting attention system was assessed by scores of trials with spatially-determinant cues subtracted from those of trials without spatially predictive cues. The executive control attention system was assessed by subtracting scores of trials with incongruent information from those of trials with congruent information. In the ANT, a target stimulus is represented with a central arrow (← or →) which points leftward or rightward surrounded by two flankers on each side. This measure was designed with three flanker types (congruent, incongruent, and neutral) and four cue conditions (center, double, no spatial). Specifically, a neutral flanker was presented with dashes, a congruent flanker was shown with arrows pointing in the same direction of the central target arrow, and an incongruent flanker involved arrows that pointed in the opposite direction of the target stimulus. A warning cue was presented with an asterisk (*). This cue was differently located according to the kind of cue condition: 1) in the center of the screen for the center

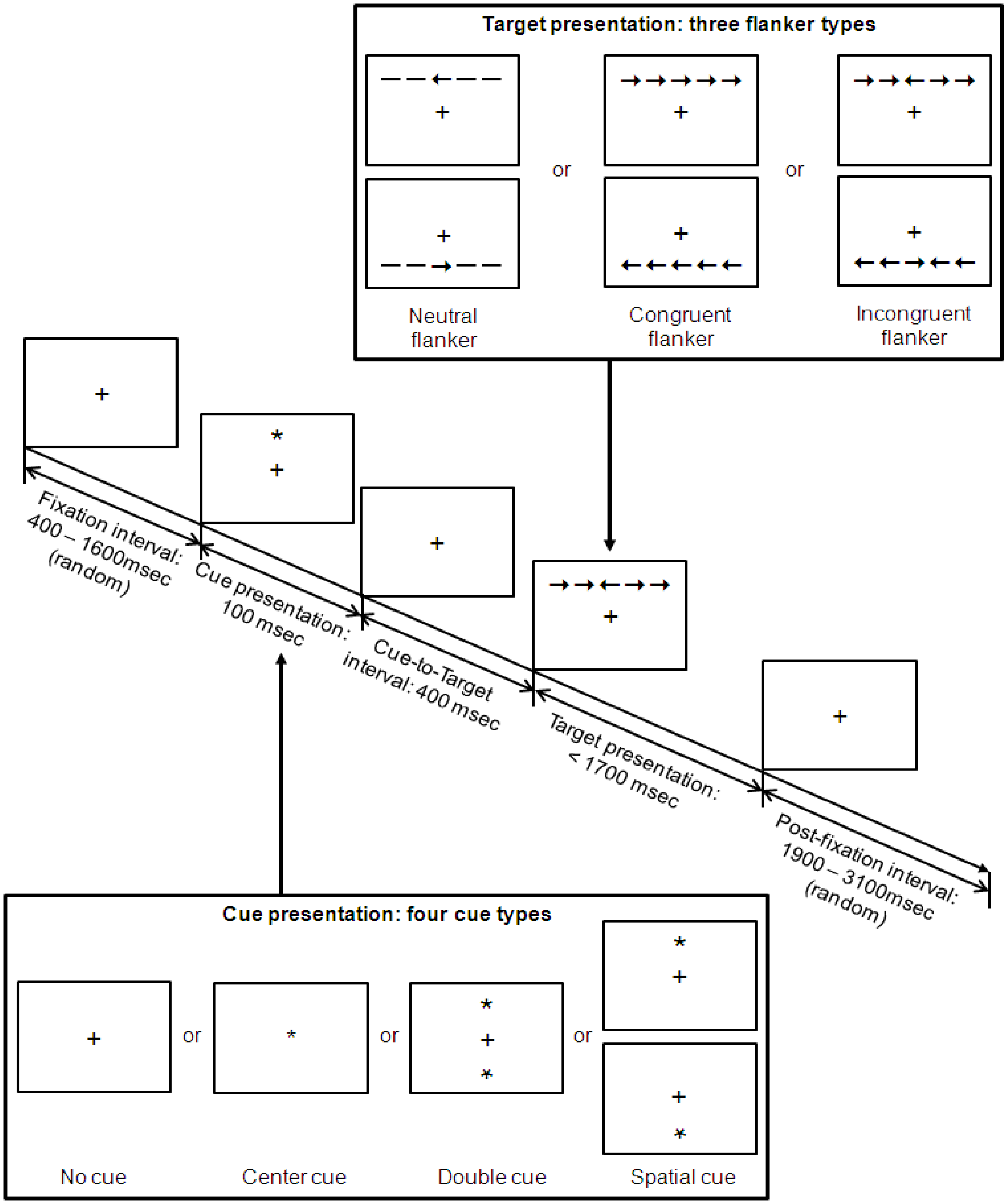

Figure 2. Time Course of the Experimental Procedures of the ANT. This figure includes a schematic of four cue types and three flanker types used in the Attention Network Test. In each trial, a fixation cross appears in the center of the screen all the time. A cue (no, center, double, or spatial) appears for 100 msec. After a cue-to-target interval (400 msec), the target (the center arrow) with flankers (congruent, incongruent, or neutral) is presented until a participant responds with a button press (no longer than 1700 msec). The target with flankers disappears immediately after the participant makes a response and a post fixation cross appears. The post fixation interval is randomly assigned between 1900 and 3100 msec.

cue; 2) above and below central fixation (+) for the double cue; 3) either above or below central fixation for the spatial cue; and 4) the presence of central fixation without displaying an asterisk for the no cue condition. The no cue condition served as the control for the alerting attention network while the double cue works to increase the alerting effect of the network. The central cue is used as the control for the orienting attention network and the spatial cue provides a better orienting effect. The congruent flanker served as the control for the executive control network, while the incongruent flanker is displayed to cause response conflict. Time course of events on the ANT was presented in the middle of Figure 2.

