A PROSPECTIVE OBSERVATIONAL STUDY INVESTIGATING COGNITIVE IMPAIRMENT AND COMORBID SYMPTOMS IN NEWLY DIAGNOSED WOMEN WITH NONMETASTATIC BREAST CANCER

by

© Nicole Rodriguez

A thesis submitted to the School of Graduate Studies

in partial fulfilment of the requirements for the degree of

Doctor of Psychology

Memorial University of Newfoundland

June 2021

St. John's, Newfoundland and Labrador

Abstract

This thesis is an investigation into the prevalence of subjective executive functioning deficits and subjective and objective cognitive impairment in women with breast cancer throughout the first year of treatment. This thesis examined the relationship between cognitive impairment and comorbid symptoms in women with breast cancer. Participants were assessed at four time points (baseline, 4, 8, and 12 months) using objective and subjective measures of cognition and sleep, and subjective measures of fatigue, mood, insomnia, and sleep quality. The final sample size was 98.

The first study used baseline data to investigate the prevalence of perceived executive functioning deficits as well as associations between perceived cognitive impairment and insomnia, fatigue, sleep quality, and mood before participants began systemic treatment and radiation. Twelve percent of the sample reported perceived executive functioning deficits and these individuals were significantly older and reported greater levels of fatigue and depressive symptoms than individuals without perceived executive functioning deficits. After partitioning out variability from other independent variables, only fatigue remained significantly associated with perceived cognitive impairment.

Using the same sample, the second study aimed to establish the prevalence of cognitive impairment throughout the first year of treatment and to examine the relationships between cognitive impairment, fatigue, insomnia, and mood using structural equation modelling. Prevalence of objective cognitive impairment ranged from 3.1 to 8.2 percent throughout the year, whereas 36.7 percent demonstrated a clinically meaningful decline in perceived cognitive impairment from baseline to 4 months, which remained relatively stable up to one year. Greater perceived cognitive impairment was associated with greater fatigue and insomnia

symptomology. Short-term fluctuations in perceived cognitive impairment, but not fatigue or insomnia, predicted future perceived cognitive impairment. Fatigue was a significant predictor of future reported symptoms of fatigue and insomnia.

General Summary

This thesis comprises two different studies that explored cognitive impairment and comorbid symptoms in newly diagnosed women with nonmetastatic breast cancer in Newfoundland and Labrador. The first chapter provides an overview of the current literature on cognition, insomnia, fatigue, and mood disturbance in women with breast cancer, discusses why this topic is germane, and concludes with the main objectives for the two studies included in this thesis. The first cross-sectional study investigated the prevalence of perceived executive functioning deficits and the factors associated with perceived cognitive impairment in women who have received surgery but have yet to commence systemic cancer treatment (e.g., chemotherapy, radiation, endocrine therapy). The second study examined the prevalence of objective cognitive impairment and changes in perceived cognitive impairment in the same sample of women with breast cancer during the first year of treatment. In addition, this study examines the relationships between perceived cognitive impairment, insomnia, fatigue, and mood over time. The final chapter reviews the results from the two studies and discusses how these findings relate and contribute to the broader literature on cognitive impairment in women with breast cancer.

Acknowledgments

Paradoxically, after four years of perpetual writing that has culminated in over 100 pages, I find myself struggling to succinctly capture my gratitude for the individuals without whom this thesis would not exist. I will do my utmost to convey my sincerest thanks, but no amount of text could ever accurately symbolize the depths of my appreciation.

First, I owe a debt of gratitude to my brilliant supervisor, Dr. Sheila Garland, who has provided me with countless clinical and research opportunities that have helped shape my professional identity over the last four years. Thank you for your mentorship, for seeing my potential, and reminding me of my strengths when I needed to hear it most. Thank you to my committee members and co-authors, Drs. Joshua Rash and Jonathan Fawcett—What was initially viewed as a herculean task is now a published paper thanks to your knowledge, expertise, and support. Thank you to the Sleep, Health, and Wellness lab volunteers and students for their tireless recruitment efforts. A similar thanks to all of the collaborating oncologists for their warm welcome into their clinics and for recognizing the importance of this work. Additionally, my deepest gratitude to all the women involved in this research for their participation during what was often described as an incredibly vulnerable and difficult period of their lives.

My success in graduate school is also largely a result of the unparalleled support from my family and friends. To my parents, Paula and Roberto, thank you for your unwavering belief in my ability to succeed and for always supporting my efforts regardless of the outcome. To Jon, you are my rock. Thank you for always bringing me back to what matters and for showing up during the most difficult times. Last but most certainly not least, I am infinitely appreciative of the most precious gift afforded to me by graduate school: My PsyD family. Cally, Megan, Emily,

Vanessa, and Jonah, thank you for the endless laughs, the beautiful memories, and the unconditional support. I still marvel at how lucky I am to get to learn from and grow with six spectacular soon-to-be clinicians.

Table of Contents

List of Tables

List of Figures

Chapter 1:

Cognitive Impairment and Comorbid Symptoms Among Women with Breast Cancer: An Overview

Cognitive Impairment and Breast Cancer

One in eight Canadian women are estimated to develop breast cancer in their lifetime, making it the most commonly diagnosed cancer type among women (Canadian Cancer Society, 2020; Statistics Canada, 2019). The current five-year breast cancer survival rate is estimated at 88 percent, and this rate is expected to increase over the next decade (Canadian Cancer Society, 2020). This reduction of breast cancer mortality over the last 20 years is in large part due to early detection and screening, and more effective treatment such as endocrine therapy combined with chemotherapy (Jarrett, 2018; Kendell et al., 2017; J. J. Tao, Visvanathan, & Wolff, 2015). That said, breast cancer and its treatment are associated with side effects that can cause significant distress and/or impairment, which can persist for years post-treatment (Ahles, Root, & Ryan, 2012; Janelsins et al., 2018; Kendell et al., 2017; Koppelmans et al., 2012). With increasingly more women experiencing long-term breast cancer survival, there is an ever-growing need to understand, prevent, and mitigate the adverse effects associated with the disease and its treatment.

Although significant progress has been made in the treatment of breast cancer, every treatment regimen takes a toll on the mind and body. Even in early-stage breast cancer, systemic treatments such as chemotherapy and endocrine therapy can cause a host of physical detriments and side effects, such as nausea, vomiting, constipation, anemia, sexual dysfunction, weight gain, and bone density loss (Partridge, Burstein, & Winer, 2001; J. J. Tao et al., 2015). Cognitive impairment (CI) associated with breast cancer has only been recognized as a significant concern by health care professionals in the past couple decades, despite its high prevalence in this population (Guo, Wei, & Ding, 2017; Joly et al., 2015; Myers, 2013). CI can present as dysfunction in a number of cognitive domains, including problems with executive functioning,

learning, memory, attention, and processing speed (Joly et al., 2015; J. J. Tao et al., 2015). Despite the growing awareness of the significance of CI, most healthcare professionals still report little understanding of how to address and manage it, which may contribute to the relatively low frequency in which they discuss these concerns with their patients (Joly, Lange, Dos Santos, Vaz-Luis, & Di Meglio, 2019). In a study of 2,537 survivors of breast cancer, only 37 percent of the 60 percent of women who reported cognitive difficulties had discussed these concerns with their physician (Buchanan et al., 2015). With more women surviving their breast cancer diagnosis and experiencing associated cognitive concerns, this highlights the need for thorough investigation into this area that has consistently been under-recognized by health care professionals and researchers.

Defining Cognitive Impairment

Although CI among individuals with breast cancer shares a number of common features, the experience of CI itself can vary drastically from one individual to another (Janelsins, Kesler, Ahles, & Morrow, 2014; Lange & Joly, 2017). CI in cancer patients can be subtle or dramatic; temporary or persistent; and stable or progressive (Janelsins et al., 2014). Some patients experience CI symptoms that wax and wane, which decreases the likelihood of detecting CI when assessing individuals in a cross-sectional manner (Janelsins et al., 2014). The ambiguity that exists in the definition of CI prompted the International Cognition and Cancer Task Force (ICCTF) to create recommended criteria for defining CI in an attempt to improve consistency of research methods across cancer studies (Wefel, Vardy, Ahles, & Schagen, 2011). The authors recommend a stepwise approach with specific cut-off scores for defining CI. They outline that CI should be defined by receiving two or more objective cognitive test scores $\geq$ 1.5 standard deviations (SDs) below the normative mean, or one objective cognitive test score $\geq$ 2.0 SDs

below the normative mean. Although these guidelines have existed for quite some time, a lack of standardized assessment and definition of CI continues to present methodological challenges with regard to this line of research.

Schilder and colleagues (Schilder et al., 2010a) demonstrated the problems associated with making cross-study comparisons with methodological inconsistency by investigating 205 breast cancer patients before they began endocrine therapy using a variety of neuropsychological measures. Using the same sample of patients, the incidence of CI varied drastically depending on the criteria used to define it, as well as the reference group used to compare test results. It is clear that there is a need for consistency across studies by following the ICCTF recommendations moving forward, which will ultimately allow clinicians to make more accurate estimates of prevalence.

Along with a lack of a universally accepted definition of CI in cancer patients, there are marked differences in the types of assessment measures used to evaluate cognitive functioning across studies (Ahles et al., 2012; Pendergrass, Targum, & Harrison, 2018). The inconsistencies in the measurement of CI also provoked the ICCTF to create recommended guidelines for assessment of cognitive function in cancer, which emphasized the use of observational, longitudinal designs with pre-treatment cognitive assessment (Wefel et al., 2011). They also recommend the use of a specific battery of measures with adequate psychometric properties and the availability of multiple test forms for repeated testing. This set of guidelines has been put forth to increase methodological consistency across studies and facilitate between-study comparisons.

Despite the ICCTF recommendations being a decade old, researchers are still failing to put forth studies that follow its guidelines. For example, a 2019 study investigated pre and post

chemotherapy cognitive functioning as well as anxiety and depression symptoms in 100 breast cancer patients (Hormozi, Hashemi, & Shahraki, 2019). Despite its longitudinal design and the inclusion of a pre-treatment assessment of cognition, CI was defined based on participants' score on the Mini Mental State Examination (MMSE). The MMSE is a neuropsychology measure used to screen severe cases of CI and is not a valid nor comprehensive measure of cognitive performance in this population (Sachdev et al., 2015). The variability in methodology by older and newer studies illuminates the importance for conducting newer longitudinal research with pre-treatment assessment that utilizes valid measures of CI.

Subjective/Perceived Cognitive Impairment

In addition to utilizing objective measures of CI, it is equally important to consider subjective or perceived CI. Gaining insight into the perception of one's cognitive functioning may bring to light aspects of the CI experience that cannot be captured by objective measures, including more subtle deficits in cognition (Janelsins et al., 2018; Lai et al., 2009). Additionally, perceived CI may occur in the presence or absence of objective CI and vice versa. For example, one study investigated pre-treatment CI in 184 women with breast cancer using a subjective measure of cognitive functioning, the Attentional Functional Index, and objective standardized tests of attention and memory, including Digit Span and the Trail Making Test (Cimprich, So, Ronis, & Trask, 2005). The objective test results demonstrated no deviation from healthy controls; however, 25 percent of women reported perceived CI before treatment. Moreover, objective CI appears to be less prevalent than what is estimated from self-report (Biglia et al., 2012; Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012). Some researchers have suggested that this is due to the strong association between perceived CI and negative affect in this population, and that the negative emotionality that often accompanies a cancer diagnosis

likely serves to increase one's perception of poor cognitive functioning (Biglia et al., 2012). Perceived CI may therefore be a more accurate indicator of the impact and functional impairment associated with these deficits, which emphasizes the importance of capturing self-report along with objective assessment (Hutchinson et al., 2012; Myers, 2013).

Perceived CI must also be regarded as an independent patient experience separate from objective CI. The majority of studies demonstrate weak or non-existent associations between objective and subjective CI (Ahles & Hurria, 2018; Hutchinson et al., 2012). Vardy et al. (2006) demonstrated this using a sample of 31 breast and colorectal cancer patients (94% breast). They found no correlation (i.e., spearman correlation coefficient <.05) between the Functional Assessment of Cancer Therapy-Cognition (measure of perceived CI) and brief computer tests (assessment of objective memory, attention, decision-making skills, and processing speed). Subsequent studies that have utilized objective neuropsychological tests have demonstrated similar results, with negligible correlations between objective and perceived CI (Jenkins et al., 2006; Schagen et al., 2008; Schilder et al., 2009).

It is clear that in addition to following the ICCTF guidelines, studies must also adequately assess for objective and subjective CI in women with breast cancer. More comprehensive assessment of CI will allow clinicians to better understand the underlying mechanisms involved, in order to be able to accurately assess CI, identify individuals at risk, and treat the accompanying symptoms.

Prevalence and Persistence of Cognitive Impairment

Cognitive difficulties are one of the most frequently reported symptoms among cancer patients and survivors, affecting individuals across a variety of stages and ages (Janelsins et al., 2014). The lack of a universal definition for and measurement of CI has made it difficult to

establish reliable prevalence estimates (Wefel et al., 2011); however, cross-sectional and longitudinal studies have reported that up to 30 percent of breast cancer patients experience objective CI prior to starting treatment (Hermelink et al., 2007; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). Using a battery of 12 neuropsychological tests (Hermelink et al., 2007), 31 percent of 101 patients with breast cancer demonstrated objective CI before beginning neoadjuvant chemotherapy (defined as ≥ 2 test scores falling below the 5th percentile). At the second assessment time point (5 months after baseline), 27 percent of women were found to meet criteria for objective CI. When considering research that incorporates definitions of CI that are subjective in nature, up to 75 percent of women experience perceived impairments in various cognitive domains throughout treatment (Janelsins et al., 2014; Joly et al., 2015).

For some women, their experience with CI is acute and time limited; however, for others, it can persist for years following treatment and remission, with up to 35 percent of patients reporting CI from 6 months to 20 years following treatment (Koppelmans et al., 2012; Yamada, Denburg, Beglinger, & Schultz, 2010). For example, Yamada and colleagues (2010) investigated cognitive functioning in 30 breast cancer survivors who were treated with chemotherapy at least 10 years prior to the conduction of the study and compared their results to 30 healthy controls. Participants completed a 3-hour battery of neuropsychological tests and were compared to a control group of 30 healthy women matched for age and education. Women treated with chemotherapy performed significantly worse on cognitive tests that measured attention, working memory, psychomotor speed, and executive functioning. Similar results were replicated by Koppelmans et al. (2012) with a larger sample size. These prevalence rates are alarming and elucidate the importance of understanding the effect of CI on everyday functioning.

Impact of Cognitive Impairment

The impact of CI is pervasive, affecting all areas of functioning, including psychological, social, and occupational domains (Boykoff, Moieni, & Subramanian, 2009; Klemp et al., 2018; Lange & Joly, 2017). The impact of perceived CI on functioning was explored in a summary of 17 qualitative studies (with a total sample size of 474 patients), 14 of which included breast cancer patients (Myers, 2013). The specific deficits noted by breast cancer patients included forgetting names, words, places, and appointments; difficulties multitasking; difficulties communicating with more than one person at a time; short and long-term memory deficits; increased confusion; and decreased sense of direction and coordination. Women reported that these deficits in cognition negatively impacted their confidence and increased their levels of anxiety and distress. Furthermore, commonalities in descriptions of the CI experience included feelings of embarrassment and stupidity; tension amongst family members related to difficulties with memory; difficulties maintaining strong interpersonal relationships; and frequent rumination about memory concerns indicating risk for potential Alzheimer's disease or dementia. These results demonstrate the negative social and psychological ramifications of CI. With up to 35 percent of women experiencing CI for months or years post treatment (Koppelmans et al., 2012; Yamada et al., 2010), this raises concerns regarding the psychological functioning of the women coping with these impairments.

The debilitating effects of CI are evident in patients' professional lives as well (Downie, Mar Fan, Houede-Tchen, Yi, & Tannock, 2006; Lange, Joly, et al., 2019; Lange, Licaj, et al., 2019). In a recent cross-sectional survey of 1610 cancer survivors (1393 breast cancer survivors), 76 percent of participants who had endorsed perceived CI reported that their ability to resume work was impacted by their impairments (Lange, Licaj, et al., 2019). Women with breast cancer and perceived cognitive impairments report that work is a stressful and distressing part of their

day as they are perpetually worried about making mistakes and/or the possibility of forgetting to complete certain tasks (Myers, 2013). In a qualitative study of the experiences of 74 breast cancer patients who were at least one-year post-treatment (Boykoff et al., 2009), women reported that their work ability was negatively impacted by changes in cognitive domains such as memory, processing speed, and comprehension. Of the women who were currently employed (54%), common experiences included decreased efficiency, increased stress levels due to forgetting, and decreased confidence due to negative perceptions of the quality of their memory and efficiency. The symptoms of CI can become so distressing for some women that they opt for early retirement or ultimately ended up leaving work due to the stress of making mistakes and/or forgetting important details of their work (Boykoff et al., 2009; Von Ah, Habermann, Carpenter, & Schneider, 2013). The pervasiveness and persistence of CI has financial, social, and psychological ramifications for women surviving their diagnosis that can collectively lead to a significant reduction in quality of life for many women.

Treatment-Induced Cognitive Impairment

The pathophysiology of CI still remains inadequately understood, which contributes to the difficulties with assessment and management. CI in cancer populations is often referred to as "chemobrain" or "chemofog" in popular media (Schilder & Schagen, 2007). There is robust evidence to support the association between chemotherapy and CI, with a particularly large number of studies focusing specifically on breast cancer patients (Hermelink et al., 2007; Janelsins et al., 2017; Kim, Jung, Kim, & Abraham, 2020; Lindner et al., 2014; Yao, Bernstein, & Rich, 2017). With regards to chemotherapy and CI, the neurotoxicity of chemotherapy has been suggested to induce impairments via increased levels of cytokines; deoxyribonucleic acid (DNA) damage and telomere shortening; reduction in frontal lobe gray matter and white matter;

and structural and functional hippocampal damage (Conroy et al., 2013; Di Iulio et al., 2019; Pendergrass et al., 2018; Peukert et al., 2020). A recent systematic review of CI following chemotherapy in non-central nervous system cancers supported an association between objective CI and chemotherapy (Di Iulio et al., 2019). The authors reviewed a total of 29 randomized controlled trials (RCTs), observational studies, and cross-sectional studies; 21 of these focused exclusively on patients with breast cancer. The majority of the studies (22 of 29) found that chemotherapy, both alone and in conjunction with hormonal therapy, negatively impacts cognitive functioning in all cancer types. Chemotherapy was associated with worse performance in various areas of cognitive functioning, including processing speed, attention, visuospatial skills, motor function, working memory, and verbal memory. Further, the review suggested that patients with breast cancer, more than any other cancer population studied, demonstrate greater impairments in functioning and reduced quality of life as a result of the cognitive deficits following chemotherapy.

There are still questions remaining regarding the direct effects of chemotherapy on brain structure and functioning, but evidence suggests that deficits in cognitive functioning following chemotherapy are not exclusive to the treatment period. The short and long-term effects of chemotherapy are evident when investigating both objective and perceived CI, with patients with breast cancer demonstrating CI 6 months to 20 years post chemotherapy (Janelsins et al., 2017; Koppelmans et al., 2012). For example, Koppelmans et al. (2012) investigated cognitive functioning in 196 breast cancer survivors who were treated with adjuvant chemotherapy, on average, 21.2 years prior to the study. Participants completed a battery of neuropsychological tests and a memory complaints questionnaire and were compared to a control group of 1,509 women without a cancer history. Women treated with chemotherapy performed significantly

worse on several cognitive tests that measured learning, immediate and delayed verbal memory, processing speed, inhibition, and psychomotor speed. They were also more likely to report subjective memory complaints (e.g., word retrieval and daily forgetting) than the control group. These findings demonstrate that the effects of chemotherapy on cognitive functioning can be persistent.

Although there is a plethora of research establishing the relationship between chemotherapy and CI, there appears to be wide discrepancy in the magnitude of CI following chemotherapy (Bernstein, McCreath, Komeylian, & Rich, 2017; Ono et al., 2015). A 2015 meta-analysis aimed to assess the degree of CI following chemotherapy in a review of 27 studies with a total of 4,361 patients with breast cancer (Ono et al., 2015). Overall, the degree of CI was quite variable, with different results depending on the type of study design used (e.g., cross-sectional, longitudinal). In cross-sectional studies, women treated with chemotherapy had CI of small, but significant magnitude compared to healthy controls. However, in longitudinal studies, women treated with chemotherapy showed significantly better performance over time, or post-chemotherapy. The authors attributed this finding to the variability in the timing of post-chemotherapy assessment, stating that CI may not be as prominent when assessing individuals after the active treatment period. Processing speed, attention, executive function, and short-term memory were, overall, more impacted by chemotherapy than long-term memory, visuospatial abilities, and language. Compared to healthy controls, women treated with chemotherapy demonstrated significantly worse performance on cognitive measures, but this finding did not persist when women who received chemotherapy were compared to patients with breast cancer who did not undergo chemotherapy. These results were replicated again in a 2017 meta-analytic review of 72 studies with 2,939 patients with breast cancer. Women treated with chemotherapy

demonstrated significant differences (i.e., worse performance) in cognitive functioning compared to healthy controls but not with other patients with breast cancer treated without chemotherapy. Taken together, these results suggest that other factors, including other treatment modalities, must also contribute to the development of CI, beyond what has been previously reported.

Other systemic treatments, including endocrine therapies such as tamoxifen and letrozole, are also associated with cognitive deficits (Ahles et al., 2012; Lange, Joly, et al., 2019; Underwood et al., 2019; Van Dyk et al., 2019). Although endocrine therapies have played a significant role in increasing the breast cancer survival rate, they also influence the anti-inflammatory, glucose transportation, and cerebral blood flow processes associated with healthy cognitive functioning (Biglia et al., 2010; Phillips et al., 2010; Schilder & Schagen, 2007). It is possible that hormonal therapy might be impacting cognition through different mechanisms, although this relationship is still not well understood. Authors from a 2016 systematic review (Lee, Tierney, Wu, Pritchard, & Rochon, 2016) sought to investigate the objective cognitive effects associated with endocrine therapy in women with breast cancer. Their review included 21 short term (duration of treatment < two years) and long term (duration of treatment >2 years) studies with a total of 2,398 breast cancer participants assessed using neuropsychological tests. Endocrine therapy administered in both the short and long term was associated with objective CI as demonstrated by significantly lower scores on neuropsychological tests of memory, learning, processing speed, and executive function than healthy controls. Research demonstrates that cognitive impairments are greater when endocrine therapy is combined with chemotherapy than with endocrine therapy alone (Wagner et al., 2020). These treatments represent only two of many factors potentially involved in CI's development, however, and researchers need to continue to

expand their investigations to more comprehensively understand what factors may influence the development of CI in women with breast cancer.

Pre-Treatment Cognitive Impairment

Although the link between systemic cancer treatment and CI is widely appreciated, the evidence from longitudinal research suggests that factors independent of treatment must also be involved. Wefel and colleagues (2004) conducted one of the first longitudinal studies to assess CI prior to and after receiving chemotherapy. The authors assessed 18 women with breast cancer before and after standard dose adjuvant chemotherapy using various validated neuropsychological tests and self-report measures, including various subtests from the Wechsler Adult Intelligence Scale (WAIS) and the Functional Assessment of Cancer Therapy-Breast module (FACT-Breast module). Sixty-one percent of women demonstrated CI six months after treatment, which supported the role of chemotherapy in CI's development. However, using published normative data adjusted for age and education, 33 percent of women demonstrated CI before commencing cancer treatment. These results were confirmed in a 2007 study with a larger sample size. Using a battery of 12 objective neuropsychological tests to assess 101 women before and after neoadjuvant chemotherapy (Hermelink et al., 2007), 31 percent of women demonstrated CI before beginning treatment (defined by ≥2 test results falling in the 5th percentile using established test norms). Other findings, however, have not supported the presence of objective CI prior to treatment, but rather, have demonstrated that subjective cognitive complaints are a larger concern (Cimprich et al., 2005). This demonstrates that, as aforementioned, assessment of both objective and perceived CI is necessary at any assessment stage.

The results of the existing literature suggest that treatment does not fully explain the presence of objective or perceived CI in women with breast cancer. There are still important questions to answer regarding the factors independent of treatment that might be impacting the development and progression of CI. One such question involves the role that comorbid symptoms, including insomnia, fatigue, and mood disturbance, could be playing in the development of CI in this population.

Insomnia and Breast Cancer

Cognitive impairments are rarely experienced in isolation and typically co-occur with other symptoms and side effects, which can exacerbate the stressful nature of the cancer experience. In addition to high rates of CI, sleep disturbances such as insomnia are also frequently reported in women with breast cancer (Caplette-Gingras, Savard, Savard, & Ivers, 2013; Fleming et al., 2019; Garland et al., 2018; J. Savard, Ivers, Villa, Caplette-Gingras, & Morin, 2011; J. Savard & Morin, 2001). Insomnia is characterized by a dissatisfaction with one's sleep patterns, difficulty falling asleep, difficulty staying asleep, or early morning awakenings, and daytime impairments that occur at least three nights per week, and have been present for at least three months despite adequate opportunity for sleep (American Psychiatric Association, 2013). An individual who meets these criteria can be diagnosed with insomnia disorder, while individuals who only meet some of these criteria can be considered to have insomnia symptoms which may be of clinical relevance. Insomnia severity is associated with reduced quality of life and can precipitate and/or exacerbate psychological and physical illness (O. Palesh et al., 2008; O. G. Palesh et al., 2010).

Between 30 and 60 percent of patients with cancer are affected by insomnia symptoms depending on the type and timing of measurement (Davidson, MacLean, Brundage, & Schulze,

2002; J. Savard et al., 2011; J. Savard & Morin, 2001). One of the few longitudinal studies in this area aimed to document the prevalence and trajectory of insomnia symptoms in 962 patients with nonmetastatic cancer (49 percent breast cancer) over an 18-month period (J. Savard et al., 2011). The authors used a prospective observational design with six assessment time points, with the first assessment occurring shortly after treatment initiation. Using a semi-structured insomnia interview, the authors placed patients into one of three categories: 1) Good sleepers (defined as the absence of a sleep complaint), 2) insomnia symptoms (presence of a sleep complaint but sub-threshold for insomnia disorder), and 3) insomnia syndrome (symptoms consistent with DSM-5 definition of insomnia disorder, except for the duration of ≥ 1 month). Using this categorization, patients with breast cancer consistently reported the highest prevalence of insomnia symptoms as well as insomnia syndrome of all cancer types. Thirty-three percent of patients with breast cancer demonstrated insomnia symptoms and 36 percent demonstrated insomnia syndrome at baseline, which decreased to 16 percent and 26 percent at 18-months, respectively. These results demonstrate that insomnia symptoms and syndrome decrease after the active treatment period for a proportion of people, but that those who had insomnia syndrome at baseline were most likely to have insomnia syndrome throughout the entire 18-month period. The authors also found that those who were considered good sleepers at baseline were less likely to develop an insomnia syndrome at a subsequent time point than those with insomnia symptoms or syndrome at baseline.

A 2019 longitudinal study (baseline to 12-months) of 173 patients with breast cancer explored a similar question to that described above (Fleming et al., 2019). The prevalence of insomnia (as measured by the Insomnia Severity Index) was high in this population, with 46 percent of women experiencing insomnia symptoms at diagnosis. The prevalence of insomnia

symptoms remained at about 50 percent throughout the following year. Additionally, 77 percent of those defined as having good sleep prior to diagnosis developed insomnia symptoms during the following year, whereas results from Savard et al. (2011) suggested that having good sleep at baseline may serve as a protective factor against future insomnia. These findings reveal that insomnia in patients with breast cancer is persistent, which has concerning physical and psychological health implications for the many women affected.

The higher prevalence of insomnia in cancer has been attributed to different factors, including the emotional burden associated with the diagnosis and its treatment (Garland et al., 2018). Additionally, ruminative anxiety and worry resulting from the uncertainty and fear engendered by the cancer experience can interfere with one's sleep (Garland et al., 2014). In terms of treatment, chemotherapy, in particular, has been identified as a risk factor for persistent insomnia (Fleming et al., 2019; J. Savard et al., 2009). A prospective study of 823 patients with cancer (50 percent breast cancer) (O. G. Palesh et al., 2010) demonstrated that 37 percent of all patients who received chemotherapy endorsed insomnia symptoms and 43 percent met criteria for insomnia syndrome during the first cycle of chemotherapy, and these rates persisted during the second cycle of treatment. Insomnia symptoms were measured by the Hamilton Depression Inventory, which includes six questions assessing duration and frequency of sleep problems as well as questions to assess severity of sleep problems in the last two weeks. Similarly, using the Pittsburgh Sleep Quality Index (PSQI) with 502 newly diagnosed patients with breast cancer, a 2017 study demonstrated that 60 percent of patients had poor sleep quality (defined by a PSQI global score > 5) before the commencement of treatment. Additionally, those who were treated with chemotherapy demonstrated higher rates of poor sleep quality than those who underwent other forms of cancer treatment (Fontes, Pereira, Costa, Goncalves, & Lunet, 2017).

The accompanying physical side effects of chemotherapy and other treatments have also been associated with higher prevalence of insomnia in cancer populations (Davidson et al., 2002; M. H. Savard, Savard, Caplette-Gingras, Ivers, & Bastien, 2013). For example, the onset or worsening of menopausal symptoms is known to contribute to sleep maintenance difficulties in breast cancer populations through increases in vasomotor symptoms (Downie et al., 2006; M. H. Savard et al., 2013). In a systematic review of 27 studies investigating risk factors for sleep disturbances in patients with breast cancer, women who experienced hot flashes as a result of their treatment regimen were 2.25 times more likely to develop sleep disturbance (defined by insomnia symptoms, insomnia syndrome, and sleep-wake disturbances) than those without hot flashes (Leysen et al., 2019). Using a variety of subjective measures and a semi-structured interview, 83 percent of 21 patients with breast cancer experienced menopausal symptoms such as hot flashes and cold sweats and approximately half of the women endorsed that their sleep was being interrupted by hot flashes during the night (Downie et al., 2006). Taken together, it appears that the psychological, physical, and neurotoxic effects of cancer treatments play a role in the higher prevalence of insomnia. These results highlight the importance of investigating sleep disturbance such as insomnia during the treatment period and to examine its relationship with CI during this time.

Insomnia and Cognition in the General Population

The connection between sleep and cognition is well established in the general population, with poor sleep quality shown to negatively impact a variety of cognitive domains (Durmer & Dinges, 2005; Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin, 2012; Gobin, Banks, Fins, & Tartar, 2015; Goel, Rao, Durmer, & Dinges, 2009). Sleep disorders such as insomnia are associated with deficits in cognition in the general population as well, with insomnia severity

positively correlated with CI (Fortier-Brochu et al., 2012; Szelenberger & Niemcewicz, 2000). In a systematic review and meta-analysis of 48 studies conducted in non-cancer populations, insomnia was significantly associated with overall poorer cognitive performance as well as worse performance in specific cognitive domains including attention, perceptual reasoning, memory retention, working memory, problem solving, and episodic memory (Wardle-Pinkston, Slavish, & Taylor, 2019).

There are several biological mechanisms that have been proposed in an effort to establish the pathways by which sleep disturbances contribute to CI. These include, but are not limited to, changes in neurotransmitter systems involved in sleep (Bekinschtein et al., 2008; Havekes, Vecsey, & Abel, 2012); neural disruptions and reduction in the volume of the hippocampus (Meerlo, Mistlberger, Jacobs, Heller, & McGinty, 2009; Riemann et al., 2007); changes in the functioning of the hypothalamic-pituitary-adrenal (HPA) axis (van Dalfsen & Markus, 2018); and changes in functionality of different brain regions involved in working memory (Chee et al., 2006; Mu et al., 2005). With documented neural changes associated with cancer treatments, it makes sense that one might see higher rates of CI among individuals with cancer, and even higher rates among individuals with cancer and sleep disturbance. Further research in this area with a focus on patients with breast cancer is necessary as these biological processes may function differently when cancer pathology is present. With a clearly defined relationship between insomnia and cognition in cancer-free populations, this relationship should undoubtedly be investigated in patients with breast cancer who demonstrate disproportionately high rates of insomnia.

Insomnia and Cognition in Breast Cancer

Research on the relationship between insomnia and cognition in patients with breast cancer is limited, with the majority of studies being cross-sectional. In a 2019 cross-sectional study with 1072 breast cancer survivors treated with an aromatase inhibitor (i.e. endocrine therapy), 52 percent of the sample reported mild to severe insomnia symptoms as measured by the Insomnia Severity Index (ISI) (Liou et al., 2019). Prevalence of dissatisfaction with one's cognitive functioning (as measured by the cognitive subscale of the Breast Cancer Prevention Trial Symptom Checklist (BCPT)) was also high, with 79 percent endorsing that they were bothered by their forgetfulness, concentration issues, and/or distractibility. Importantly, a greater degree of insomnia symptoms (defined by higher ISI scores) was associated with a greater degree of perceived CI (defined by higher scores on the BCPT).

Using the ISI, sleep diary data, and various objective and subjective measures of cognitive functioning, a 2013 cross-sectional study investigating 67 patients with breast cancer found that those with insomnia demonstrated greater perceived CI and performed worse on verbal episodic memory and executive functioning domains compared to those without insomnia (Caplette-Gingras et al., 2013). A cross-sectional online survey also demonstrated a relationship between self-reported sleep difficulties and cognitive complaints (Lange, Licaj, et al., 2019). Those with cognitive complaints were also more likely to have pre-existing knowledge about chemotherapy-related cognitive problems, suggesting that prior knowledge may serve to make women more anxiously aware and attuned to the subtle changes in cognition that they may not have noticed previously. Considering that some women will experience CI symptoms that wax and wane (Janelsins et al., 2014), more longitudinal studies with pre-treatment assessment are required to better understand the relationship between insomnia and CI in this population.

Cancer-Related Fatigue and Breast Cancer

In addition to insomnia, women with breast cancer are also at increased risk of experiencing fatigue. Cancer-related fatigue, or CRF, is defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (National Comprehensive Cancer Network, 2020). CRF is distinct in that it appears to be more intense, persistent, and burdensome than normal fatigue experienced by individuals without a cancer history (Cella, Lai, Chang, Peterman, & Slavin, 2002). CRF can present before diagnosis, during treatment, and after treatment completion, with many individuals experiencing CRF symptoms years into remission (Gosain & Miller, 2013; Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007). During active treatment, 30 to 60 percent of women with breast cancer endorse moderate to severe fatigue (Joly et al., 2019). CRF is associated with reduced quality of life and has a profound impact on everyday functioning, with depression, pain, and a decline in both physical and cognitive functioning implicated in patients affected (de Lima et al., 2017; Joly et al., 2019; X. S. Wang & Woodruff, 2015). In addition to impeding the ability to live a normal life, many patients with CRF also elect to reduce treatment dosage or discontinue treatment altogether due to exhaustion, which can ultimately impede recovery and/or worsen prognosis (X. S. Wang & Woodruff, 2015). CRF is therefore a crucial component to consider in breast cancer research, both on its own and in conjunction with accompanying side effects.

Cancer-Related Fatigue Etiology

CRF's etiology is multi-factorial and complex, with a variety of demographic, psychosocial, behavioral, and biological factors implicated in its development (Bower, 2014; Donovan, Small, Andrykowski, Munster, & Jacobsen, 2007). Evidence suggests that cancer and

its treatments lead to increases in pro-inflammatory cytokines, which subsequently leads to neural, physiological, and behavioral changes that are responsible for the symptoms of fatigue (Bower, 2014). Other biological mechanisms have also been implicated, including HPA axis, neurotransmitter, hormonal, and autonomic nervous system dysregulation (Bower & Ganz, 2015; Bower, Ganz, Irwin, Arevalo, & Cole, 2011; Crosswell, Lockwood, Ganz, & Bower, 2014). These biological mechanisms are still not fully understood, and are not always observed in every patient, suggesting that other factors also contribute to CRF's development (Bower, 2014).

Other risk factors for developing CRF have been identified, including physical deconditioning, mood disturbance, social isolation, low income, pre-treatment fatigue, undergoing multiple cancer treatments, and sleep disturbance (Bower, 2014; Donovan et al., 2007; Joly et al., 2019). Although insomnia and CRF are often considered independently, research has demonstrated that insomnia contributes to the development and severity of fatigue in cancer patients and survivors (Goedendorp, Gielissen, Verhagen, & Bleijenberg, 2013; Mao et al., 2018; O. G. Palesh et al., 2010; Pertl, Hevey, Collier, Lambe, & O'Dwyer, 2014). In a 2012 study with 114 women with breast cancer (Minton & Stone, 2012), the prevalence of insomnia syndrome in patients with fatigue was 44% compared to 16% in those without fatigue. Furthermore, objective and subjective sleep quality was investigated along with fatigue in a 2012 study of 97 patients with breast cancer undergoing chemotherapy (Lianqi Liu et al., 2012). Women were assessed once before chemotherapy, three times during the first cycle of chemotherapy, and three times during the fourth cycle of chemotherapy using the Multidimensional Fatigue Symptom Inventory- Short Form (MFSI-SF), the Pittsburgh Sleep Quality Index (PSQI), and Actigraphy– a device that measures gross motor activity to estimate objective sleep parameters. Fatigue increased significantly over the six assessments, whereas

subjective sleep quality remained the same. However, the mean total PSQI scores prior to treatment initiation was above 5, suggesting that women were experiencing poor sleep before treatment even began. Fatigue and subjective sleep quality were associated even after controlling for confounding factors such as cancer stage, treatment regimen, age, and education; however, no relationship was found between fatigue and objective sleep parameters (e.g., total sleep time (TST)). Total daytime and nighttime sleep time (as measured by actigraphy) increased significantly over the treatment period, with significantly greater TST values during chemotherapy than at the pre-treatment assessment. These results also demonstrate that regardless of sleep duration, fatigue levels persist and worsen over the course of treatment.

Despite the combined pervasiveness and impact of CRF and insomnia, the exact mechanisms underlying these symptoms remain poorly understood. Researchers have suggested a multifactorial mechanism whereby physiological and biological factors (e.g., hormonal changes, increases in inflammatory cytokines), psychosocial factors (e.g., depression, anxiety, stress), chronobiological factors (e.g., altered circadian rhythms), and behavioral factors (e.g., decreased activity, increased napping) co-occur and interact along with patients' unique characteristics to create sleep disturbance and symptoms of CRF (L. Liu et al., 2005; Lianqi Liu et al., 2012; Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003). Given that insomnia and fatigue likely share similar underlying mechanisms, it is imperative that both are investigated in relation to cognition in women with breast cancer. Additionally, it is possible that fatigue influences cognition indirectly through sleep as sleep quality has been shown to be directly linked to cognition (Xu et al., 2017).

Cancer-Related Fatigue and Cognition

Cognitive exhaustion is a defining feature of CRF; however, relatively little research on the relationship between fatigue and CI has been conducted. One of few studies investigating CI and concurrent symptoms in women with breast cancer involved assessment of 75 women over the course of two years (Lyon et al., 2016). Participants were assessed five times during this period using an objective neurocognitive computer-based test, as well as the Brief Fatigue Inventory (BFI) and other demographic and psychological self-report measures. Fatigue severity varied across the two-year period, with fatigue levels being the lowest (mean BFI score of 2.89) prior to treatment initiation and highest (mean BFI score of 4.30) at the second assessment time-point following the initiation of chemotherapy. A decrease in fatigue severity to near baseline-levels was observed one year following treatment, suggesting that fatigue was most prevalent during the active treatment period. Importantly, while anxiety, depression, and stress were associated with worse performance on the neuropsychological test, fatigue remained the strongest predictor of CI and was consistently associated with CI throughout the entire study period. A follow up study utilizing the same sample of patients demonstrated that attention, executive functioning, and processing speed had the strongest relationships with fatigue severity and interference over the two-year period (Gullett et al., 2019).

Cross sectional data has also demonstrated a relationship between fatigue and objective CI. A 2018 study of 189 patients with breast cancer demonstrated this relationship in women who had received chemotherapy, surgery, and/or radiation, but had not yet begun endocrine therapy (Van Dyk, Bower, Crespi, Petersen, & Ganz, 2018). Using the Multidimensional Fatigue Symptom Inventory and a battery of neuropsychological tests endorsed by the ICCTF, the authors demonstrated that total fatigue scores were negatively correlated with executive functioning, such that greater fatigue scores were related to worse executive functioning. The

physical domain of fatigue was related to worse attention, executive function, and processing speed. Sleep quality, as measured by the PSQI, was also significantly related to learning, memory, attention, and executive function.

Fatigue is also related to perceived CI among women with breast cancer. In a recent cross-sectional study of 204 patients with breast cancer who were post-surgery and about to receive chemotherapy or currently receiving chemotherapy, fatigue (measured by the Functional Assessment of Chronic Illness Therapy-Fatigue) was negatively associated with perceived CI (as measured by the PCI subscale of the Functional Assessment of Cancer Therapy-Cognitive Function), even after accounting for education, age, and chemotherapy (Li, Yu, Long, Li, & Cao, 2015). Fatigue has been documented as one of the most burdensome symptoms related to cancer, and its ability to exacerbate other side effects such as CI suggests that more research into this area is necessary.