A participant was asked to answer the direction of the central target arrow by pressing the left mouse button for leftward arrows and the right mouse button for rightward arrows. The participant was required to fixate on a central fixation point (+) and respond to each target stimulus as quickly and accurately as possible. One practice test of 24 trials was provided and the participant was expected to obtain at least 75% average accuracy. During the actual test, 288 trials were provided; specifically, 96 congruent, 96 incongruent, and 96 neutral trials, and 72 trials were assigned to each cue condition. Error rates and reaction times were computed for analyses.

All instructions associated with test performance were translated into Korean. Except for the test instructions, the original version of the ANT was administered without further translation because all stimuli displayed in the ANT were symbols such as cross, asterisk, linear line, and arrows (see Appendix A3). In this study, preliminary analyses were performed to evaluate the structure of the ANT because this measure has not been used in the Korean population. Specifically, these analyses were conducted to examine four goals as follows: 1) to determine whether error rates and reaction times were different between left-pointing and right-pointing targets in any condition, 2) to assess effects of three attention networks on behavioral performance, 3) to determine whether scores on the three attention networks were correlated, and 4) to explore the main effects of cue and flanker types. Based on the structural analysis, the ANT is useful in evaluating three aspects of attention network function, alerting, orienting, and executive control attentional function in Korean women. Detailed analyses are described in the Appendix B1.

Attentional Function Index. The Attentional Function Index (AFI) (Cimprich, 1990) is a self-report measure designed to assess the perceived effectiveness in performing daily life activities requiring directed attention and working memory (see Appendix A4). This instrument was originally developed as a 16-item index to measure detrimental effects of cognitive fatigue on daily functioning in women newly diagnosed with early stage breast cancer. Specifically, various aspects of daily activities requiring attention and working memory were described to identify the impact of cognitive fatigue in daily living, such as effectiveness in establishing goals, carrying out plans, thinking clearly, initiating and completing intended activities, and regulating self for maintaining social functioning (Cimprich, 1990). The 16-item AFI was designed as a visual analogue scale ranging from 0, ‘not at all’, to 100, ‘extremely well’ or ‘a great deal.’ Higher scores indicated better perceived effectiveness in executive functioning at the time of administration (Cimprich, 1990; Cimprich, Visovatti, & Ronis, 2011). For this study, a 10-point Likert scale format was chosen with 0 indicating ‘not at all’ and 10 ‘extremely well' or 'a great deal' for each item. A participant was asked to circle the number that best described her functioning associated with purposeful activities.