Mood Disturbance and Breast Cancer

The co-occurrence of insomnia, fatigue, and mood disturbance suggests that this is an important symptom cluster in cancer patients (Sanford et al., 2014). Just as insomnia and fatigue are highly correlated in this population, mood disturbance, particularly depressive symptoms, are also highly correlated with fatigue (Avis, Levine, Case, Naftalis, & Van Zee, 2015; Biglia et al., 2012; Gullett et al., 2019) and insomnia (O. G. Palesh et al., 2010). Between 40 to 82 percent of cancer patients report clinically significant depressive symptoms during chemotherapy treatment (Massie, 2004). A 2015 systematic review on breast cancer and psychological variables found that prevalence of depressive symptoms ranged from 9.4% to 66.1% and anxiety symptoms ranged from 17.9% to 33.3% in women who had received their breast cancer diagnosis one year prior. Receiving a cancer diagnosis and undergoing cancer treatment are inherently stressful

experiences that can lead to emotional overwhelm and distress, and subsequent symptoms or clinical levels of depression and anxiety. Mood disturbance is yet another contributor to reduced quality of life in this population and can influence morbidity and treatment course (Croyle & Rowland, 2003). As such, it is important to explore mood disturbance in the context of breast cancer.

Similar to fatigue, the trajectory of anxiety and depression symptoms appears to vary across time and treatment (Martino et al., 2020). Martino et al. (2020) reported that postmenopausal patients with breast cancer (N=51) endorsed significantly higher levels of anxiety (as measured by the Hamilton Anxiety Rating Scale) and depression (as measured by the Beck Depression Inventory-II) than healthy controls before starting endocrine therapy and 6 months later. Unlike controls, breast cancer participants demonstrated significant reductions in depression and anxiety symptoms at the 6-month assessment. However, mean total symptom scores still remained significantly higher than the control group. The authors attributed the higher levels of mood disturbance at the baseline assessment to the initial shock of a cancer diagnosis and emotional distress associated with the uncertainty and fear that is present during the early stages of diagnosis and treatment. The fact that mood disturbance still remained significantly greater at the follow-up assessment suggests that emotional difficulties persist even after the acute adjustment period. Although high rates of depressive and anxious symptoms have been established in patients with breast cancer, less is known about how these might be related to CI.

Mood Disturbance and Cognition

Cognitive difficulties are among the list of symptoms for depressive disorders and are frequently observed as a consequence of cognitive interference associated with anxiety symptomology and anxiety disorders (Ramalho, Fontes, Ruano, Pereira, & Lunet, 2017). Given

the higher prevalence of mood-related concerns among women with breast cancer, it is thus appropriate to question the relationship between these concerns and CI in this population. Mood-related symptoms have been inconsistently associated with cognitive impairments among women with breast cancer (Di Iulio et al., 2019; Yang & Hendrix, 2018). A recent systematic review of 29 RCTs and observational studies (21 with exclusive focus on breast cancer) on cancer and cognition concluded that there appears to be a stronger relationship between depression and anxiety symptoms and perceived CI than objective CI. For example, Pullens et al. (2013) compared 74 patients with breast cancer before and after chemotherapy to 63 healthy controls. They found that greater depressive (as measured by the Centre for Epidemiological Studies-Depression Scale) and anxiety (as measured by the State-Trait Anxiety Inventory) symptoms at the pre-chemotherapy assessment significantly predicted worse satisfaction with cognitive functioning and greater frequency of cognitive complaints (as measured by the Cognitive Failures Questionnaire and the World Health Organization Quality of Life assessment instrument) at the second assessment time-point. Another similar longitudinal study of 40 patients with breast cancer was conducted pre and post chemotherapy using a battery of objective and subjective cognitive measures, the Hospital Anxiety and Depression Inventory, the Montgomery Asberg Depression Rating Scale, and a quality of life questionnaire (Biglia et al., 2012). Depression and anxiety were significantly negatively associated with perceived CI but were unrelated to objective CI. The finding that depression, anxiety, and/or psychological distress is not related to objective CI has been replicated in other studies (Hermelink et al., 2007; Schilder et al., 2012; Stewart et al., 2008; Wefel, Saleeba, Buzdar, & Meyers, 2010). It has been recommended that studies continue to explore mood in the context of CI with emphasis on exploring both perceived and objective CI (Di Iulio et al., 2019). This emphasizes further the

importance of comprehensive assessment of cognition in the context of cancer, and the idea that perceived CI may be a more accurate indicator of the functional impairment experienced by women throughout treatment.

Given the frequency of the co-occurrence of insomnia, fatigue, and mood disturbance, it is possible that these symptoms may result from shared physiological and/or behavioral mechanisms that may together contribute to CI above and beyond the contribution of a single side effect alone. It is also possible that tri-directional relationships exist among these symptoms, whereby the presence of one exacerbates the other, which further contributes to CI. Additionally, insomnia, fatigue, and mood disturbance are all, by definition, subjective experiences, and the dissatisfaction and negative affectivity associated with disturbed sleep, energy levels, and psychological functioning may serve to highlight even further the subtle changes in cognitive functioning that can accompany these side effects.

Behavioral and psychological variables are insufficiently investigated when studying the presence and severity of CI in women with breast cancer over time. Studies that have attended to additional factors typically include small sample sizes, lack of pre-treatment assessment, and/or inconsistent and invalid use of measurement tools. In addition, cross-sectional studies are not sufficient, particularly given that the nature of CI and other cancer-related symptoms have been shown to change over time. It is thus clear that increased attention is required in order to fully understanding the course of CI and the factors involved in patients with breast cancer.

Primary Research Objectives

The primary research objectives of this thesis are as follows:

Chapter 2 objectives:

1) To establish the prevalence of pre-treatment perceived deficits in executive functioning in women with non-metastatic breast cancer.

2) To examine the relationships between pre-treatment perceived CI, insomnia, total sleep time, sleep efficiency, sleep quality, fatigue, and mood disturbance.

Chapter 3 objectives:

1) To characterize the prevalence of objective CI and change in perceived CI among women with breast cancer during the first year of treatment.

2) To examine the relationships between perceived CI, insomnia, fatigue, and mood over time.

Chapter 2:

Prevalence and Factors Associated with Executive Functioning Difficulties and Cognitive Impairment in Women After Diagnosis of Non-Metastatic Breast Cancer

Abstract

OBJECTIVE: This cross-sectional study assessed the prevalence of perceived deficits in executive functioning among women with breast cancer prior to systemic treatment and radiation. This study also investigated associations between perceived CI and insomnia, fatigue, sleep quality, and mood.

METHODS: Participants were recruited after receiving their breast cancer diagnosis. Each participant was assessed using validated subjective measures of cognition, subjective and objective measures of sleep, and self-report measures of fatigue and mood.

RESULTS: The final sample included 98 women with an average age of 60.1 years. Twelve percent of participants (n=12) reported perceived global executive dysfunction, and these individuals were significantly older than those without global executive functioning deficits. Participants with reported global executive functioning deficits also demonstrated significantly greater fatigue and depressive symptoms than participants without reported global executive functioning deficits. After partitioning out variability from other independent variables, only fatigue remained significantly associated with perceived CI, accounting for 16.2% unique variance. Poor sleep quality, insomnia symptoms, and mood disturbance were not significantly associated with perceived CI.

CONCLUSION: Women who reported executive function deficits (12%) were older and experienced more symptoms of fatigue and depression. Fatigue, particularly general and mental fatigue, had the strongest associations with perceived CI. Sleep disturbance and mood were not significantly associated with perceived CI. Fatigue management strategies may prove useful for women who seek to reduce their fatigue and improve their perceived cognitive functioning.

Introduction

Breast cancer is the most commonly diagnosed cancer type among women (Canadian Cancer Society, 2020). Therapeutic advances have led to a significant increase in the survival rate, but are often associated with short and long term side effects (Pendergrass et al., 2018). Cognitive impairment (CI) is one of the many difficulties that women face throughout their breast cancer experience and can present as dysfunctions in executive functioning, learning, memory, concentration, and processing speed (Joly et al., 2015; J. J. Tao et al., 2015). CI can impact psychological, social, and occupational function (Boykoff et al., 2009; Lange & Joly, 2017; Myers, 2013) and has been reported by up to 75 percent of women undergoing active treatment for breast cancer (Janelsins et al., 2014; Joly et al., 2015).

Few studies have investigated the prevalence of CI prior to initiating cancer treatment despite over a decade of research indicating that CI can be present prior to the onset of such treatment. Executive function is a broad term used to define a complex set of cognitive processes involved in day-to-day tasks, such as driving, cooking, and interacting with others. In addition to working memory, executive functioning is involved in inhibiting impulses, self-monitoring, and regulating emotions. Neuroimaging studies have demonstrated changes in executive functioning in individuals with breast cancer following chemotherapy (L. Tao et al., 2017; L. Wang, Yan, et al., 2016). Executive functioning is seldom explored prior to treatment and is typically only investigated using objective neuropsychological tests or neuroimaging tools such as functional magnetic resonance imaging (fMRI). Given that subjective reported cognitive complaints are more vigorously correlated with quality-of-life and emotional wellbeing than objective impairment (Hutchinson et al., 2012; Myers, 2013), it is important to capture the prevalence of perceived executive functioning difficulties prior to initiating treatment.

Research to date has also not explored the impact that psychological and behavioral factors (e.g., sleep quality, insomnia, fatigue, and mood disturbance) may have on the development and progression of pre-treatment CI among women with breast cancer. This is surprising given that between 30 and 60 percent of patients with cancer are affected by insomnia symptoms, with the highest rates being reported among woman with breast cancer (Davidson et al., 2002; J. Savard & Morin, 2001). Moreover, women with breast cancer are at increased risk of experiencing fatigue, defined as persistent physical, emotional, and/or cognitive exhaustion that is not relieved or improved by adequate rest or sleep (Berger, Mooney, Alvarez-Perez, & et al., 2015; Zachariae et al., 2018a). Insomnia is a known contributing factor to, and predictor of, fatigue in patients and survivors of cancer (Goedendorp et al., 2013; Minton & Stone, 2012; Pertl et al., 2014). Fatigue and insomnia also frequently exist with other cancer side effects including depression, suggesting that these symptoms may result from shared physiological and/or behavioral mechanisms that may contribute to CI.

Objectives

The primary objective of the current study was to characterize the prevalence of perceived deficits in executive function among post-operative women with breast cancer prior to the onset of systemic treatment and radiation. The secondary objective was to examine the associations between perceived CI and insomnia, sleep quality, subjective and objective total sleep time and sleep efficiency, fatigue, and mood before the onset of treatment for breast cancer.

Methods

Participants

One-hundred women with breast cancer were recruited from the Dr. H. Bliss Murphy Cancer Centre in St. John's, Newfoundland, Canada after receiving their breast cancer diagnosis

(i.e., after receiving surgery but prior to beginning systemic treatment and radiation). Eligibility criteria were: 1) female sex; 2) English-speaking; 3) over 18-years of age; 4) having a diagnosis of stage I-III breast cancer; and 5) scheduled to receive adjuvant hormone therapy (i.e., tamoxifen or an aromatase inhibitor), chemotherapy, radiation, or trastuzumab if indicated. Exclusion criteria included: 1) previous treatment for cancer or currently undergoing treatment; 2) presence of a sleep disorder other than insomnia that was not currently managed, such as sleep apnea; 3) presence of a psychological disorder that was not stable and/or would impair the individual's ability to participate in the study, such as schizophrenia; and 4) a score lower than 24 on the Mini Mental State Examination (MMSE), which is suggestive of clinically significant cognitive impairment.

Procedure

The oncologists screened clinical charts to identify potentially eligible women prior to their appointment. Assessments with interested women were arranged to occur shortly after their clinic visit. After informed consent was obtained, a medical, psychological and sleep disorder screen was administered to rule out the presence of a medical/psychological disorder, and the MMSE (Folstein, Folstein, & McHugh, 1975) was administered to rule out the presence of clinically significant cognitive impairment.

All assessments were conducted by trained graduate students and completed in person or remotely via telehealth for those located in rural areas. Self-report measures and an actigraph to assess sleep were mailed to those completing telehealth assessments along with a postage paid return envelope.

Measures

All clinical variables were extracted from medical charts, and a demographics

questionnaire was used to characterize the sample (i.e., age, ethnicity, employment status, educational history, etc.).

Subjective Cognitive Measures

Perceived executive functioning deficits were measured using the Behaviour Rating Inventory of Executive Function-Adult (BRIEF-A). The BRIEF-A is a self-report measure composed of 75 items within nine non-overlapping theoretically and empirically derived clinical scales, three validity scales, two summary index scales (Behavioural Regulation and Metacognition), and an overarching summary score (Global Executive Composite). The Behavioral Regulation Index captures the ability to maintain appropriate regulatory control over own's behavior and emotional responses. The Metacognition Index captures the individual's ability to initiate activities and generate problem-solving ideas, sustain working memory, plan ahead, and organize one's materials and environment. Higher scores on the BRIEF-A reflect greater executive functioning difficulties. The test is normed to a sample of 1,136 adults from a wide range of racial/ethnic backgrounds, educational backgrounds, and geographic locations. Reliability, validity, and clinical utility as a sensitive measure to executive functioning impairments in individuals with a wide range of conditions have been established, and it is an ecologically sensitive measure of executive functioning in individuals with a range of conditions (Rabin et al., 2006).

Perceived CI was measured using the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog), version 3. The FACT-cog v3 is a self-report questionnaire with 37-items that map onto four cognitive subscales: perceived cognitive impairment (PCI), impact on quality of life, perception and comments from others, and perceived cognitive abilities (Jacobs, Jacobsen, Booth-Jones, Wagner, & Anasetti, 2007; Wagner, Sweet, Butt, Lai, & Cella,

2009). Participants are asked to rate questions as they relate to the past seven days. The PCI subscale was used to characterize perceived CI based on recommendations put forth by the FACT-Cog scale developers (FACITQuestionnaires, 2020). Higher scores are indicative of fewer cognitive problems and better quality of life. This instrument has demonstrated acceptable reliability in patients with breast cancer (Jansen, 2013).

Subjective Sleep Measures

The Insomnia Severity Index (ISI) (Morin, 1993) is a seven-item self-report measure that assesses difficulty falling asleep, difficulty staying asleep, early morning awakenings, satisfaction with current sleep patterns, interference with daily functioning, sleep-related impairment, and distress level caused by sleep problems. Each question is rated on a five-point Likert scale with scores ranging from zero to 28. Higher scores in the ISI reflect more severe insomnia symptoms. The optimal cut off scores are zero–seven (no clinically significant insomnia), eight–14 (sub-threshold insomnia), 15–21 (moderate insomnia), and 22–28 (severe insomnia). The ISI has demonstrated internal consistency, reliability, construct validity, specificity, and sensitivity in a representative sample of 1,670 cancer patients (M. Savard, Savard, Simard, & Ivers, 2005).

The Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) was used to assess subjective sleep quality. The PSQI is a 19-item self-report measure that probes seven areas related to sleep quality in the past month: sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, subjective sleep quality, use of sleeping medication, and daytime dysfunction. The items operate on a four-point Likert scale, with global scores equal to or greater than five indicative of poor sleep quality. The PSQI demonstrates discriminant and convergent validity, internal homogeneity, and test-retest reliability (Carpenter

& Andrykowski, 1998). It has been validated in a sample of 502 newly diagnosed patients with breast cancer (Fontes et al., 2017).

Sleep Continuity Measures

Participants completed a sleep diary and wore an actigraph over a seven-day period. The Consensus Sleep Diary (CSD) is a reliable and valid patient report of sleep continuity variables (Carney et al., 2012). The Micro Motionlogger sleep watches (Ambulatory Monitoring Inc., Ardsley, NY, USA) provide 95% sensitivity, 65% specificity, and 90% agreement to polysomnography, the current gold standard in objective sleep measurement (Rupp & Balkin, 2011). Actigraphy data were analyzed using dedicated software from the manufacturer (ActionW, Version 2.7.2; Ambulatory Monitoring Inc., Ardsley, NY, USA) which uses the Cole-Kripke algorithm (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992). For the present analysis, only sleep efficiency (SE) and total sleep time (TST) were assessed as they encompass sleep onset latency and wake after sleep onset into their calculations, allowing for a more parsimonious, yet comprehensive evaluation of sleep continuity measures.

Secondary Comorbid Symptom Measures

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report questionnaire with two subscales that assess anxiety and depression symptoms in the past week. Both subscales consist of seven items scored on a four-point Likert scale, with scores that can range from 0-21 within each scale. Established cut-offs are zero–seven (not significant), eight–10 (subclinical) and 11–21 (clinically significant depression/anxiety). The HADS has been used extensively in various cancer populations (A. J. Mitchell, Meader, & Symonds, 2010).

The Multidimensional Fatigue Inventory-Short Form (MFSI-SF) is a 30-item self-report measure and is comprised of five empirically derived subscales (general, emotional, physical,

mental, vigor) and a total fatigue score. The measure does not include cut-off scores; however, higher scores are indicative of greater levels of fatigue. The MFSI-SF has been validated for the multidimensional assessment of cancer-related fatigue in a sample of 304 individuals with cancer and appropriate convergent and discriminant validity have been demonstrated (Stein, Jacobsen, Blanchard, & Thors, 2004).

Data Examination

One participant was excluded from the analysis due to missing more than 50% of their data; all remaining participants were screened for potential outliers. Scores were winsorized for the 10 univariate outliers that exceeded the recommended cut off z-score of 3.29 (Tabachnick & Fidell, 2012). One participant was identified as a multivariate outlier (Mahalanobis distance exceeding the $\chi^2(9)$ critical of 37.70) (Tabachnick & Fidell, 2012), and their data were removed. Skewness and kurtosis were evaluated by dividing estimates of skew and kurtosis by their respective standard errors (Meneses-Echávez, González-Jiménez, & Ramírez-Vélez). Values in excess of 3.29 ($p < .001$) were considered to be skewed or kurtotic. Nine variables were considered to be significantly skewed. Non-linear transformations were used to create variables with normal distributions. Non-transformed variables were used in analyses to aid in interpretation given that the pattern of results was the same when using non-transformed variables or transformed variables.

Statistical Analyses

Prevalence of perceived deficits in executive function

Frequencies were tabulated to characterize the sample. Perceived executive functioning deficits were categorized into global executive functioning deficits, behavioral regulation deficits, and metacognition deficits using the overarching summary score and the two summary

index scores from the BRIEF-A. Deficits in these areas were defined as scoring ≥ 1.5 SD *above* established cut offs. Frequencies were tabulated to characterize the prevalence of perceived executive functioning deficits. Independent samples t-tests were performed to examine group differences in mood, sleep, fatigue, and demographic variables.

Associations between perceived CI and potential confounding factors

A hierarchical regression was used to examine associations between symptoms of insomnia, sleep (objective & subjective sleep efficiency [SE] and total sleep time [TST]), sleep quality, fatigue, mood, and perceived CI as measured by the PCI subscale of the FACT-Cog, after statistically adjusting for age and education. Zero-order and partial correlations were used to examine the relative importance of individual predictors. Statistical significance was set at $p<.05$ for all analyses.

Results

Demographic & Clinical Characteristics

Three hundred and forty-three women with breast cancer were approached between January of 2017 and February of 2019; refer to Figure 1 for a study flow diagram. After further screening, 38 patients were deemed ineligible based on exclusion criteria and 205 declined to participate. One-hundred participants completed a baseline assessment and data were excluded from two. On average, participants were 60.1 years of age (range 29–83) and had 13.6 years of education (range 7–25). Caucasians made up 95.9% of the sample. The majority of the sample reported no clinically significant insomnia symptoms (62.2%), with 22.4% reporting sub-threshold insomnia and 15.4% reporting moderate to severe insomnia. The majority of the sample were deemed poor sleepers as characterized by the PSQI (70.4%). The majority of the

sample did not endorse significant symptoms of anxiety (71.4%) or depression (87.8%); refer to Table 1 for demographics and clinical characteristics.

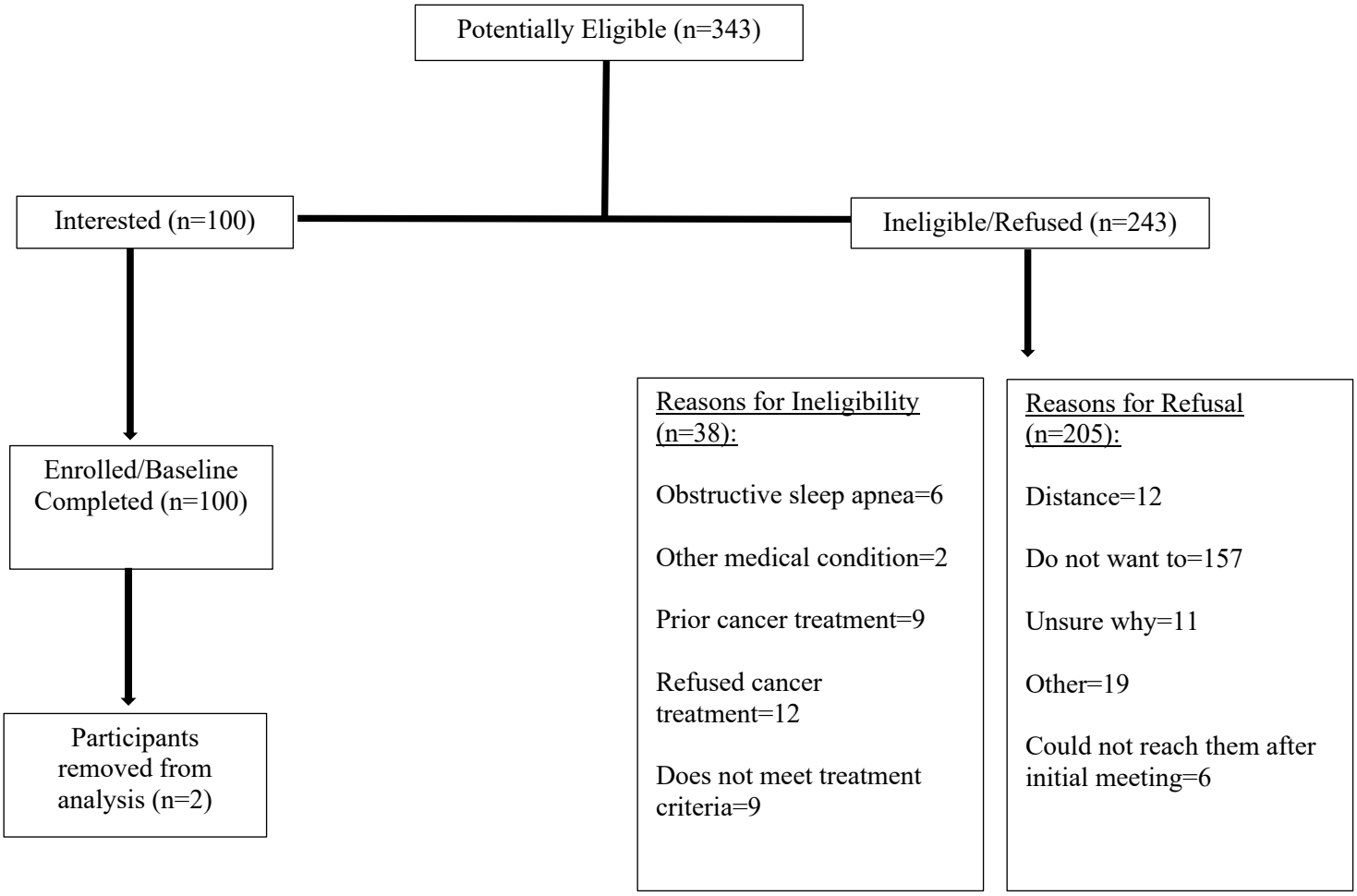


Figure 1. Study Flow Diagram

Table 1. Demographic and Clinical Characteristics

		(*N*=98) *N* (%)
Age at enrollment (mean±SD)		60.12±11.05 (range = 29-83)
Marital Status	Married/In a committed relationship	70 (71.4%)
	Divorced	7 (7.1%)
	Single	8 (8.2%)
	Widowed	12 (12.2%)
	Other	1 (1.0%)
Number of children	None	8 (8.2%)
	One – two	50 (51.1%)
	Three or more	40 (40.8%)
Race	White/Caucasian	94 (95.9%)
	Other	4 (4.1%)
Education	Some high school (<11 years)	16 (16.3%)
	High school (11 years)	18 (18.4%)
	College (12-14)	28 (28.6%)
	Post-secondary (≥15)	36 (36.7%)
Currently Employed	Yes	36 (36.7%)
	No	62 (63.3%)
Pre-menopausal	Yes	25 (25.5%)
	No	71 (72.4%)
	Unsure	2 (2.0%)
Surgery	Lumpectomy	40 (40.8%)
	Simple mastectomy	48 (49.0%)
	Modified radical mastectomy	10 (10.2%)
	Sentinel node biopsy	74 (75.5%)
	Axillary lymph node dissection	15 (15.3%)
T Stage	T1	67 (68.4%)
	T2	24 (24.5%)
	T3	6 (6.1%)
	T4	1 (1.0%)
Estrogen Receptor Positive	Yes	98 (100.0%)
	No	0 (0.0%)
Progesterone Receptor Positive	Yes	91 (92.9%)
	No	7 (7.1%)
HER-2 Positive	Yes	5 (5.1%)
	No	93 (94.9%)
Insomnia	No insomnia	61 (62.2%)
	Sub-threshold insomnia	22 (22.4%)
	Moderate insomnia	12 (12.2%)
	Severe insomnia	3 (3.2%)

Sleep Quality	Good sleepers	29 (29.6%)
	Poor sleepers	69 (70.4%)
Anxiety	Non-significant anxiety	70 (71.4%)
	Sub-threshold anxiety	14 (14.3%)
	Clinically significant anxiety	14 (14.3%)
Depression	Non-significant depression	86 (87.8%)
	Sub-threshold depression	9 (9.2%)
	Clinically significant depression	3 (3.1%)

Abbreviations: HER-2, human epidermal growth factor receptor-2

Prevalence and Factors Associated with Perceived Executive Functioning Difficulties and Cognitive Impairment

As shown in Table 2, deficits in global executive functioning were reported in 12.2% of the sample. Fourteen participants (14.3%) reported behavioral regulation deficits and nine (9.2%) reported metacognition deficits. Despite age being adjusted for during the scoring of the BRIEF-A, those with global executive functioning deficits were significantly older (67.33±8.75) than those without global executive functioning deficits (59.12±11.00). Participants with reported global executive functioning deficits also demonstrated significantly greater fatigue (30.25±16.39) and depressive symptoms (4.67±3.42) than participants without reported global executive functioning deficits (fatigue; 16.89±14.15; depressive symptoms; 2.81±3.02). No significant differences were noted between groups on anxiety, sleep quality, insomnia, subjective or objective TST or SE scores. Although not statistically significant, differences between groups approached significance for anxiety and objective total sleep time and were characterized by medium effect sizes (Cohen's $d > 0.50$); see Table 3.

A hierarchical regression model was used to examine associations between PCI measured by the FACT-Cog and symptoms of insomnia, objective and subjective SE, TST, sleep quality, fatigue, and mood. After adjusting for age and education, the overall model was significant [$F(9,86)=7.06$, $p<.001$], accounting for 41% of unique variance in PCI; refer to Table

4. Zero-order correlations indicated significant bivariate associations between PCI and insomnia severity (r=-.325), sleep quality (r=-.384), fatigue (r=-.605), depressed mood (r=-.391), and anxious mood (r=-.363), demonstrating that as these symptoms increased, so did the perception of CI. After partitioning out variability from other independent variables, only fatigue remained significantly associated with PCI [$F(1,86)=25.17$, $p<.001$], accounting for 16.2% unique variance.

A follow up hierarchical regression was performed to explore associations between PCI and the five facets of fatigue. After adjusting for age and education, the full model was significant, [$F(5,90)=19.17$, $p<.001$], accounting for 50% of unique variance in PCI; refer to Table 5. Zero-order correlations revealed significant bivariate associations between PCI and general fatigue (r=-.527), physical fatigue (r=-.441), emotional fatigue (r=-.354), and mental fatigue (r=-.673). After partitioning out variability from other independent variables, only mental and general fatigue remained significantly associated with PCI [$F(1,86)=25.17$, $p<.001$], accounting for 48% of unique variance in PCI.

Table 2. Prevalence of Perceived Executive Functioning Deficits as Measured by the BRIEF-A

		(*N*=98) *N* (%)
BRIEF-A Global Executive Functioning[a]	Global executive functioning deficits	12 (12.2%)
	No global executive functioning deficits	86 (87.8%)
BRIEF-A Behavioral Regulation	Behavioral regulation deficits	14 (14.3%)
	No behavioral regulation deficits	84 (85.7%)
BRIEF-A Metacognition	Metacognition deficits	9 (9.2%)
	No metacognition deficits	89 (90.8%)

Abbreviations: BRIEF-A, Behaviour Rating Inventory of Executive Function-Adult

[a]Participants were considered to have perceived executive functioning deficits if they received scores ≥ 1.5 standard deviations above established cutoffs.

Table 3. Independent t-test Comparing Participants with Global Executive Functioning Deficits vs. No Global Executive Functioning Deficits as Measured by the BRIEF-A

	Global Executive Function Deficits n=12 *Mean* (SD)	**No Global Executive Function Deficits** n=86 *Mean* (SD)	***t***	***df***	***p***	**Cohen's *d***
Age (Years)	67.33 (8.75)	59.12 (11.00)	2.476	96	**.015**	0.76
Years of Education	12.25 (3.60)	13.84 (3.69)	-1.405	10.46	.163	0.43
Depression	4.67 (3.42)	2.81(3.02)	1.957	96	**.053**	0.60
Anxiety	7.83 (4.97)	5.57 (3.89)	1.825	96	.071	0.56
Fatigue	30.25 (16.39)	16.89 (14.15)	3.004	96	**.003**	0.93
Sleep Quality	7.42 (3.75)	6.96 (3.86)	0.380	96	.705	0.12
Insomnia	8.33 (5.80)	6.60 (6.10)	0.937	96	.351	0.29
TST (Objective/Mins)	439.71 (82.10)	392.59 (81.60)	1.873	96	.064	0.58
TST (Subjective/Mins)	416.62 (111.13)	412.62 (81.72)	0.150	96	.881	0.04
SE (Objective)	82.25 (10.86)	78.38 (10.78)	1.163	96	.248	0.36
SE (Subjective)	77.33 (12.81)	80.85 (11.61)	-0.971	96	.334	0.30

Abbreviations: BRIEF-A, Behaviour Rating Inventory of Executive Function-Adult; SE, sleep efficiency; TST, total sleep time

Table 4. Hierarchical Regression Examining Associations Between FACT-Cog PCI Subscale and Comorbid Symptoms

Predictor	*b*	SE *b*	t	p	R^2	R^2 change	Zero-order Correlation	Partial Correlation
Step 1					.038	.038		
Age	-.122	.098	-1.244	.217			-.170	-.127
Education	.283	.293	0.964	.337			.150	.098
Step 2					**.447[a]**	**.409[a]**		
Insomnia	-.227	.224	-1.016	.312			**-.325[a]**	-.109
Sleep Quality	-.037	.401	-0.014	.927			**-.384[a]**	-.010
TST (Objective)	-.013	.017	-0.786	.434			.099	-.085
TST (Subjective)	.022	.020	1.103	.273			.142*	.118
Sleep Efficiency (Objective)	.103	.131	0.788	.433			.194	.085
Sleep Efficiency (Subjective)	-.170	.138	-1.231	.222			.219	-.132
Fatigue	-.452	.090	-5.017	**.000[a]**			**-.605[a]**	**-.476[a]**
Depression	.327	.434	0.754	.453			**-.391[a]**	.081
Anxiety	.009	.312	0.029	.977			**-.363[a]**	.003

Abbreviations: PCI, perceived cognitive impairment; SE, sleep efficiency; TST, total sleep time
[a]p<.001

Table 5. Hierarchical Regression Examining Associations Between FACT-Cog PCI Subscale and Fatigue

Predictor	*b*	SE *b*	t	p	R^2	R^2 change	Zero-order Correlation	Partial Correlation
Step 1					.038	.038		
Age	-.122	.098	-1.244	.217			-.170	-.127
Education	.283	.293	0.964	.337			.150	.098
Step 2					**.534[b]**	**.496[b]**		
General fatigue	-.617	.234	-2.633	**.010[a]**			**-.527[b]**	**-.267[a]**
Physical fatigue	-.066	.295	-0.224	.823			**-.441[b]**	-.024
Emotional fatigue	.252	.261	0.966	.337			**-.354[b]**	.101
Mental fatigue	-1.364	.233	-5.856	**.000[b]**			**-.673[b]**	**-.525[b]**
Vigor	-.171	.201	-0.855	.395			.189	-.090

Abbreviations: PCI, perceived cognitive impairment; SE, sleep efficiency; TST, total sleep time
[a]p<.01
[b]p<.001

Discussion

Prevalence of Pre-Treatment Difficulties with Executive Function

This study is one of the first to investigate executive functioning deficits and perceived CI before systemic treatment and radiation among women with breast cancer, and possible associations with sleep quality, insomnia, mood, and fatigue. The majority of the sample were deemed poor sleepers as characterized by the PSQI (70.4%) and over a third reported sub-threshold or moderate to severe insomnia, suggesting that poor sleep quality and insomnia symptoms are prominent shortly after diagnosis.

After receiving surgery but prior to initiating other treatments, 12.2% of the sample reported global deficits in executive functioning. Those with global executive functioning deficits were significantly older than those without global executive functioning deficits. Participants with reported global executive functioning deficits also demonstrated significantly greater fatigue and depressive symptoms than participants without reported global executive functioning deficits. This mirrors results from a 2016 cross-sectional study that compared 50 men and women with colorectal cancer at various stages of treatment (pre-treatment, after surgery only, and after systemic treatment) and 50 men and women without colorectal cancer (Visovatti, Reuter-Lorenz, Chang, Northouse, & Cimprich, 2016). Individuals with colorectal cancer reported significantly worse cognitive control and attention than individuals without colorectal cancer; however, worse perceived attention and cognitive control were significantly associated ($p < .001$) with greater fatigue irrespective of cancer status. These results demonstrate that the relationship between executive functioning deficits and fatigue exists in other cancer populations as well but may represent a larger issue for individuals with breast cancer given the higher prevalence of self-reported CI and fatigue.

The existence of a relationship between executive functioning, mood, and fatigue suggests the importance of comprehensive assessment among patients with breast cancer who have yet to undergo treatment. Targeting mood and fatigue prior to treatment may have important implications for the progression of perceived executive functioning deficits in the months that follow. The preponderance of research that exists in this area focuses on objective executive functioning during and after the treatment period. There is a dearth of research focusing on executive functioning deficits that includes pre-treatment assessment. Without the inclusion of a baseline indicator of cognition, one cannot conclude that changes in executive

functioning deficits are due to treatment. Future research should aim to include pre-treatment assessment in effort to address this concern.

Factors Associated with Perceived Cognitive Impairment

Only fatigue remained significantly associated with perceived CI, after partitioning out variability from sleep quality, insomnia, mood, and fatigue. Fatigue—often referred to as cancer related fatigue (CRF)—is one of the most common symptoms experienced by cancer patients and can present prior to diagnosis and treatment (Hofman et al., 2007; Koyama et al., 2017). General fatigue (e.g., I am worn out) and mental fatigue (e.g., I make more mistakes than usual) had the strongest associations with perceived CI. CRF is associated with reduced quality of life and has a profound impact on everyday functioning, with depression, pain, and a decline in both physical and cognitive functioning implicated in patients affected (de Lima et al., 2017; X. S. Wang & Woodruff, 2015). A recent prospective longitudinal study assessing 75 women with breast cancer over two years demonstrated that CRF severity was significantly associated with compromised attention and lower processing speed throughout the entire 2-year period, including prior to treatment commencement (Gullett et al., 2019). A 2015 cross-sectional study assessed 204 women with breast cancer using the Chinese version of the FACT-cog, Version 3, the HADS, the Functional Assessment of Chronic Illness Therapy-Fatigue, and the PTSD Checklist-Specific Stressor Version (Li et al., 2015). After controlling for chemotherapy, age, and education, fatigue, in addition to hyperarousal symptoms, accounted for the largest proportion of variance in perceive CI. Higher fatigue scores were also significantly associated ($p<.001$) with higher PCI scores. The authors speculated that the strength of the relationship between fatigue and CI may be explained by their shared underlying mechanisms (e.g., cellular inflammation).

The identification of fatigue as a potent factor associated with perceived CI may help researchers and clinicians develop more targeted and effective interventions.

CRF is debilitating and not improved by adequate sleep or rest (Berger et al., 2015). As such, it is possible that women are so acutely aware of and bothered by their fatigue, that they are not focused on their sleep, even if it is objectively bad. The majority of participants experienced poor sleep quality (70.4%), but only 37.8% of the sample reported insomnia symptoms. This discrepancy highlights the importance of measuring multiple forms of sleep disturbance as insomnia and poor sleep quality do not always coincide. Insomnia is a more severe dissatisfaction with one's sleep characterized by difficulty falling or staying asleep despite adequate opportunity. Research in breast cancer populations have demonstrated an association between insomnia symptoms and severity of CI (Liou et al., 2019), a relationship that is not similarly observed with poor sleep quality. The lower prevalence of moderate to severe insomnia symptomology in our sample (15.4%) likely limited our ability to be able to detect these smaller magnitude associations. The same can be said for mood disturbance, where 14.3% reported clinically significant anxiety and 3.1% reported clinically significant depression. Studies with larger samples are needed to better understand associations between CI, insomnia, and mood disturbance.

Strengths

This study is one of the most comprehensive investigations into pre-treatment CI to-date. It is characterized by a number of strengths, including the use of valid and reliable measures of cognitive functioning in combination with objective and subjective sleep outcomes that are empirically supported and frequently utilized in breast cancer populations. Together, the utilization of the measures in this study will facilitate comparison to future studies, which will

allow for an enriched discussion of CI and associated factors in women with breast cancer. This study also controlled for confounding factors that can impact the assessment of cognitive functioning, including depression, fatigue, insomnia, and sleep disturbance.

Limitations

The results of this study must be interpreted with limitations in mind. First, the present study cannot control for selection bias which introduced the possibility that individuals who opted to participate may differ systematically from the larger breast cancer population. Second, the cross-sectional design does not allow for the inference of causality or the ability to determine the direction of the observed associations. Third, racial and ethnic minorities were under-represented, which may impact the generalizability of our findings to the larger population of women with breast cancer. Finally, results from regression analyses may be impacted by common method variance. This may influence the strength of associations relying on self-report and reflect a patient's propensity to respond in a certain manner.

Conclusion & Implications

The present study suggests that fatigue significantly contributes to a perception of executive functioning difficulties and CI, above that of objective and subjective sleep disruption and mood disturbance. As such, fatigue may represent a meaningful, first-line treatment target in women with breast cancer and perceived CI, prior to even commencing treatment. Future investigations should include pre-treatment assessment of fatigue, mood, and sleep to better inform intervention for CI.

Chapter 3:

Factors Associated with Cognitive Impairment During the First Year of Treatment for Non-Metastatic Breast Cancer[1]

[1] **Chapter Reference for Publication:**

Rodriguez, N., Fawcett, J. M., Rash, J. A., Lester, R., Powell, E., MacMillan, C. D., & Garland, S. N. (2021). Factors associated with cognitive impairment during the first year of treatment for nonmetastatic breast cancer. *Cancer Medicine, 10,* 1191 –1200. doi:10.1002/cam4.3715

Abstract

BACKGROUND: Women with breast cancer are more likely to develop cognitive impairment (CI), insomnia, fatigue, and mood disturbance than individuals with other cancers. The main objectives of this study were to establish the prevalence of CI and examine the relationships between CI, insomnia, fatigue, and mood over the first year of breast cancer treatment.

METHODS: Participants were recruited after diagnosis and completed validated measures of insomnia, objective and perceived CI, fatigue, and mood disturbance at four time points during the first year of treatment. A random intercepts cross-lagged panel model assessed relationships among symptoms over time.

RESULTS: The sample included 98 women. Prevalence of objective CI ranged from 3.1% to 8.2% throughout the year, whereas 36.7% demonstrated a clinically meaningful decline in perceived CI from baseline to 4 months, which remained relatively stable. Greater perceived CI was associated with more fatigue ($\beta = -.78$, $z = 17.48$, $p < .01$) and symptoms of insomnia ($\beta = -.58$, $z = 5.24$, $p < .01$). Short-term fluctuations in perceived CI ($p < .05$), but not fatigue or insomnia, predicted future perceived CI. Fatigue ($p < .001$) was a significant predictor of future reported symptoms of fatigue and insomnia.

CONCLUSION: Subjective CI is more prevalent than objective impairments. Fatigue, insomnia, and perceived CI remain stable and are associated during the first year of treatment. Changes in insomnia and fatigue may have little effect on future perceived cognition. Women with breast cancer likely require targeted intervention for these side effects.

Background

Women with breast cancer are confronted with a number of challenges from the time they are diagnosed to years following remission. For many, the grueling nature of the cancer experience is compounded by the presence of cognitive impairment (CI), which presents as difficulties with memory, learning, attention, executive function, and/or processing speed (Joly et al., 2015; J. J. Tao et al., 2015). Prevalence estimates vary widely as a result of inconsistency in definitions and measurement of CI; however, research suggests that up to 33 percent of patients with breast cancer experience CI prior to treatment, which increases to 75 percent during active treatment, and remains at 35 percent in the months and years after treatment completion (Janelsins et al., 2014).