The AFI was translated into Korean using a back translation technique for this research project. Two native Korean health care professionals were selected to translate this instrument from English to Korean. The PI compared two versions for equivalence and created one Korean version. The Korean translation of the instrument was back translated to English by a Korean-English speaking translator who was a post-doctoral student in the area of cancer research. The PI and the back translator reviewed the back translated English versions and made some minor suggestions for wording. Finally, the PI made the change to the Korean translation and produced the final translation of the AFI.

Studies conducted in women with breast cancer showed that the internal consistency coefficients ranged from .89 to .94 and validity was confirmed in the cancer population (Cimprich, 1992a, 1993, 1999; Cimprich et al., 2005; Cimprich et al., 2011; Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008; Lehto & Cimprich, 1999). Based on recent published findings about construct validity, the instrument was refined to 13 items and categorized into three subscales: effective actions, attentional lapses, and effective interpersonal relations (Cimprich et al., 2011). The internal consistency coefficients of the reduced 13-item AFI were 0.91 for the total items, and ranged from 0.75 to 0.93 for these three subscales. In the present study, the translated AFI was first used in Korean women with and without breast cancer so validity and reliability of the translated AFI were examined. Detailed information is provided in the Appendix B2.

Physical and Psychological Symptoms

Physical and psychological symptoms were assessed by well-established self-report measures. Specifically, fatigue was assessed with the Functional Assessment of Cancer Therapy-Fatigue (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). Anxiety and depressed mood were measured with the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983). Sleep problems were assessed with the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Except for the above mentioned symptoms, number and severity of symptoms were measured with the Breast Cancer Prevention Trial symptom checklist (Stanton, Bernaards, & Ganz, 2005). All measures were determined as sensitive tools extensively used in cancer and non-cancer populations.

Functional Assessment of Cancer Therapy-Fatigue Scale. The Functional Assessment of Cancer Therapy-Fatigue (FACT-F) scale was commonly used to measure the degree of perceived fatigue for individuals with cancer or other chronic illness (Yellen et al., 1997). It included 13 items with responses ranging from 0 ‘not at all’ to 4 ‘very much’ as presented in Appendix A5. Satisfactory reliability and concurrent validity were established in cancer patients with fatigue (Cella, Lai, Chang, Peterman, & Slavin, 2002; Cella et al., 1993). Conceptually, five items were classified into fatigue experience and the other eight items were categorized into fatigue impact (Cella, Lai, & Stone, 2010). In this study, the overall mean score was computed for analyses. Higher score indicated greater degree of perceived fatigue. Again, the FACT-F scale was translated into Korean by using the same procedure to translate the AFI. The internal consistency coefficient was 0.93 in this study.

Hospital Anxiety and Depression Scale. The Hospital Anxiety and Depression Scale (HADS) is a well-validated measure of psychological distress including anxiety and depression (see Appendix A6). Since the HADS was developed by Zigmond and Snaith (1983), this scale has been extensively used to identify anxiety and depression among patients in both psychiatric and nonpsychiatric clinics as well as general populations in communities (Bjelland, Dahl, Haug, & Neckelmann, 2002; Zigmond & Snaith, 1983). Especially, the recent study of Krespi Boothby and colleagues (2010) suggested that the HADS can effectively detect psychological distress in breast cancer patients, as compared with other measures such as the General Health Questionnaire-12 (Krespi Boothby et al., 2010). This instrument was originally divided into an anxiety (HADS-A) subscale and a depression (HADS-D) subscale, which consisted of 7 items, respectively. A subject was asked to choose 1 of 4 alternatives to closely represent how she has been feeling in the past week. Each item was designed using 4-point Likert scale ranging from 0 to 3, indicating that higher scores reflected greater levels of anxiety and depression. A Korean version of the HADS was developed and confirmed as a reliable, valid, sensitive, and specific measure through a study conducted in 66 patients diagnosed with anxiety, 74 patients with major depression, and 189 normal controls (Oh, Min, & Park, 1999). Cronbach’s alpha coefficients for internal consistency were 0.89 for the HADS-A and 0.86 for the HADS-D. In this study, the internal reliability coefficients were 0.87 for the anxiety subscale and 0.82 for the depression subscale.

Pittsburgh Sleep Quality Index. The Pittsburgh Sleep Quality Index (PSQI) is a self-report measure to evaluate various factors relating to sleep quality during the previous month (Buysse et al., 1989). It consisted of 19 self-rated items that were classified into seven domains, namely, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (see Appendix A7). Scores in each sleep domain range from 0 'no difficulty' to 3 'severe difficulty' and the sum of all subscores represented overall sleep quality. Higher scores indicated worse sleep quality. In a study conducted in 62 patients with sleep disorders, 34 patients with major depressive disorder, and 52 healthy control participants without sleep complaints, the reliability and the validity of the PSQI were established. The internal consistency coefficient for the overall sleep quality was 0.83 and correlations between the individual domain and the overall sleep quality ranged from 0.62 to 0.85. A score of 5 on the overall sleep quality was suggested as a sensitive cut-off point for distinguishing good and poor sleepers (Buysse et al., 1989). The PSQI has been documented as a sensitive and valid instrument to detect changes in sleep quality depending on age, gender, physical problems, or psychological distress (Buysse et al., 1989; Buysse et al., 1991; Hayashino et al., 2010). The PSQI was translated into Korean and administered in Korean populations including cancer patients and women with depressive symptoms (Cho, 2009; Kim & Han, 2002). The internal consistency coefficient was 0.75 in 128 Korean women with or without depressive symptoms during the late postpartum period (Cho, 2009). The internal consistency reliability estimate in this study was 0.76 for the overall sleep quality.

Breast Cancer Prevention Trial Symptom Checklist. The Breast Cancer Prevention Trial (BCPT) symptom checklist was originally designed to assess perceived distress of physical and psychological symptoms in relation to breast cancer treatment and menopause. For this study, 18 selected items were designated to measure the extent to which women have been bothered by the symptoms during the preceding four weeks (see Appendix A8). The 18-item BCPT symptom checklist consists of cognitive symptoms (forgetfulness, difficulty concentrating, easily distracted), vasomotor symptoms (hot flashes, night sweats), musculoskeletal pain (general aches and pain, joint pains, muscle stiffness, arm swelling, decreased range of motion in arm on surgery side), gastrointestinal symptoms (nausea, vomiting), body concern (weight gain, unhappy with the appearance of body), dyspareunia (vaginal dryness, pain with intercourse), and bladder control (difficulty with bladder control when laughing or crying, difficulty with bladder control at other times). This BCPT symptom checklist was translated into Korean using the back translation technique. All procedures in relation to the back translation were conducted in the same procedure used to translate the AFI. All items were rated from 0 ‘not at all’ to 4 ‘extremely’, indicating that the higher scores represented higher levels of symptom distress. The internal consistency coefficient of the original BCPT symptom checklist was 0.81 and validity of this instrument was evaluated by exploratory and confirmatory factor analyses (Cella et al., 2008; Stanton et al., 2005; Terhorst, Blair-Belansky, Moore, & Bender, 2010). The internal consistency coefficient in this study was 0.91 for the total items, and ranged from 0.65 to 0.88 for each subscale, indicating that reliability for the Korean version of the BCPT symptom checklist was adequate for assessing symptom distress, although the reliability estimate for body concern did not exceed 0.70.

Cultural Characteristics

Cultural characteristics included women’s attitude toward traditional gender role performance, perceived burden regarding performing housework, and child-rearing in all participants (see Appendix A9). Self-blame tendency related to having breast cancer diagnosis was assessed in women of the breast cancer group (see Appendix A10).

Cultural attitude of collectivism. To assess cultural attitude of collectivism, a self-report measure of the Value on Gender Role (VGR) (Park, 2009) was used. This measure specifically assessed women's attitudes toward performing roles traditionally ascribed to married women. The VGR consists of five items ranging from 1 'strongly agree' to 5 'strongly disagree.' Scores of all items were reversed so higher scores indicated greater tendency of collectivism-rooted Korean traditional values in performing women's role. The internal consistency coefficient was 0.59 in this study.