CI seldom occurs in isolation and is typically observed alongside other distressing symptoms, including insomnia, fatigue, and psychological distress (Sanford et al., 2014). As is the case with CI, women with breast cancer are more likely to develop insomnia (Davidson et al., 2002; J. Savard & Morin, 2001), fatigue (Cella et al., 2002; National Comprehensive Cancer Network, 2020), and mood disturbance (Maass, Roorda, Berendsen, Verhaak, & de Bock, 2015; Martino et al., 2020) than individuals with other cancers and their non-cancer peers. The limited research available to date supports an association between CI, insomnia, fatigue, and mood symptoms. Initial cross-sectional data has illustrated that patients with breast cancer and mild, moderate, and severe insomnia symptoms report greater perceived CI than patients without insomnia symptoms (Liou et al., 2019). Studies have also demonstrated a relationship between subjective CI and fatigue (Gullett et al.; Kim et al., 2020), as well as anxiety (Janelsins et al., 2017; Ramalho et al., 2017), and depression (Janelsins et al., 2017; Van Dyk et al., 2017). Given the frequency of their co-occurrence, it is possible that these symptoms may result from shared

physiological and/or behavioral mechanisms that may together contribute to CI above and beyond the contribution of a single side effect. It is also possible that a relationship exists among these symptoms, whereby the presence of one exacerbates the others, which further contributes to greater overall symptom burden and worse CI. Additionally, insomnia, fatigue, and mood disturbance are all, by definition, subjective experiences, and the dissatisfaction and negative affectivity associated with disturbed sleep, energy levels, and psychological functioning may serve to highlight even further the subtle changes in cognitive functioning that can accompany these side effects. Prospective studies are needed to explore the relative contribution of insomnia, fatigue, and mood disturbance to CI during the first year of active treatment.

Objective

The first objective of the current study was to characterize the prevalence of objective CI and change in perceived CI among women with breast cancer during the first year of treatment. The second objective was to examine the relationships between perceived CI, insomnia, fatigue, and mood over time. We hypothesized that symptoms of insomnia, fatigue, and mood disturbance at an earlier time would predict higher levels of perceived CI at a later time.

Methods

Participants

One-hundred women with breast cancer were recruited from the Dr. H. Bliss Murphy Cancer Centre in St. John's, Newfoundland after receiving their breast cancer diagnosis (i.e., after receiving surgery but prior to beginning systemic treatment and radiation). Eligibility criteria were: 1) female sex; 2) English-speaking; 3) over 18-years of age; 4) having a diagnosis of stage I-III breast cancer; and 5) scheduled to receive adjuvant hormone therapy (i.e., tamoxifen or an aromatase inhibitor), chemotherapy, radiation, or trastuzumab if indicated.

Exclusion criteria included: 1) previous treatment for cancer or currently undergoing treatment; 2) presence of a sleep disorder other than insomnia that was not currently managed, such as sleep apnea; 3) presence of a psychological disorder that was not stable and/or would impair the individual's ability to participate in the study, such as schizophrenia; and 4) a score lower than 24 on the Mini Mental State Examination (MMSE; i.e., a score suggestive of clinically significant cognitive impairment).

Procedure

The oncologists screened clinical charts to identify potentially eligible women prior to their appointment. Assessments with interested women were arranged to occur shortly after their clinic visit. After informed consent was obtained, a medical, psychological and sleep disorder screener and the MMSE (Folstein et al., 1975) were administered to evaluate inclusion and exclusion criteria. Participants were assessed four times over the course of one year: prior to treatment (i.e. T1), and 4- (i.e. T2), 8- (i.e. T3), and 12-months after commencing treatment (i.e. T4).

All assessments were conducted by trained graduate students and completed in person or remotely via telehealth for those located in rural areas. Self-report measures were mailed to those completing telehealth assessments along with a postage paid envelope.

Measures

All clinical variables were abstracted from medical charts, and a demographics questionnaire was used to characterize the sample (i.e., age, ethnicity, employment status, educational history, marital status, etc.).

Subjective Cognitive Measures

Perceived cognitive impairment was assessed using the Functional Assessment of Cancer Therapy– Cognitive Function (FACT-Cog), version 3. The FACT-cog v3 is a 37-item self-report questionnaire with four cognitive subscales as they relate to the past seven days: perceived cognitive impairment (PCI), impact on quality of life, perception and comments from others, and perceived cognitive abilities (Jacobs et al., 2007; Wagner et al., 2009). The PCI subscale was used to characterize perceived cognitive impairment based on recommendations put forth by the FACT-Cog scale developers (FACITQuestionnaires). When rating questions that comprise PCI, participants rated the items on a five-point Likert scale (0 = never to 4 = several times a day). Negatively worded items were reverse scored to create subscale scores, with higher scores on the FACT-cog reflecting fewer perceived cognitive problems and better quality of life. To classify perceived declines in cognitive functioning, cut-offs have been established for the FACT-Cog (Bell, Dhillon, Bray, & Vardy, 2018). These cut-offs are defined as a decline of 10.0 points on the FACT-Cog total score or a decline of 5.6 points on the PCI subscale. This instrument has demonstrated acceptable reliability in patients with breast cancer (Jansen, 2013).

Objective Cognitive Measures

The use of the following objective cognitive measures was based on the recommendations put forth by the International Cognition and Cancer Task Force (ICCTF) to improve research design, facilitate comparisons between individual studies and meta-analyses by increasing consistency, and increase confidence in prevalence estimates (Wefel et al., 2011). Considering the rural and remote population distribution of Newfoundland and Labrador, only measures that have been validated for administration via telehealth assessments were used (Scurrey, Garland, Thoms, & Laing, 2019).

The Hopkins Verbal Learning Test-Revised (HVLT-R) is a measure of verbal learning and memory, including immediate recall, delayed recall, and delayed recognition. Participants are asked to learn, recall, and recognize a list of 12 nouns drawn from each of three semantic categories. The HVLT-R consists of several different forms, and each form consists of a list of 12 nouns with four words drawn from each of three different semantic categories. Four different forms were used to assess each participant at all four time points. The HVLT-R has demonstrated high test-retest reliability, and its construct, concurrent, and discriminant validity are well-established (Brandt, 1991). Higher scores are reflective of better verbal learning and memory abilities. The use of the HVLT-R via telehealth assessment has been shown to be comparable to in-person evaluation and is deemed valid for administration via telehealth (Munro Cullum, Hynan, Grosch, Parikh, & Weiner, 2014).

The Controlled Oral Word Association Test (COWAT) is a subtest of the Multilingual Aphasia Examination that requires participants to generate words from initial letters under time constraints. The COWAT measures verbal fluency and cognitive speed that involves areas of executive functioning such as cognitive flexibility, strategy utilization, suppression of interference, and response inhibition (Benton, Hamsher, Rey, & Sivan, 1994). Two alternate forms are available, and one was used for the baseline assessment (i.e. T1) while the other was used for the 12-month assessment (i.e. T4). The COWAT was not administered at the T2 and T3 assessments. Higher scores are indicative of better verbal fluency and executive functioning. The COWAT has been deemed valid for the use of telehealth assessment and its use has been shown to be comparable to in-person evaluation (Turner, Horner, Vankirk, Myrick, & Tuerk, 2012).

Letter-Number Sequencing (LNS) is a supplemental subtest of the Weschler Adult Intelligence Scale- Fourth Edition (WAIS-IV) that measures working memory, attention, and

cognitive control. The LNS requires participants to verbally recall a series of letters in alphabetical order as well as numbers in increasing order. Higher scores reflect better verbal working memory, attention, and cognitive control. The use of the LNS subtest via telehealth is comparable to the Digit Span subtest, the main subtest of working memory on the WAIS-IV, which has been deemed valid for assessment via telehealth (Munro Cullum et al., 2014).

Measure of Insomnia

The Insomnia Severity Index (ISI) (Morin, 1993) was used to assess patient-reported insomnia severity. The ISI is a seven-item measure that assesses difficulty falling asleep, difficulty staying asleep, early morning awakenings, satisfaction with current sleep patterns, interference with daily functioning, sleep-related impairment, and distress level caused by sleep problems over the last two weeks. Each insomnia symptom is rated on a five-point Likert scale ranging from 0 to 4. Scores can range from 0 to 28, and higher scores are indicative of more severe insomnia symptoms. The optimal cut off scores are 0-7 (no clinically significant insomnia), 8-14 (sub-threshold insomnia), 15-21 (moderate insomnia), and 22-28 (severe insomnia). The ISI has demonstrated internal consistency, reliability, construct validity, specificity, and sensitivity in a sample of 1670 cancer patients (M. Savard et al., 2005).

Measure of Mood

The Hospital Anxiety and Depression Scale (HADS) was used to assess mood. The HADS is a 14-item self-report measure with subscales that measure anxiety and depression symptoms in the past week. Each subscale consists of seven items scored on a four-point Likert scale, with maximum scores of 21 within each scale. Established cut-offs are 0–7 (not significant), 8–10 (subclinical) and 11-21 (clinically significant depression/anxiety). The HADS

has been used extensively in various cancer populations (A. J. Mitchell et al., 2010).

Measure of Fatigue

The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) was used to assess fatigue. The MFSI-SF is a 30-item self-report measure used to assess the various manifestations of fatigue and is comprised of five empirically derived subscales (general, emotional, physical, mental, vigor) and a total fatigue score. The measure does not report cut-off scores; however, higher scores are reflective of greater levels of fatigue. Internal consistency ranges from 0.87 to 0.92 with test-retest reliabilities ranging from 0.51 to 0.70. Appropriate convergent and discriminant validity have been demonstrated (Stein et al., 2004). The MFSI-SF has been validated for the multidimensional assessment of cancer-related fatigue in a sample of 304 individuals with cancer (Stein et al., 2004).

Statistical Analysis

Missing data analysis

One participant discontinued participation halfway through the first assessment and was removed due to the large proportion of missing data. One participant was identified as a multivariate outlier (Mahalanobis distance exceeding the $\chi^2(9)$ critical of 37.70) (Tabachnick & Fidell, 2012), and their data was removed. Little's test for missing completely at random (MCAR) indicated that data were missing completely at random, $\chi^2 = 2588.223$, $p > .999$. Missing data was singly imputed using estimation-maximization in SPSS 26.

Prevalence of decline in perceived CI

Difference scores in perceived CI relative to baseline were calculated over time and prevalence of decline in perceived CI was quantified as the proportion of women who experienced a change greater than the recognized cutoff of 5.6 points on the PCI subscale. Lower

scores on the FACT-cog PCI subscale are indicative of worse perceived CI.

Changes in perceived CI, insomnia, fatigue, and mood across time

A series of four (Time: T1, T2, T3, T4) repeated measures analysis of variances (ANOVAs) were conducted with cognition, insomnia, fatigue, and mood as dependent variables to evaluate change across time. Greenhouse-Geisser corrections were used in cases where sphericity was violated. Significant time effects were followed up with pairwise comparisons using the Bonferroni correction to adjust for inflation in family-wise error associated with performing multiple statistical tests.

Prevalence of objective CI

Objective cognitive impairment was defined in concordance with the International Cancer and Cognition Task Force (ICCTF) recommendations of ≥ 2 standard deviations (SD) *below* published normative means on at least one objective cognitive test or ≥ 1.5 SD *below* published normative means on two or more objective tests (Wefel et al., 2011). Frequencies were tabulated to characterize the prevalence of objective cognitive impairment at each time point.

Relationship between cognition, insomnia, fatigue, and mood across time

Structural equation modelling was used to examine how perceived CI related to insomnia and fatigue over time. Our original intention was to evaluate symptoms of insomnia, fatigue and mood; however, mood was excluded from the analysis as the correlation between mood and fatigue was in excess of .80 at each individual time point which raised concerns of multicollinearity. The inclusion of mood into the model did not appreciably alter results. Cross-lagged panel models (CLPM) estimate the covariation of multiple variables across time points – whilst accounting for all other variables in the model – to infer causal influences. We used a

Random Intercepts Cross-Lagged Panel Model (RI-CLPM) to assess causal pathways involving the following factors: perceived CI, insomnia, and fatigue. The RI-CLPM breaks down observed variables into two latent components, including trait-like, time-invariant, or "between-person" factors that are controlled for and state-like, time-varying, or "within person" factors that are used to estimate autoregressive and cross-lagged effects for hypothesis testing. We chose the random intercepts variant of the CLPM because our interest was in evaluating the within-person causal relations between variables after taking between-person factors that are stable over time into account. For further details on the RI-CLPM, see Hamaker and colleagues (Hamaker, Kuiper, & Grasman, 2015) and Lim and colleagues (Lim, Rodebaugh, Zyphur, & Gleeson, 2016).

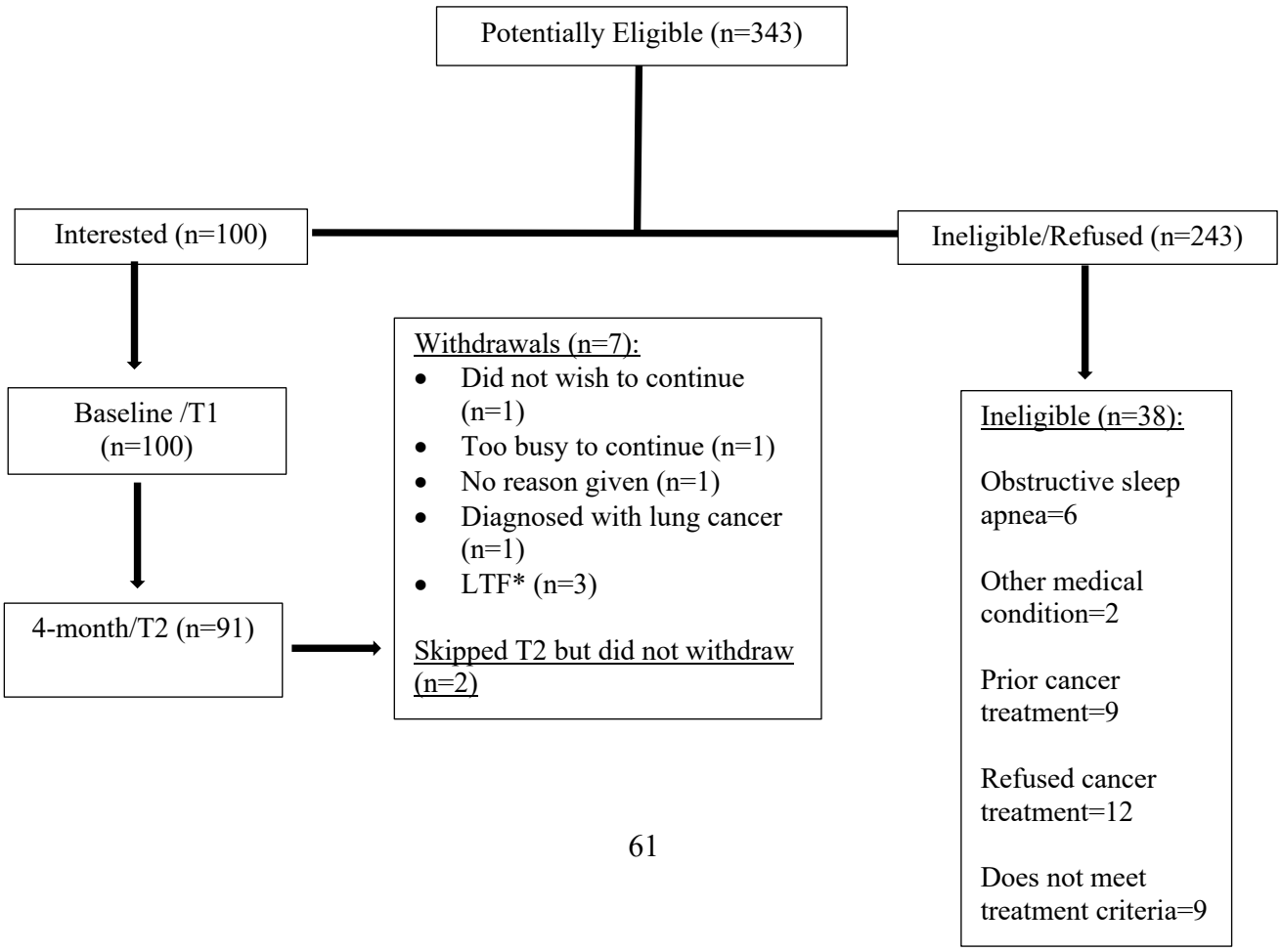
Syntax for the RI-CLPM was generated using the R-package *riclpmr* (Flournoy, 2020), which was implemented using *lavaan (Rosseel, 2012)* in the *R* programming language (R Core Team, 2019). To simplify, we evaluated a model in which the lagged effects (i.e., cross paths and stability paths) and correlated error terms at 4-, 8-, and 12-months were constrained to be equal over time; constraining our terms in this manner implicitly assumes that the nature and magnitude of the relationship between a given variable at *T-1* and another variable at time *T* is always the same from one time window to the next. The constraint indicates a fluctuation in a given variable at one time point will always have a similar impact on another variable at the following time interval. Supporting this decision, the more parsimonious constrained model was favored over a model where these parameters were free to vary as evaluated using either the Akaike Information Criterion (ΔAIC = 9.6 in favour of the simpler model) or the Bayesian Information Criterion (ΔBIC = 87.1 in favour of the simpler model). Model fit was evaluated using the Tucker-Lewis incremental fit index (TLI(Tucker, 1973)), and root mean square error of

approximation (RMSEA(Steiger, 1980)) where values ≥ .90 and ≤ .08 were considered good fit, respectively (Hooper, Coughlan, & Mullen, 2008).

Results

Demographic & Clinical Characteristics

Three hundred and forty-three women with breast cancer were approached between January of 2017 and February of 2019; refer to Figure 2 for a study flow diagram. After further screening, 38 patients were deemed ineligible based on exclusion criteria and 205 declined to participate. One-hundred participants completed a baseline assessment and data were excluded from two. Fifteen participants withdrew from the study: seven at T2, five at T3, and three participants at T4. On average, participants were 60.1 years of age (range 29-83) and had 13.6 years of education (range 7-25). Caucasians made up 95.9% of the sample; refer to Table 6 for demographic and clinical characteristics.