Housework burden. Perceived burden associated with women's role performance was measured by the household chore subscale in the Life Stress for Korean Housewives instrument (Chon & Kim, 2003). This instrument consisted of six items (e.g., I am always worn out because of performing household chores) ranging from 1 'not at all' to 5 'extremely', with higher scores indicating higher level of burden regarding household chores. The internal consistency coefficient estimate was reported as 0.86 by the original developers (Chon & Kim, 2003). Similarly, the internal consistency coefficient in this study was 0.87.

Childrearing burden. The Maternal Stress Inventory was used to assess women's burden about childrearing which is a primary responsibility traditionally ascribed to women (Pearlin & Scholler, 1978). The participant was asked to answer seven items ranging from 1 'rarely' to 4 'very much' and higher scores represent higher level of burden in childrearing. This measure was translated and used in Korean women with children (Chun, 1984). The internal consistency coefficient in this study was 0.88.

Self-blame tendency. Self-blame tendency was measured with two standardized questions which were developed to assess behavioral (i.e. how much do you blame yourself for the kinds of things you did?) and characterological (i.e. how much do you blame yourself for the kind of person you are?) self-blame in women with newly diagnosed breast cancer (Glinder & Compas, 1999). Self-blame questions were translated through the same procedure used to translate the AFI. A participant was asked to answer the two questions using 4- point Likert scale ranging from 1 ‘not at all’ to 4 ‘completely’, indicating that higher scores represented greater self-blame tendency associated with having breast cancer. A mean score of each single item was separately used in analyses because each item assessed a semantically different area of self-blame tendency. The internal consistency coefficient in this study was 0.86.

Demographics and Medical Characteristics

Demographic characteristics were obtained from the participants following cognitive screening by the K-MMSE. Selected demographic information was as follows: 1) current age, 2) years of education, 3) marital status, 4) family structure (number of family members living together, number of children, having a son, number of sons, having a daughter, and number of daughters), 5) employment status, and 6) annual household income (see Appendix A11).

Medical information included general health and breast cancer characteristics. General health characteristics were: 1) current menopausal status, and 2) presence of current comorbidity. Breast cancer characteristics were obtained through medial chart review for the group of women treated for breast cancer. Specifically, selected medical information included: 1) time since diagnosis, 2) type of breast cancer, 3) stage of disease, 4) date and type of surgery, 5) time since the completion of the last cycle of chemotherapy, 6) chemotherapy schedule (start and end date), 7) number of chemotherapy cycles, 8) chemotherapeutic medication administered, and 9) other adjuvant treatment prescribed (see Appendix A12).

Procedures

Recruitment Procedures

Permission was obtained from the UM Health Sciences and Behavioral Sciences Institutional Review Board and Chungnam National Hospital Institutional Review Board prior to the start of participant recruitment. In order to make sure breast cancer survivors met eligibility criteria for this research project, the principal investigator (PI) or a hired trained recruiter confirmed detailed eligibility by accessing a medical information website used in the hospital and then consulting with a designated nurse coordinator of the Chungnam National University Hospital Cancer Center (CNUHCC). The PI and the recruiter had a license as a registered nurse in Korea. Breast cancer survivors who were eligible for this study were approached to ask their interest about participation in the study. A brief introduction about this research was provided with the brochure including research purposes, importance of cognitive health, participants' rights and responsibilities, and contact information. Potential participants were also informed that they could change their mind and withdraw their participation at any time if they did not want to participate in the study. When potential participants verbally agreed to participate, the PI or the recruiter arranged an appointment to administer cognitive tasks and questionnaires at their earliest convenience. All recruitment procedures were conducted in the CNUHCC.

With regard to recruiting women without breast cancer, registered nurses in the CNUH total health promotion center provided the list of women who received routine screening mammograms. Also, some women having a negative mammogram within six months were referred by other participants in the study. They were asked to participate in the study using the same procedure for recruiting breast cancer survivors. Recruitment was conducted from 3/26/2010 to 5/30/2011 and the targeted sample of 64 Korean women was enrolled in this study.

Testing Procedures

All data collectors were Korean registered nurses and had clinical experiences and knowledge about breast cancer treatment. Before working as a data collector, they were trained to administer neuropsychological tests and surveys in an appropriate and reliable way. Standardized procedures for neuropsychological tests were taught during a training session. In addition, the data collectors were trained to deal with participants' responses relating to fatigue, anxiety or other emotional burdens.