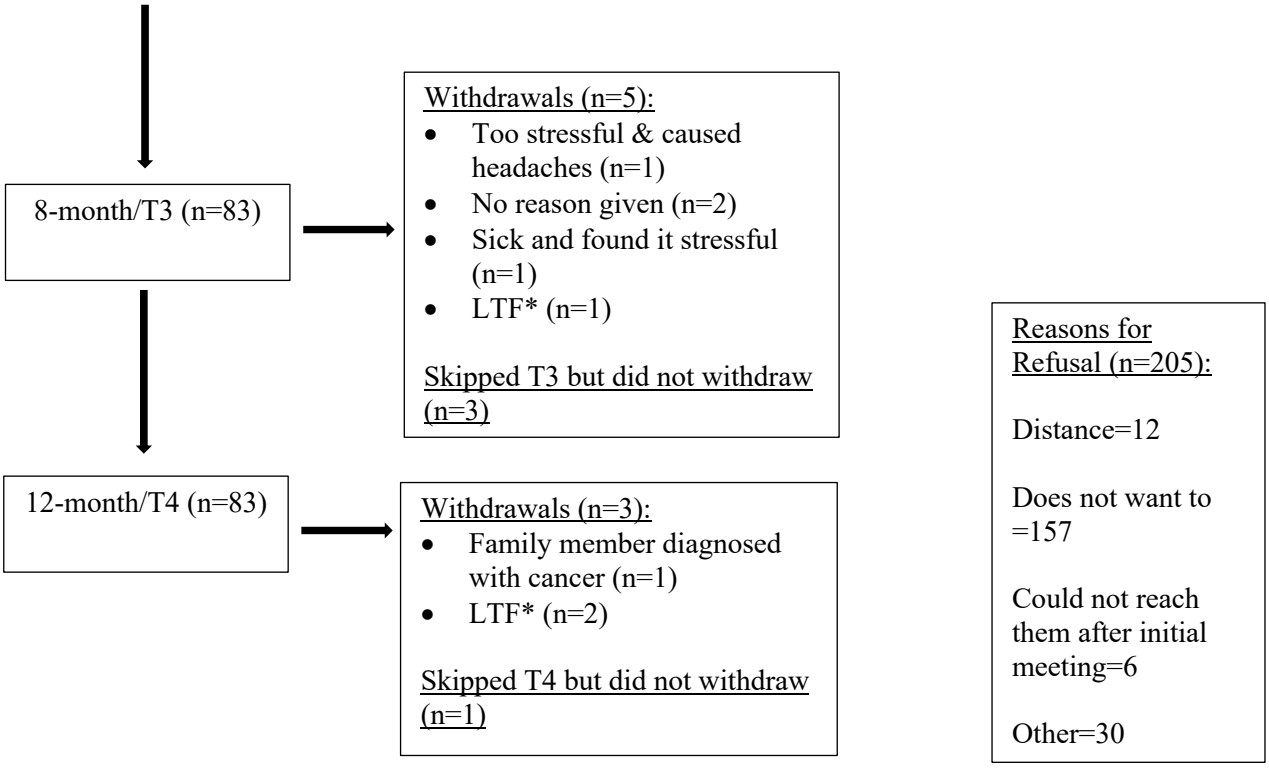


Figure 1. Study Flow Diagram for the First Year of Treatment
*LTF= Lost to follow up

Table 6. Demographic and Clinical Characteristics

		(*N*=98) *N* (%)
Age at enrollment (mean±SD)		60.12±11.05 (range = 29-83)
BMI (mean±SD)		29.70±7.26 (range = 17.02-51.70)
Marital Status	Married/In a committed relationship	70 (71.4%)
	Divorced	7 (7.1%)
	Single	8 (8.2%)
	Widowed	12 (12.2%)
	Other	1 (1.0%)
Number of children	None	8 (8.2%)
	One – two	50 (51.1%)
	Three or more	40 (40.8%)
Race	White/Caucasian	94 (95.9%)
	Other	4 (4.1%)
Education	Some high school (<11 years)	16 (16.3%)
	High school (11 years)	18 (18.4%)
	College (12-14)	28 (28.6%)

	Post-secondary (≥15)	36 (36.7%)
Currently Employed	Yes	36 (36.7%)
	No	62 (63.3%)
Pre-menopausal	Yes	25 (25.5%)
	No	71 (72.4%)
	Unsure	2 (2.0%)
Surgery	Lumpectomy	40 (40.8%)
	Simple mastectomy	48 (49.0%)
	Modified radical mastectomy	10 (10.2%)
	Sentinel node biopsy	74 (75.5%)
	Axillary lymph node dissection	15 (15.3%)
Adjuvant Therapy	Chemotherapy	22 (22.4%)
	Radiation	52 (53.1%)
	Trastuzumab	3 (3.6%)
Hormone Therapy	Tamoxifen	19 (19.4%)
	Aromatase inhibitor I	79 (80.6%)
	No hormonal therapy	0 (0.0%)
T Stage	T1	67 (68.4%)
	T2	24 (24.5%)
	T3	6 (6.1%)
	T4	1 (1.0%)
Estrogen Receptor Positive	Yes	98 (100.0%)
	No	0 (0.0%)
Progesterone Receptor Positive	Yes	91 (92.9%)
	No	7 (7.1%)
HER2 Positive	Yes	5 (5.1%)
	No	93 (94.9%)

Abbreviations: BMI, Body Mass Index; HER2, human epidermal growth factor receptor 2

Prevalence of Objective CI and Changes in Perceived CI

Prior to commencing chemotherapy, radiation, and/or hormonal therapies, 6.1% of participants met the ICCTF criteria for objective CI at baseline; 8.2% met criteria at 4-months; 7.1% at 8-months; and 3.1% at 12-months. In contrast, 36.7% of participants demonstrated a clinically meaningful decline in perceived CI from baseline to 4 months and this remained relatively constant throughout the study period. See Table 7. Exploratory comparisons were performed to determine whether those who reported a clinically meaningful decline in perceived

CI differed from those who did not report a decline on demographic, clinical, or symptom measures. Individuals with perceived CI at 4 months reported more hours of physical activity at baseline (4.49±4.72) than those without perceived CI (2.76±2.77), $t(96) = 2.29$, $p = .02$, Cohen's $d = 0.48$. Those with greater perceived CI also reported greater insomnia (11.74 vs. 8.64; $p = .02$, Cohen's $d = 0.50$), greater fatigue (22.71 vs. 7.47; $p = .001$, Cohen's $d = 0.78$), and greater depressive symptoms (5.58 vs. 2.98; $p = .002$, Cohen's $d = 0.73$) than those without perceived CI. No other differences were observed between groups on demographic, clinical, or symptom characteristics.

Table 7. Prevalence of Objective CI and Changes in Perceived CI Across Time

		(*N*=98) *N* (%)
Pre-Treatment Assessment (T1)	Objective cognitive impairment	6 (6.1%)
4-Month Assessment (T2)	Objective cognitive impairment	8 (8.2%)
	Significant decline in perceived cognition from T1 to T2	36 (36.7%)
8-Month Assessment (T3)	Objective cognitive impairment	7 (7.1%)
	Significant decline in perceived cognition from T1 to T3	35 (35.7%)
12-Month Assessment (T4)	Objective cognitive impairment	3 (3.1%)
	Significant decline in perceived cognition from T1 to T4	35 (35.7%)

Abbreviation: CI, cognitive impairment
[a]Participants were considered cognitively impaired if they received a score ≥ 2 standard deviations below published normative means on at least one neurocognitive test or a score ≥ 1.5 standard deviations below published normative means on two or more neurocognitive tests.
[b]A significant decline in perceived cognitive functioning was defined by a reduction of 5.6 points or more on the perceived cognitive impairment (PCI) subscale of the Functional Assessment of Cancer Therapy-Cognition (FACT-cog)

Changes in Perceived CI, Insomnia, Fatigue, and Mood

There was a statistically significant difference in perceived CI across the 12 months [$F(2.629, 255.049) = 8.60$, $p < .001$]. Perceived CI scores at baseline were significantly better

than perceived CI scores at 4-, 8-, and 12-months. There was a statistically significant difference in insomnia severity between time points [$F(3, 291) = 11.13$, $p < .001$]. Insomnia increased at 4-months and remained stable across the remaining assessments. Fatigue scores changed significantly over time [$F(2.337, 226.658) = 7.47$, $p < .001$], with increases from baseline observed at both 4- and 8-months. Fatigue scores decreased again at 12-months but was not significantly different from any other time point. There was a statistically significant difference in depression scores over time [$F(3, 291) = 4.14$, $p = .007$]. Depression scores at baseline were significantly lower than scores at 4-months. The remaining pairwise comparisons between T2, T3, and T4 were not statistically significant. There was not a statistically significant difference in anxiety symptoms over time [$F(3, 291) = .338$, $p = .798$]. See Table 8.

Table 8. One-way ANOVAS Demonstrating Changes in Perceived Cognitive Impairment, Insomnia, Fatigue, and Mood Across Time

		T1	T2	T3	T4	*F*	*p*
PCI[c]	Mean	56.45	**52.96[b]**	**52.68[b]**	**52.62[b]**	8.60	**.000**
	SD	10.09	10.65	10.73	10.79		
Insomnia	Mean	6.81	**9.91[b]**	**9.24[b]**	**8.48[a]**	11.13	**.000**
	SD	6.03	6.10	6.04	6.08		
Fatigue	Mean	5.84	**12.77[b]**	**13.10[b]**	10.03	7.47	**.000**
	SD	17.95	19.85	18.56	17.31		
Depression	Mean	3.04	**3.97***	3.64	3.34	4.14	**.007**
	SD	3.12	3.61	2.99	2.85		
Anxiety	Mean	5.85	5.88	5.98	5.66	.338	.798
	SD	4.07	3.70	3.60	3.51		

Abbreviations: PCI, perceived cognitive impairment; SD, standard deviation
[a]Statistically different from T1 with $p < .05$

[b]Statistically different from mean T1 score with p <.001
[c]Lower scores on the PCI subscale of the FACT-cog are indicative of worse perceived cognitive impairment

Relationships Between Change in Cognition, Insomnia, and Fatigue Over Time

The RI-CLPM evaluating covariation between change in perceived cognition, insomnia, and fatigue over time indicated good model fit, TLI = .97, RMSEA = .058; for simplification purposes, an example of the RI-CLPM is illustrated in Figure 3 using two variables. See Figure 4 for full RI-CLPM model. At the trait-like level, there was a strong negative association between perceived CI and fatigue (β = -.78, z = 17.48, p < .01) and symptoms of insomnia (β = -.58, z = 5.24, p < .01), indicating that women who reported high perceived CI reported high fatigue and symptoms of insomnia. There was also a strong positive trait-level association between fatigue and symptoms of insomnia (β = .74, z = 9.70, p < .01), indicating that women who reported high fatigue reported high symptoms of insomnia. See Table 9 for model estimates of the means, residual variance, and random effects variance for all measures and time points.

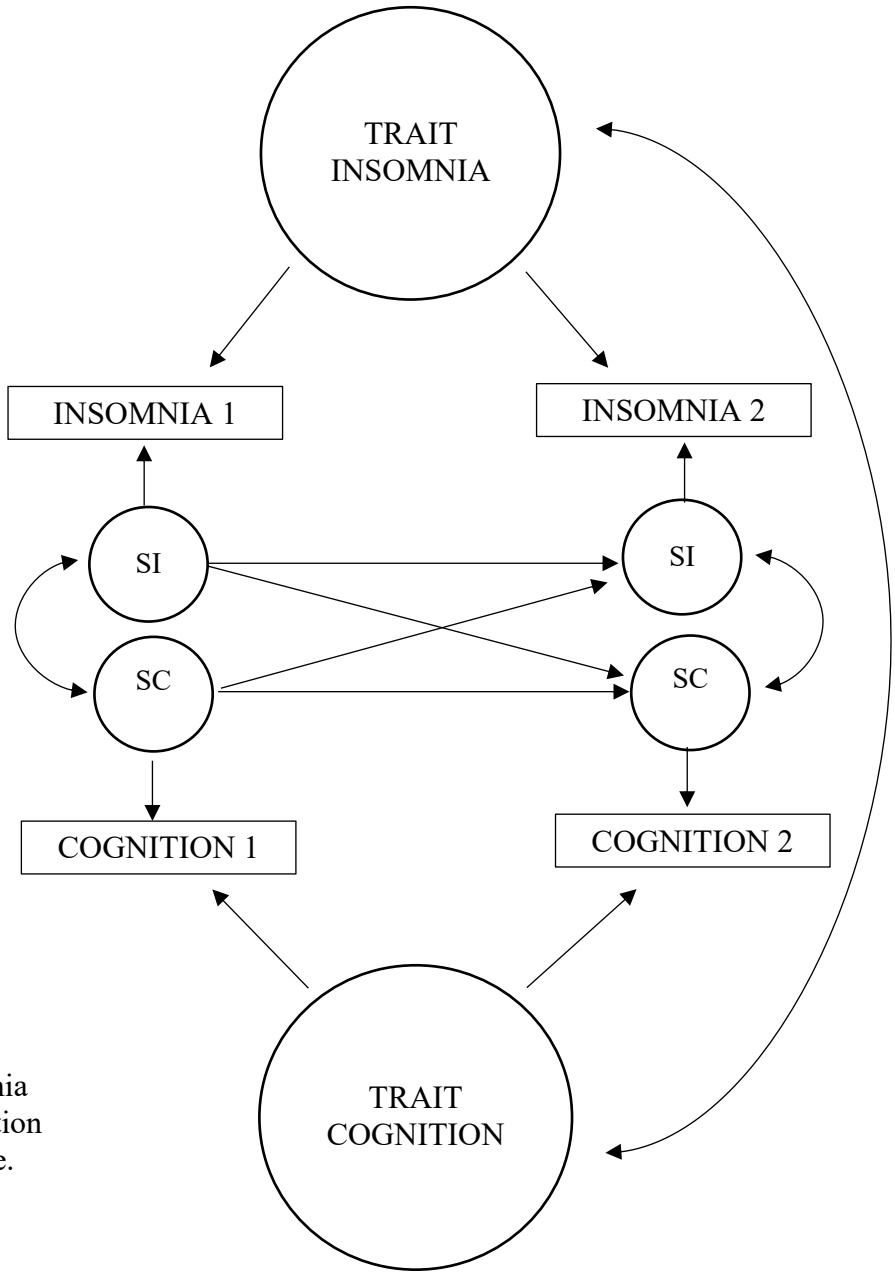
After accounting for the above trait-level associations, perceived CI at a preceding timepoint predicted perceived CI at the following measurement (p < .05). Neither symptoms of insomnia, nor fatigue predicted future perceived CI. A similar association was found for fatigue, wherein fatigue experienced at one timepoint predicted future reported fatigue (p < .01). Neither symptoms of insomnia, nor perceived CI from one time point predicted future reported fatigue. In contrast, symptoms of insomnia at one timepoint did not predict symptoms of insomnia at the following measurement. Fatigue (p < .001), but not perceived cognitive impairment, was a significant predictor of future reported symptoms of insomnia.

Table 9. Mean, Residual Variance, and Random Effect Variance Estimates for Cognition, Fatigue, and Insomnia

		T1	T2	T3	T4
PCI	Mean	56.45	52.96	52.68	52.62
	Residual Variance	37.13	43.60	43.60	43.60
	RI Variance[a] = 68.58				
Fatigue	Mean	5.84	12.77	13.09	10.03
	Residual Variance	155.59	170.50	170.50	170.50
	RI Variance = 148.00				
Insomnia	Mean	6.81	9.91	9.25	8.49
	Residual Variance	17.67	13.83	13.83	13.83
	RI Variance = 37.13				

Abbreviations: PCI, perceived cognitive impairment

[a]RI Variance = Variance corresponding to the random effect of each variable



SI = state insomnia
SC = state cognition
SF = state fatigue.

Figure 3. RI-CLPM Example

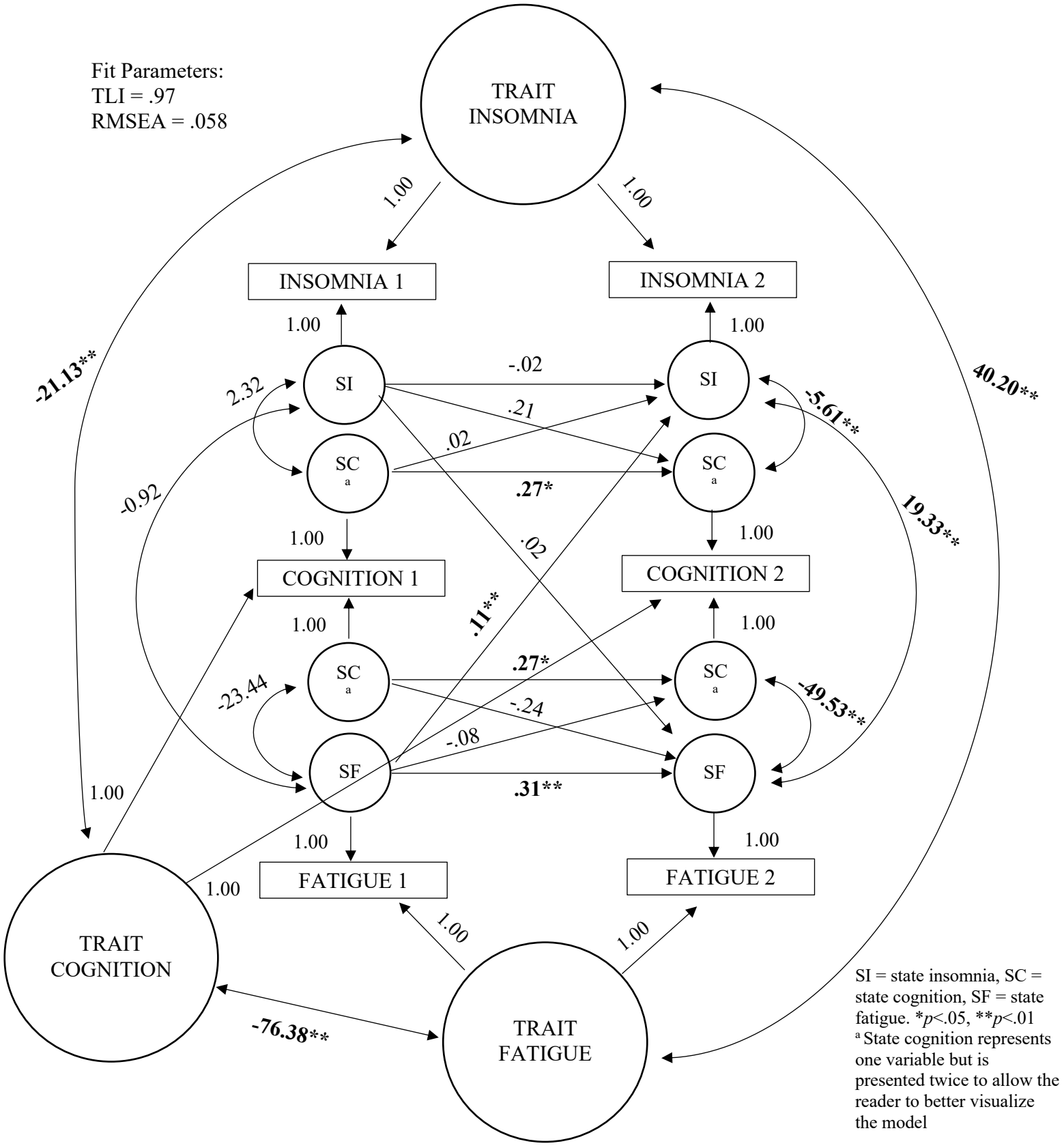


Figure 4. RI-CLPM Depicting the Relationship Between Cognitive Impairment, Insomnia, and Fatigue

Discussion

Prevalence of Objective Cognitive Impairment Over Time

This study is one of the first to investigate objective and perceived CI before and during the first year of systemic treatment and radiation among women with breast cancer, and relationships between cognition, insomnia, fatigue, and mood. Prevalence of objective CI remained relatively consistent across the first year of treatment, with prevalence ranging from 3.1% to 8.2%. Prior to receiving any treatment, 6.1% of our sample presented with objective CI. Other research has found that women who exhibit pretreatment objective CI do so on only the most challenging attention and memory tests (Kaiser et al., 2019). While the prevalence of objective CI observed in this study during and after breast cancer treatment is lower than reported in previous studies, it appears to be consistent with prevalence rates observed in healthy, cancer-free populations (Sachdev et al., 2015). The discrepancy between the prevalence rates observed in the present study and estimates found in other studies may be attributable to different sample characteristics and/or the lower sample sizes reported in some of the previous research, which would affect the generalizability of the results to the larger population of women with breast cancer. This discrepancy may also be attributable to differences in the definition and measurement of CI (Schilder et al., 2010b). Specifically, we assessed for objective CI using three objective measures. Thus, it is possible that the lower number of tests included in this study resulted in a more conservative estimate of CI. More research that follows recommended guidelines for assessment of CI is needed to increase confidence in the findings and make more accurate comparisons across studies.

Changes in Perceived Cognitive Impairment, Insomnia, Fatigue, and Mood Over Time

In addition to a worsening of insomnia, fatigue, and depression, just over one third of the sample reported clinically meaningful declines in their perception of their cognitive functioning that persisted throughout the study duration. When compared to prevalence of objective CI, these results suggest that it is the perception of cognitive functioning that is of greater concern among women undergoing breast cancer treatment. A number of studies on cognition and cancer have reported weak or absent associations between objective and subjective cognition (Ahles & Hurria, 2018; Hutchinson et al., 2012). As such, perceived CI may be a more accurate reflection of the impact of even subtle changes in cognition on functioning and quality of life (Hutchinson et al., 2012; Myers, 2013). Studies with larger samples are required to better understand associations between perceived and objective CI, insomnia, fatigue, and mood disturbance over time.

Fatigue scores at T2 and T3 were statistically different from T1 fatigue scores. That is, fatigue scores were higher overall at these time points, suggesting that systemic cancer treatment may play a role in the worsening of fatigue. Overall fatigue scores at T4 were not statistically different from baseline fatigue scores, suggesting that fatigue levels may eventually return to pre-systemic treatment levels. These results are similar to those found in a recent prospective longitudinal study (Gullett et al., 2019), where fatigue severity increased significantly following chemotherapy initiation but returned to moderate levels similar to those found at baseline at the last assessment time point (i.e., 2 years after chemotherapy initiation). Furthermore, insomnia severity at T2, T3, and T4 was statistically worse than insomnia severity at T1. Mean insomnia scores at the second, third, and fourth assessment time-points fell in the sub-threshold insomnia range and remained relatively consistent throughout the year. A 2019 longitudinal study of 173 patients with breast cancer explored the trajectory of insomnia syndrome and symptoms from

baseline to 12-months (Fleming et al., 2019). The prevalence of insomnia (as measured by the Insomnia Severity Index) was high in this population, with 46 percent of women experiencing insomnia symptoms and insomnia syndrome at diagnosis. The prevalence of insomnia symptoms and syndrome remained at about 50 percent throughout the following year. Taken together, insomnia symptoms appear to increase with cancer treatment and remains stable throughout the treatment period. Lastly, a statistically significant difference was observed in depression scores from T1 to T2; however, a difference in means less than 1 point is not clinically significant (i.e., the minimal clinically important difference is an approximate 2-point difference) (Lemay, Tulloch, Pipe, & Reed, 2019; Wynne et al., 2020). As such, caution is warranted in interpreting these results as meaningful.

Relationships Between Change in Cognition, Insomnia, and Fatigue Over Time

Results from the structural equation modelling demonstrated that trait-like symptoms of fatigue, insomnia, and perceived CI endured over the 12-month study duration. These side effects were also strongly associated, suggesting that women who experience problems in one domain were more likely to report problems in others. After accounting for trait-like associations, neither insomnia nor fatigue were predictive of later CI, which refuted our initial hypothesis and suggests that recent fluctuations in insomnia and fatigue may have little effect on perceived cognition months later. Short-term fluctuations in fatigue did, however, predict subsequent fatigue and insomnia. These results, in part, mirror results from previous research indicating that the presence of fatigue earlier in treatment is one of the strongest predictors of post-treatment fatigue (Bower, 2014; Kim et al., 2020). Women with breast cancer also have worse performance on measures of processing speed when they report relatively high levels of fatigue (Small, Jim, Eisel, Jacobsen, & Scott, 2019).

Prompt intervention may change the trajectory of insomnia, fatigue, and perceived CI over time given that women are experiencing these concerns early on in treatment. Physical activity (both aerobic and resistance/strength training) is considered a category 1 recommendation (i.e., highest level of evidence) for fatigue by the National Comprehensive Cancer Network (National Comprehensive Cancer Network, 2020). A meta-analysis of randomized controlled trials demonstrated significant reductions in fatigue levels following exercise interventions (Juvet et al., 2017). Physical activity has also proven beneficial for CI, which may be at least partially explained by improvements in symptoms of depression that result from increased behavioral activation (Bedillion, Ansell, & Thomas, 2019). Further, there is evidence that even low intensity exercises can benefit cognition (Gokal, Munir, Ahmed, Kancherla, & Wallis, 2018). Physicians and their patients would thus benefit from discussions around the incorporation of physical activity into the treatment plan at diagnosis and before beginning treatment.

In the present study, state-like insomnia did not predict itself over time, suggesting that the trait-like component represents a more meaningful target for intervention due to its overriding importance over time. Thus, the best interventions for insomnia will be those with enduring long-term effects (e.g., Cognitive Behaviour Therapy for Insomnia; CBT-I). CBT-I has demonstrated immediate and long-lasting effects for reduction of insomnia severity in cancer patients, (Ma et al., 2020) and has been shown to reduce fatigue over time (Zachariae et al., 2018b). As such, CBT-I might be an important first-line treatment option for patients with breast cancer and a primary insomnia complaint and secondary fatigue symptoms.

Strengths and Limitations

The present study's unique use of objective measures of cognitive function recommended by the ICCTF in combination with an empirically validated subjective cognitive measure increases the confidence in the prevalence estimates observed. This study is also the first to use structural equation modeling to investigate the relationships between perceived CI, insomnia, fatigue and mood throughout the first year of treatment. This statistical method allowed us to explore directionality of associations between symptoms; however, we cannot fully infer causality because of the potential influence of other unmeasured variables. Lastly, the present model is calibrated only to detect fairly slow associations (e.g., the impact that having fatigue a few months prior would have on cognitive abilities today). If more rapid relations existed, we would be unable to detect them using the chosen analysis.

Conclusion & Implications

Women report symptoms of CI, insomnia, and fatigue at cancer diagnosis, and these concerns are associated and remain stable across the first year of treatment. Naturally occurring fluctuations in fatigue and insomnia at any given point in time do not predict future CI symptomatology, suggesting that early identification and targeted interventions are required to bring about meaningful improvements in perceived CI. To address this issue, it would be beneficial to invest in the development of multi-component interventions that can be effectively tailored to address diverse distressing concerns among patients with breast cancer in a manner that is cost-effective. Future research should focus on the early identification and delivery of interventions for cognitive, psychological, and behavioral concerns in women with breast cancer in order to improve overall recovery and well-being.

Chapter 4:

Final Discussion

Summary of Main Findings

This thesis focused on cognitive impairment and comorbid symptoms in 98 newly diagnosed women with non-metastatic breast cancer in Newfoundland and Labrador. The first study in this investigation examined the prevalence of executive functioning deficits and factors associated with perceived cognitive impairment after diagnosis but before systemic treatment and radiation in patients with breast cancer. The majority of the sample were deemed poor sleepers as characterized by the PSQI (70.4%), 22.4% reported sub-threshold insomnia, and 15.4% reported moderate to severe insomnia. Approximately twenty-nine percent of the sample endorsed sub-threshold to clinically significant symptoms of anxiety and 12.3% endorsed sub-threshold to clinically significant symptoms of depression. Deficits in global executive functioning were reported in 12.2% of the sample, and these individuals were significantly older and experienced more symptoms of fatigue and depression than those who did not demonstrate perceived global executive functioning deficits. A hierarchical regression model examining associations between perceived CI and symptoms of insomnia, objective and subjective SE, TST, sleep quality, fatigue, and mood revealed that after partitioning out variability from other independent variables, only fatigue remained significantly associated with perceived CI. A follow up hierarchical regression was performed to explore associations between perceived CI and the five facets of fatigue. After partitioning out variability from other independent variables, only mental and general fatigue remained significantly associated with perceived CI.

The second study in this investigation examined the prevalence of objective CI and change in perceived CI over the course of the first year of systemic treatment and radiation for breast cancer. The main objective of the second study was to investigate the relationships between perceived CI, insomnia, fatigue, and mood over time using structural equation

modelling. Six (6.1%) participants met criteria for objective CI prior to commencing systemic treatment and radiation (i.e., T1); eight participants (8.2%) met criteria at T2; seven participants (7.1%) at T3; and three participants (3.1%) at T4. Thirty-six participants (36.7%) demonstrated a clinically relevant decline in perceived CI (i.e., ≥ 5.6 points on the PCI subscale) from T1 to T2; 35 participants (35.7%) from T1 to T3; and 35 participants (35.7%) from T1 to T4. At the trait-level, there was a strong negative association between perceived CI (i.e., higher perceived CI scores = better perceived CI and quality of life), and fatigue and symptoms of insomnia. There was also a strong positive trait-level association between fatigue and symptoms of insomnia. After accounting for these trait-level associations, short-term fluctuations in perceived CI, but not fatigue or insomnia, predicted future perceived CI. Fatigue from a given measurement window predicted future reported fatigue and insomnia.

Challenges and Limitations

One of the main limitations of the present research is the potential for selection bias. That is, those who chose not to enrol in the study may have differed on the outcome variables in some meaningful way from those who did enrol in the study (e.g., objective or perceived CI may have influenced decisions to enrol in a research investigation). Additionally, the nature of the prospective longitudinal study design increases the possibility of selection bias as a result of loss to follow-up, increasing the risk of differential results among dropouts compared with those who completed all timepoints. That said, the loss rate in the present study did not exceed 20% as a result of various techniques implemented by the research team (e.g., fostering relationships with participants, keeping participants informed on study progress, flexibility in assessment location, the use of telehealth to increase access for participants in rural and remote areas). In addition to these techniques, imputation helped reduce the impact of missing data on study outcomes.

A second limitation of the present research is that the sample consisted primarily of Caucasian women. Because racial and ethnic minorities were under-represented, this impacts the generalizability of our findings to the larger population of women with breast cancer. Black women, for example, face a number of unique stressors related and unrelated to cancer that can worsen their cancer experience. In addition, compared to Caucasian women, they are at greater risk of dying from breast cancer, experience a greater number of complications related to treatment, report lower satisfaction with their social supports throughout their cancer journey, experience greater cancer-related stigma, and report worse quality of life as a result of their cancer experience (Blackman & Masi, 2006; Curtis, Quale, Haggstrom, & Smith-Bindman, 2008; Gerend & Pai, 2008; Ooi, Martinez, & Li, 2011). Racial and ethnic disparities are well-documented in the breast cancer literature and highlight the importance of exercising caution when attempting to extend these results to non-white populations. However, the implications of our findings suggest the importance of early and targeted intervention for cognitive, psychological, and behavioral side effects. Black women and women of color with breast cancer would likely similarly benefit from targeted intervention but may require unique tailoring of said interventions that acknowledges and functions around the unique stressors and barriers that these marginalized populations often face.

The cross-sectional design of the first study does not allow for the inference of causality or the ability to determine the direction of the observed associations. Having data from only one assessment time point provides a snapshot in time that may not be representative of the general experience of these patients during this period. Nonetheless, there is a paucity in baseline, or pre-systemic treatment and radiation data in the breast cancer literature, and the results from the first study provide novel and meaningful information that can help inform clinicians and researchers

alike on the importance of early intervention for cognitive, behavioral, and psychological side effects associated with breast cancer. Furthermore, although the second study was longitudinal in nature, the RI-CLPM model used was calibrated only to detect relatively slow associations (e.g., the impact that having fatigue months prior would have on cognitive abilities today). If faster-acting temporal relations existed (e.g., the impact of being fatigued yesterday on cognition today), the RI-CLPM would be unable to detect them. More rapid associations would require more intensive longitudinal methodology such as experience sampling.

Lastly, the main results from the first study pertained to perceived CI and results from regression analyses may be impacted by common method variance in this cross-sectional design (i.e., the strength of associations relying on self-report could be inflated and reflect a patient's propensity to respond in a certain manner). Certain procedural strategies were used, however, to help reduce common method bias, including attempts to reduce evaluation apprehension through assurance of no right or wrong answers and the importance of responding as honestly as possible.

Strengths

The present research is unique in its methodology and analytic approach and thus possesses many noteworthy strengths. First, this research utilized valid and reliable measures of objective cognitive functioning recommended by the ICCTF in addition to a measure of subjective cognitive functioning. As previously described, the majority of studies demonstrate weak or non-existent associations between objective and perceived CI (Ahles & Hurria, 2018; Hutchinson et al., 2012). As such, perceived CI must be recognized as an independent patient experience and studied along with objective CI assessment. Many studies do not incorporate a measure of both constructs in their research; as such, this is a strength that sets this research apart from other investigations of this nature. The first study in the present research also utilized

objective *and* subjective sleep outcomes that are empirically supported and consistently utilized in breast cancer populations. The utilization of the measures in this study will allow future researchers to compare and contrast results with our findings and ensures that this research contributes meaningfully to the overall breast cancer literature.

There are a number of confounding factors that can impact the assessment of cognitive functioning in patients with breast cancer, including depression, fatigue, sleep disturbance, age, education level, history of stroke, and Alzheimer's Disease. In addition, these factors can account for changes in cognition observed during cancer treatment. Without proper screening and assessment of these confounds, one cannot fully attribute changes in cognition to other factors. The present study controlled for these confounding factors using a variety of methods, including rigorous screening, assessment, and statistical procedures, and inclusion of these factors into the analysis.

It is important that telehealth technology is utilized when conducting research in the geographically distinct province of Newfoundland and Labrador (NL) in order to recruit women outside of the city of St. John's and increase the heterogeneity of the sample. Considering the rural and remote distribution of NL, our utilization of telehealth technology enabled us to recruit more participants and capture a more representative sample of women with breast cancer in Newfoundland and Labrador. Only measures deemed valid for administration via telehealth were used (Scurrey et al., 2019), with all objective cognitive measures shown to be comparable to in-person evaluation.

Finally, a unique strength of the present research is that it included a baseline assessment that occurred after diagnosis but prior to systemic treatment and radiation. Despite its recommendation by the ICCTF, most investigations of cognitive impairment and comorbid

symptoms in patients with breast cancer do not include pre-treatment assessment. Lack of pre-treatment assessment significantly reduces the ability to examine the factors associated with these cancer-related side effects that are not attributable to systemic treatment, which highlights the importance of the inclusion of this assessment time point in this work.

Clinical Implications and Directions for Future Research

Cognitive impairment and behavioral and psychological side effects such as insomnia and fatigue are consistently identified as an area of concern among cancer patients across the globe. With the undeniable presence, high prevalence, and persistence of these side effects having been established for the last decade or more, research in this area has begun to shift its focus more and more on designing and evaluating interventions that will mitigate symptoms and increase the quality of life among cancer patients world-wide. This section will summarize the clinical implications of the present research and outline some of the more recent research in this area whose findings are particularly relevant for the breast cancer population.

This investigation found that after controlling for variability from other variables, only fatigue, specifically general and mental fatigue, remained significantly associated with perceived CI at baseline. These results are, in part, a replication of findings from Li et al. (2015), who discovered that fatigue (measured by the Functional Assessment of Chronic Illness Therapy-Fatigue) was significantly associated with perceived CI (as measured by the PCI subscale of the FACT-cog), even after accounting for education and age (Li et al., 2015) in women with breast cancer who were scheduled to receive chemotherapy. Findings from the present study are also similar to a more recent investigation (Lycke et al., 2017), where higher levels of fatigue (measured by the Patient-Reported Outcome Measures) predicted baseline objective CI (measured using a validated neuropsychological battery) in 125 cancer patients (44 percent

breast cancer). As such, fatigue may represent a meaningful first-line treatment target among women with breast cancer and perceived CI, prior to even commencing treatment.

This investigation also found that women with breast cancer report symptoms of perceived CI, fatigue, and insomnia at cancer diagnosis, and these concerns remain stable and are associated throughout the first year of treatment, suggesting that women who experience problems in one domain are more likely to report problems in others. Naturally occurring fluctuations in fatigue and insomnia at any given point in time did not predict future CI symptomatology. Short-term fluctuations in perceived CI predicted future CI, and this was similarly observed for fatigue. Short-term fluctuations in insomnia symptoms did not predict future insomnia symptomology. These findings indicate that early identification and targeted interventions are likely required to bring about meaningful improvements in these symptoms. This does not imply, however, that interventions designed for one particular symptom per se, will not beget symptom reduction for other side effects experienced by this population. In fact, as discussed below, certain interventions (e.g., physical activity) have been proven beneficial for more than one comorbid symptom.

Cognitive Impairment

There is limited evidence of potent intervention strategies for CI, which has been attributed to its unestablished etiology and the fact that therapeutic interventions for CI in patients with cancer remains a novel area of research (Joly et al., 2019). Of the non-pharmacological interventions that exist, physical activity, relaxation, and cognitive rehabilitation/cognitive training have been the most extensively studied. Results of the effectiveness of these interventions is mixed (Gokal et al., 2018; Joly et al., 2019), but offer some hope for the cognitive functioning of the breast cancer population.

Physical activity—both aerobic and resistance exercise of at least moderate intensity—has been shown to improve cognition in individuals over 50 with age-related cognitive decline (Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018), which has led cancer researchers to investigate its effectiveness for those with CI following cancer treatment. Campbell et al. (2018) conducted an RCT to evaluate the efficacy of a 24-week individualized aerobic exercise intervention compared to a "usual lifestyle" control group among 19 post-menopausal survivors of breast cancer who were between the ages of 40 and 65. All women reported perceived CI following chemotherapy. Study outcomes were assessed at baseline and 24-weeks using the FACT-cog and a neuropsychological battery. Women in the exercise intervention demonstrated a significant increase in processing speed post-intervention; however, no improvements were observed in perceived CI. Results from an RCT with a larger sample size (87 breast cancer survivors) demonstrated similar findings. Hartman et al. (2018) randomly assigned participants who were, on average, 2.5 years post-surgery to a 12-week physical activity group (individualized program but increased to 150 minutes of moderate to vigorous activity per week by the end of the study) or control group (scheduled emails on various women's health topics). Participants were assessed at baseline and then 12 weeks later using the National Institutes of Health Cognitive Toolbox (measure of objective CI) and the Patient-Reported Outcomes Measurement Information System scales (measure of perceived CI). Both groups showed improvement in objective cognitive functioning across the 12 weeks. The only significant difference between groups was found on a measure of processing speed, where the exercise group demonstrated faster processing speed than the control group. No significant differences were found between groups in perceived CI. These results further demonstrate the weak correlation between objective and perceived CI and the importance of assessing both in

intervention-focused research. It also demonstrates the difficulty in targeting perceived CI in treatment.

One of the first RCTs to investigate the efficacy of a 12-week moderate intensity walking program demonstrated that walking may serve as a protective factor against a decline in perceived CI (Gokal et al., 2018). The authors randomly assigned 50 patients with breast cancer who were scheduled to begin chemotherapy to the walking group or usual care group and assessed them pre- and post-intervention using a battery of neuropsychological tests and the Cognitive Failures Questionnaire (CFQ). Participants in the intervention group demonstrated stable perceived CI (as measured by the Cognitive Failures Questionnaire) scores, which was not similarly observed in the control group (i.e., a declined in perceived CI was observed). No differences in objective CI (measured by a neuropsychological battery) were observed between groups, which is discrepant with findings aforementioned. Results from the present investigation revealed that declines in perceived CI appear to be a larger concern for women undergoing breast cancer treatment; as such, interventions that protect against the experience of feeling as if one's cognitive functioning is deteriorating may have positive implications for quality of life and emotional well-being. Findings on the effectiveness of physical activity interventions for perceived and objective CI are limited and mixed, and studies that do exist report small sample sizes and inconsistent methodology. As such, future investigations should aim to increase consistency with regards to assessment of CI and increase their sample size. Physical activity interventions will be discussed again in subsequent sections in the context of its efficacy for CRF.

In addition to physical activity, interventions with a relaxation and/or mindfulness-based component may offer some benefit for women with CI as well. For example, Myers and

colleagues (2019) evaluated the efficacy of Qigong (a mindfulness-based exercise originating from Chinese medicine involving diaphragmatic breathing, gentle movements, and mindfulness meditation) on cognitive functioning in 50 women who were 2 months to 8 years post-treatment with perceived CI (as measured by a score lower than 59 on the PCI subscale of the FACT-cog). Participants were randomized to one of three groups: 1) qigong, 2) gentle exercise, or 3) survivorship support. Participants were blind to study condition, but the investigators were not. They were assessed at baseline, 8-weeks, and 12-weeks using the neuropsychological battery recommended by the ICCTF as well as the FACT-cog. Attrition rates were high and thus power was significantly impacted by the end of the study period; nevertheless, results still suggested that the Qigong group demonstrated significant improvements in PCI, processing speed, and distress compared to the other two groups. It is important to note, however, that the investigators were aware of group membership which introduces the risk of experimental bias (i.e., investigators may have unduly influenced study outcomes).

Derry et al. (2015) also found positive results from their RCT with 200 breast cancer survivors with cognitive complaints. Participants were randomized to a 12-week Hatha yoga intervention (focus on mind, body, and breath) or a wait-list control group and assessed three times (baseline, post-intervention, and 3 months later) using the Breast Cancer Prevention Trial Cognitive Problems Scale. No significant differences were found in cognitive complaints between groups at the post-intervention assessment. However, participants in the yoga group reported significantly less cognitive complaints (an average of 23 percent less) than the wait-list control group 3 months after the intervention was first delivered. In their systematic review, (Cifu, Power, Shomstein, & Arem, 2018) highlighted the research gaps in this area, noting that findings on the effectiveness of mindfulness-based interventions for CI are mixed (highlighting

that four of the six studies reviewed showed some improvements in objective and/or perceived cognitive functioning). Similar to other areas of research, they emphasize the need for consistency in methodology and larger sample sizes moving forward in order to make definitive conclusions about the benefits of mindfulness interventions on CI.

Lange and Joly have cited cognitive rehabilitation or cognitive training interventions as the most promising of all the strategies studied for CI in cancer patients (Lange & Joly, 2017). One of the largest existing studies (242 participants; 89 percent breast cancer) randomly assigned participants with self-reported cognitive complaints to the cognitive training intervention or to the control group who received standard care (Bray et al., 2017). Participants were assessed at baseline, 15-weeks (T2), and 6-months post intervention (T3) using the FACT-cog, a computer-based neuropsychological battery, and secondary symptom measures (FACT-fatigue and the General Health Questionnaire). All participants received a phone consultation and were given compensatory strategies for cognition prior to random assignment. The intervention group consisted of a web-based program known as Insight, which uses cognitive exercises that target various cognitive domains. Participants were told to engage in this program four times for 40-minutes per week for 15 weeks. Despite an average total cognitive training time of 25 hours (a little over 50% of the recommended 40 hours), the intervention group demonstrated improvement in perceived CI, with significantly better scores on all FACT-cog subscales at T2 and T3 compared to the control group. Anxiety, depression, and fatigue scores also significantly improved for the intervention group compared to the control group, and the authors speculate that an expectancy effect or increase in self-efficacy may help explain these differences. No differences were found between groups in objective test scores.

To examine the effects of training in memory and processing speed on cognitive function, (Von Ah et al., 2012) conducted an RCT with 82 breast cancer survivors who endorsed perceived CI and were more than one-year post-treatment. Participants were randomized to one of three groups: 1) memory training, 2) processing speed training, and 3) a wait-list group. Both intervention groups consisted of 3-6 women and involved 10 different hour-long training sessions over 6–8 weeks. In the memory group, participants were taught various mnemonic strategies (e.g., visualization, story mnemonic, etc.) in order to increase their memory capacity. In the processing speed training group, a computer-based program was used to deliver increasingly difficult tasks to increase the speed at which participants' process information. Memory and processing speed were assessed using various objective tests, perceived CI was measured using the FACT-cog, and fatigue was measured using the FACT-fatigue at three different time-points: baseline, post-intervention, and 2-month follow-up. Compared with the wait-list participants, both intervention groups demonstrated significantly improved scores on objective tests. Participants in the processing speed intervention demonstrated positive improvements more rapidly than those in the memory intervention group, and the benefits also generalized to improvements in memory. Improvements in perceived cognitive functioning were demonstrated by both groups compared to wait-list participants. Interestingly, compared to the wait-list controls, those who received the processing speed intervention demonstrated a significantly lower score on the FACT-fatigue measure at both follow-up assessments, implying once again that there is a relationship between CI and fatigue. These findings are quite positive and suggest a worthwhile intervention type for patients with breast cancer, cognitive concerns, and fatigue.