Participants were tested at one time point. Specifically, women in the breast cancer group were tested within four months after the completion of the last cycle of the chemotherapy. Women in the healthy control group were tested within six months following routine negative screening mammograms. Testing was conducted in a quiet consultation room at the CNUHCC, free from distracting stimuli such as noise. A more detailed explanation of this study was provided to the participant and then written informed consent was obtained before starting any test. After agreement to participate in the study was established, a cognitive screening test and subsequent tests were performed. It took approximately 45 to 60 minutes to complete self-report questionnaires and cognitive tests including the DSF, the DSF, the COWA, and the ANT. Participants were given a monetary incentive ($20.00) in appreciation of their time and effort after they completed the cognitive tests and surveys.

Statistical Analysis

All procedures for statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows. Descriptive analyses were used to describe demographic and general health characteristics with all participants and to delineate breast cancer-specific characteristics with women in the breast cancer group. All measures administered in women both groups were analyzed and described with mean, standard deviation, and range. Prior to testing the main specific aims, the ANT and the AFI were examined to confirm validity and reliability.

Specific Aim 1. To investigate the incidence and severity of deficits in attention and working memory in Korean women treated with adjuvant chemotherapy for early stage breast cancer

To compare objective performance and subjective perception of attention and working memory function between women treated for breast cancer and women without breast cancer, the independent t-test was performed. Effect size estimates (Cohen's d) for group mean differences were calculated for four cognitive tests (DSF, DSB, COWA part A, and COWA part B) and the total cognitive score which was an index to represent attention and working memory function. In order to compare changes in error rates and reaction times in the alerting, the orienting, and the executive control network systems on the ANT, the paired t-test was used for within-group analyses and the repeated measured analysis of variance (ANOVA) for between-group analyses. Cohen's d statistic was calculated for group mean differences in error rates and reaction times on the ANT.

Specific aim 2. To explore the factors (demographic and general health characteristics, physical and psychological symptoms, and cultural characteristics) associated with deficits in attention and working memory in Korean women

To examine the relationships between possible factors and cognitive performance and perceived effectiveness of attention and working memory function, the Pearson Product Moment Correlation coefficients were computed. Mean differences and variance differences of possible predictors were additionally examined. All possible predictors of cognitive function were identified in demographic and general health characteristics, physical and psychological symptoms, and cultural characteristics. Dependent variables were objective performance (the total cognitive score, error rates in the ANT, and reaction times in the ANT) and perceived effectiveness (the total mean score of the AFI) of attention and working memory. A series of Multiple Linear Regression analyses were performed to determine whether there were significant predictors to explain the variance in objective performance and perceived effectiveness of cognitive function, respectively.

Computation of Scores on Cognitive Test Performance

Data analyses were performed using scores that were computed as follows:

1. Scores on the DSF represented the total number of digits correctly recited in forward sequence prior to two consecutive failed trials.
2. Scores on the DSB represented the total number of digits correctly recited in backward sequence prior to two consecutive failed trials.

3. Scores on the COWA part A were determined by the sum of the number of all correct words verbally generated using three target letters.
4. Scores on the COWA part B were determined by the sum of the number of all correct words verbally generated using two target categories.
5. A total cognitive score which is an index of attention and working memory function was computed by adding the standardized z scores of the DSF, the DSB, the COWA part A, and the COWA part B. The standardized z score on each selected measure was calculated using the total sample mean and standard deviation of each cognitive test, respectively: then a single variable, namely the total cognitive index was derived from the sum of z scores of these tests.
6. In the Attention Network Test, the overall error rate was computed by calculating the average of error rates in all four cue (center, double, no, and spatial) and three flanker conditions (congruent, incongruent, and neutral). In the same way, the overall reaction time was computed with the mean scores of reaction times in all four cue and three flanker conditions. The values to assess three attention networks were computed by subtracting error rates and reaction times on the associated cue or flanker conditions as following:
    a. Alerting attention network = no cue condition – double cue condition
    b. Orienting attention network = center cue condition – spatial cue condition
    c. Executive control attention network = incongruent flanker condition – congruent flanker condition