In contrast to results described previously, Damholdt and colleagues (2016) conducted a three-arm RCT 157 survivors of breast cancer and randomly assigned them to a 30-session web-based cognitive training group with computer games for various cognitive domains, telephone support, or wait-list control. No differences were found between groups on measures of objective or perceived CI. Although the authors caution against generalizing these results due to many limitations (e.g., visually presented tasks with auditory-based assessment), these findings do suggest that more research is needed in this area in order to distill the specific components of interventions that may be most useful for various cognitive domains.

Given that CI can manifest quite differently in patients, it is also possible that, similar to physical activity interventions, cognitive training programs need to be tailored appropriately based on an individual patient's unique concerns. In addition to tailoring programs, it is also likely that patients with a large number of cognitive complaints or a high degree of perceived CI may benefit from learning more about their objective test results. Given that objective and perceived CI often do not correlate, and perceived CI appears to be a larger concern for women with breast cancer, it is possible that allowing patients to see that objectively, their performance is in the typical range (if that indeed is the case) may be therapeutic in and of itself. This strategy may help patients restructure their thinking about their cognition and help to see things in a more accurate light.

Fatigue

Fatigue, or CRF, is documented as one of the most burdensome and troubling side effects in women with breast cancer (National Comprehensive Cancer Network, 2020; Pertl et al., 2014). Findings from this thesis reveal that fatigue represents an important target for treatment in this population. Myriad of pharmacological and non-pharmacological interventions exist for

CRF. There is no current "gold standard" treatment for all individuals with CRF, which authors have attributed to the multifactorial etiology of the side effect and the variability in its manifestation (Bower & Ganz, 2015, Joly & lange et al., 2019). That said, the most well-researched and most effective of the non-pharmacological interventions to-date is physical activity (Joly et al., 2019). The National Comprehensive Cancer Network (National Comprehensive Cancer Network, 2020) has put forth guidelines for patients with cancer and CRF, with physical activity listed as a Category 1 recommendation (i.e. highest-level of evidence). They state that an exercise routine must be individualized to patients with cancer but should include aerobic activity (~150 minutes per week), resistance/strength training (2-3 sessions per week) and stretching. Physical activity is thought to improve fatigue through reduction in inflammation and associated neurological activation (Bower, 2014). Ultimately, physical activity interventions are thought to increase one's capacity for prolonged movement, build muscle strength, and reduce the physical deconditioning that results as a consequence of decreased activity from being fatigued (Meneses-Echávez et al., 2015).

In the context of fatigue, exercise interventions appear to be so robust that changes in fatigue levels can be observed even when adherence to the intervention is low. Huang and colleagues (2019) evaluated the efficacy of a 12-week home-based walking program on reducing fatigue in 159 patients with breast cancer by randomly assigning patients to the walking group (with progressively increased intensity, frequency, and duration of exercise over the 12 weeks) or to an attention-control group (received phone calls with advice on managing chemo-related side effects). Participants were assessed a total of eight times: at baseline (first day of 2nd chemo cycle), two times during the 12-week intervention, and five times after the 12-week period (up to 36 weeks after the intervention). Fatigue levels increased over time for both groups; however, the

exercise group reported significantly lower levels of fatigue than the control group, and these findings were maintained throughout the entire study period despite low-adherence rates to the walking program. Participants who reported more frequent physical activity prior to their cancer diagnosis also reported less fatigue overall, suggesting further the importance of early intervention for fatigue.

Schmidt et al. (2015) found that participants who were randomly assigned to a 12-week resistance training intervention (60-minute machine-based group strength training twice per week) did not show increases in fatigue over time, while participants assigned to the control group (supervised, group-based muscle-relaxation program with similar schedule) did. The authors randomly assigned 95 patients with breast cancer to one of the 12-week programs and assessed them at baseline and post-intervention, during which participants were completing their first or second cycle of chemotherapy. The resistance exercise group demonstrated significantly better quality of life scores and lower fatigue scores than the control group post-intervention. The authors reported that their results demonstrate that the effects of group-based resistance exercise are not strictly psychosocial in nature and may be attributed to the physical changes that occur as a result of strength training.

A recent meta-analysis of 25 RCTs (total of 3,418 patients with breast cancer) investigating exercise interventions (aerobic, strength, mobility exercises and coordination) for fatigue sought to explore the differences in results between treatments delivered at different time points (Juvet et al., 2017). Some of the RCTs included in the study implemented the intervention during adjuvant treatment while others assessed the efficacy of exercise interventions post adjuvant treatment. The results reflected those discussed above, where patients in the exercise groups exhibited significantly lower fatigue levels independent of when the intervention was

initiated, and these results were maintained in studies who included 6-months follow-up assessment. More specifically, the effects of the exercise interventions were more evident in patients who received the intervention after treatment rather than during treatment. This is not to say that exercise interventions should only be delivered post-adjuvant treatment, however, as the authors attributed this finding to the fact that exercise during treatment is for the purposes of symptom reduction and not rehabilitation. The authors also found that patients who engaged in a combination of resistance and aerobic exercise had lower levels of fatigue and higher levels of physical functioning than those who engaged in strictly aerobic or resistance/strength exercise, which is in line with NCCN's guidelines aforementioned.

In sum, a large number of studies have evaluated the impact of exercise on fatigue in the active treatment phase or shortly following treatment. Results from these studies suggest that a significant symptom reduction and increased quality of life can be observed when patients with breast cancer and CRF actively engage in physical activity interventions. Given the ubiquity of this side effect and our finding that fatigue may represent an important treatment target, it follows that physicians and their patients would benefit from increased discussions around the incorporation of physical activity into the treatment plan. A paucity still exists in the data available on longer-term CRF (Joly & Lange, 2019). Henceforth, an important topic for future research would be to investigate the efficacy of physical activity interventions on survivors of breast cancer who have completed treatment years prior, or to follow up on whether or not the effects of these physical interventions endure over a longer period of time.

Insomnia

In the present investigation, state insomnia did not predict itself over time, suggesting that the trait-like component represents a more meaningful target for intervention due to its

overriding importance over time. Thus, the best interventions for insomnia will be those with enduring long-term effects, such as Cognitive Behaviour Therapy for Insomnia or CBT-I. CBT-I has proven its worth for treating insomnia in the general population and is considered the gold-standard treatment for chronic insomnia (Trauer, Qian, Doyle, Rajaratnam, & Cunnington, 2015). CBT-I is an adaptation of CBT and involves five core components, including stimulus control, sleep restriction, relaxation training, sleep hygiene, and cognitive restructuring (Kamen et al., 2019). The effects of CBT-I appear to be long-lasting (Koffel, Koffel, & Gehrman, 2015; M. D. Mitchell, Gehrman, Perlis, & Umscheid, 2012), which provides hope for the sleep health of patients and survivors of breast cancer.

A recent meta-analysis of 14 RCTs (1,363 participants) has firmly established the efficacy and durability of CBT-I for women with breast cancer and chronic insomnia (Ma et al., 2020). All studies included in their analysis incorporated, at minimum, the two main components of CBT-I: sleep restriction and stimulus control. All interventions were delivered weekly, either individually or in a group-based format, with variability in the duration of intervention (15 minutes to 2 hours) and length of follow-up (one to twelve months). Pooled effect sizes were medium to large and demonstrated that CBT-I is more efficacious than wait-list control for reducing insomnia symptomology and improving sleep quality at post-intervention and short-term follow up. Small effect sizes were observed for its efficacy at long-term follow-up. Importantly, there were no significant differences in effect sizes between delivery modalities. That is, virtual CBT-I was similarly as efficacious as in-person delivery. These findings are particularly relevant and hopeful in light of the global shift toward virtual delivery of psychological interventions with the COVID-19 pandemic.

Zachariae and colleagues demonstrated the efficacy of internet delivered CBT-I (iCBT-I) by randomly assigning 255 women with breast cancer to iCBT-I or waitlist control (Zachariae et al., 2018a). Outcomes were assessed using the ISI, PSQI, consensus sleep diary, and the Functional Assessment of Chronic Illness Therapy for Fatigue at pre-intervention, post-intervention (9 weeks), and follow-up (15 weeks). The results of their study were impressive: large effect sizes were found for reduction in insomnia severity, sleep quality, and sleep efficiency, while medium effect sizes were found for increased total sleep time and decreased early morning awakenings. Interestingly, a small effect size was found for fatigue reduction at post-treatment, but a medium effect size was found at 15-week follow-up. Improvements in sleep were also maintained at follow-up, with large effect sizes for both sleep quality and insomnia severity reduction. Fatigue severity continued to decrease over time for the iCBT-I group, which was not the case for the control group. This suggests that while the effects of iCBT-I may be more immediate for insomnia and sleep quality, it may improve fatigue at a slower pace.

CBT-I interventions have also proven to reduce depressive symptoms in those with comorbid mood and insomnia concerns (Carney et al., 2017). In an RCT of 67 survivors of cancer (69% breast cancer), a 7-week CBT-I intervention led to significantly lower depression scores (as measured by the Patient Health Questionnaire) at post-intervention and 3-month follow-up as compared to the waitlist condition (Peoples et al., 2019). Cognition may also be indirectly targeted by CBT-I interventions, although this data is based on non-cancer populations. In a recent RCT of 410 participants with insomnia who were assigned to a digital CBT-I intervention or wait-list control, individuals who received the active treatment demonstrated significantly lower perceived CI (as measured by the British Colombia Cognitive Complaints Inventory) 10 weeks after the initiation of the treatment and six months later. There

is still question as to whether this finding holds true for patients with breast cancer. The findings discussed in this section point to important clinical implications for women with breast cancer experiencing symptom comorbidity. Given that it may take longer to observe the effects of CBT-I on outcomes other than sleep, more research is also needed to determine whether the effects persist and strengthen over a longer period of time.

Future Directions in Assessment of Cognitive Impairment

Changes in the structure and function of various brain regions have been detected following chemotherapy using neuroimaging tools such as magnetic resonance imaging (MRI) in both cross-sectional and longitudinal research (Jung et al., 2017; Reuter-Lorenz & Cimprich, 2013; L. Wang, Apple, et al., 2016). For example, Wang et al. (2016) investigated brain activation in 29 participants (14 controls and 15 patients who had completed 3 or more cycles of chemotherapy in the last 6 months) using functional magnetic resonance imaging (fMRI), a non-invasive method of monitoring brain activation. Patients with cancer were only eligible if they met ICCTF criteria for objective CI and controls were only eligible if they did not meet ICCTF criteria (assessed using a battery of neuropsychological tests). Results revealed that during a working memory task, patients with cancer showed reduced activation in the frontal lobe and the left hippocampus, specifically the dorsolateral pre-frontal cortex, when compared to controls. Neuropsychological test performance and neuroimaging findings were not associated with patient reported outcome measures.

A more recent study with a much larger sample size similarly investigated CI using various methods, including fMRI, self-report measures, and neuropsychological testing in 126 women with breast cancer (J. L. Vardy et al., 2019). Women were assigned to one of three groups: 1) received adjuvant chemotherapy and reported perceived CI (as measured by the

FACT-Cog); 2) received adjuvant chemotherapy and did not report perceived CI; and 4) did not receive chemotherapy. fMRI results revealed that during a working memory task, women who had received chemotherapy (groups 1 and 2), showed decreased activation in the frontal and parietal brain regions as compared to the group who did not receive chemotherapy. Women who received chemotherapy and reported perceived CI demonstrated more activation in the frontal lobe than women who received chemotherapy but did not report CI, however this difference was only observed on increasingly difficult working memory tasks. Similar to results found by Wang et al., no differences were observed between groups on objective neuropsychological testing and no relationship was found between perceived CI and objective CI. Unlike the fMRI and objectively measured CI data, self-reported CI was associated with increased fatigue, symptoms of anxiety and depression, and reduced quality of life.

The integration of neuroimaging tools into breast cancer and cognition research is limited. The inclusion of fMRI and other neuroimaging tools undoubtedly provides a more nuanced understanding of CI in the breast cancer population and brings us closer to identifying the underlying neural processes that are most affected by cancer and its treatment. However, studies that have included its use in their exploration of CI corroborate further that assessment of self-reported CI is absolutely necessary if one is to appropriately recognize patients' experienced cognitive difficulties that are distinctly connected to quality of life and other important outcomes. The utilization of a comprehensive assessment battery that allows for measurement of all facets of CI in any cancer population is ideal, although authors must be cautious of the increased likelihood to detect changes in cognition with a greater number of tests and ensure that stringent criteria are being used to avoid overinflation of CI prevalence.

Conclusion

This study provides important data relating to cognitive, psychological, and behavioral side effects and their relationship to one another in women with breast cancer. Prevalence of objective CI appears to be less of an issue for women undergoing treatment for breast cancer; however, perception of executive functioning deficits and cognitive impairment may be of greater importance from a quality-of-life perspective, highlighting the need to target beliefs about cognitive functioning in this population. Fatigue and perceived CI are significantly associated at baseline; thus, fatigue may represent a first-line treatment target (i.e., physical activity interventions) in this population and its reduction may bring about meaningful changes in perceived CI and other associated side effects. This investigation also found that women report symptoms of CI, insomnia, and fatigue at cancer diagnosis, and these concerns are associated and remain stable across the first year of treatment. Early identification of symptomology and the implementation of targeted interventions should be of utmost importance in the provision of care for patients with breast cancer. Future research should thus continue to focus on the delivery of interventions for these concerns with appropriate assessment of these side effects. It is clear that inconsistent methodology is a contributor to the discrepancies in study results across all areas of observational, prevention, and intervention research. More research that follows recommended guidelines for assessment are thus needed in order to be able to increase confidence in the findings and make more accurate comparisons across studies. Additionally, studies with larger samples are needed to better understand associations between CI, insomnia, and mood disturbance.

More women are surviving their breast cancer diagnosis than ever before, and while this is a positive change observed as a result of advancement in treatment technologies, it is also important to recognize that increasingly more women are facing the negative acute and long-

term behavioral and psychological side effects as well. In order to address this issue, it is necessary to continue to invest in in the development of multi-component interventions that can be appropriately tailored to meet the individual and unique experiences of each patient. Combatting breast cancer is a grueling experience that can take a toll on the body and mind. The closer we get to understanding the nature of the side effects experienced by this population, the more likely we are at helping create more positive cancer experiences for patients that will enable them to increase engagement with and enjoyment of the aspects of their life that are most meaningful and fulfilling.

References

Ahles, T. A., & Hurria, A. (2018). New Challenges in Psycho-Oncology Research IV: Cognition and cancer: Conceptual and methodological issues and future directions. *Psycho-oncology, 27*(1), 3-9. doi:10.1002/pon.4564

Ahles, T. A., Root, J. C., & Ryan, E. L. (2012). Cancer- and cancer treatment-associated cognitive change: an update on the state of the science. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 30*(30), 3675. doi:10.1200/JCO.2012.43.0116 [doi]

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. Washington: DC: American Psychiatric Association.

Avis, N. E., Levine, B. J., Case, L. D., Naftalis, E. Z., & Van Zee, K. J. (2015). Trajectories of depressive symptoms following breast cancer diagnosis. *Cancer Epidemiol Biomarkers Prev, 24*(11), 1789-1795. doi:10.1158/1055-9965.epi-15-0327

Bedillion, M. F., Ansell, E. B., & Thomas, G. A. (2019). Cancer treatment effects on cognition and depression: The moderating role of physical activity. *Breast (Edinburgh, Scotland), 44*, 73-80. doi:10.1016/j.breast.2019.01.004

Bekinschtein, P., Cammarota, M., Katche, C., Slipczuk, L., Rossato, J. I., Goldin, A., . . . Medina, J. H. (2008). BDNF is essential to promote persistence of long-term memory storage. *Proc Natl Acad Sci U S A, 105*(7), 2711-2716. doi:10.1073/pnas.0711863105

Bell, M. A.-O., Dhillon, H. M., Bray, V. J., & Vardy, J. L. (2018). Important differences and meaningful changes for the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog). LID - 48. *J Patient Rep Outcomes, 12*(2), 018-0071.

Benton, A. L., Hamsher, K., Rey, G. L., & Sivan, A. B. (1994). *Multilingual Aphasia Examination* (3rd ed. ed.). Iowa City, IA: AJA Associates.

Berger, A. M., Mooney, K., Alvarez-Perez, A., & et al. (2015). Cancer-related fatigue, version 2.2015: Clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network, 13*(8), 1012-1039.

Bernstein, L. J., McCreath, G. A., Komeylian, Z., & Rich, J. B. (2017). Cognitive impairment in breast cancer survivors treated with chemotherapy depends on control group type and cognitive domains assessed: A multilevel meta-analysis. *Neurosci Biobehav Rev, 83*, 417-428. doi:10.1016/j.neubiorev.2017.10.028

Biglia, N., Bounous, V. E., Malabaila, A., Palmisano, D., Torta, D. M., D'Alonzo, M., . . . Torta, R. (2012). Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study. *Eur J Cancer Care (Engl), 21*(4), 485-492. doi:10.1111/j.1365-2354.2011.01320.x

Blackman, D. J., & Masi, C. M. (2006). Racial and ethnic disparities in breast cancer mortality: are we doing enough to address the root causes? *J Clin Oncol, 24*(14), 2170-2178. doi:10.1200/jco.2005.05.4734

Bower, J. E. (2014). Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol, 11*(10), 597-609. doi:10.1038/nrclinonc.2014.127

Bower, J. E., & Ganz, P. A. (2015). Symptoms: Fatigue and Cognitive Dysfunction. *Advances in Experimental Medicine and Biology, 862*, 53. doi:10.1007/978-3-319-16366-6_5 [doi]

Bower, J. E., Ganz, P. A., Irwin, M. R., Arevalo, J. M., & Cole, S. W. (2011). Fatigue and gene expression in human leukocytes: increased NF-κB and decreased glucocorticoid signaling

in breast cancer survivors with persistent fatigue. *Brain Behav Immun, 25*(1), 147-150. doi:10.1016/j.bbi.2010.09.010

Boykoff, N., Moieni, M., & Subramanian, S. K. (2009). Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response. *Journal of cancer survivorship : research and practice, 3*(4), 223-232. doi:10.1007/s11764-009-0098-x [doi]

Brandt, J. (1991). The Hopkins Verbal Learning Test: Development of a new verbal memory test with six equivalent forms. *The Clinical Neuropsychologist*(5).

Bray, V. J., Dhillon, H. M., Bell, M. L., Kabourakis, M., Fiero, M. H., Yip, D., . . . Vardy, J. L. (2017). Evaluation of a Web-Based Cognitive Rehabilitation Program in Cancer Survivors Reporting Cognitive Symptoms After Chemotherapy. *J Clin Oncol, 35*(2), 217-225. doi:10.1200/jco.2016.67.8201

Buchanan, N. D., Dasari, S., Rodriguez, J. L., Lee Smith, J., Hodgson, M. E., Weinberg, C. R., & Sandler, D. P. (2015). Post-treatment Neurocognition and Psychosocial Care Among Breast Cancer Survivors. *Am J Prev Med, 49*(6 Suppl 5), S498-508. doi:10.1016/j.amepre.2015.08.013

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research, 28*(2), 193. doi:0165-1781(89)90047-4 [pii]

Campbell, K. L., Kam, J. W. Y., Neil-Sztramko, S. E., Liu Ambrose, T., Handy, T. C., Lim, H. J., . . . Boyd, L. A. (2018). Effect of aerobic exercise on cancer-associated cognitive impairment: A proof-of-concept RCT. *Psycho-oncology, 27*(1), 53-60. doi:10.1002/pon.4370

Canadian Cancer Society. (2020). Breast cancer statistics. Retrieved from http://www.cancer.ca/en/cancer-information/cancer-type/breast/statistics/?region=on

Caplette-Gingras, A., Savard, J., Savard, M. H., & Ivers, H. (2013). Is insomnia associated with cognitive impairments in breast cancer patients? *Behav Sleep Med, 11*(4), 239-257. doi:10.1080/15402002.2012.672940

Carney, C. E., Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Krystal, A. D., Lichstein, K. L., & Morin, C. M. (2012). The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep, 35*(2), 287-302. doi:10.5665/sleep.1642 [doi]

Carney, C. E., Edinger, J. D., Kuchibhatla, M., Lachowski, A. M., Bogouslavsky, O., Krystal, A. D., & Shapiro, C. M. (2017). Cognitive Behavioral Insomnia Therapy for Those With Insomnia and Depression: A Randomized Controlled Clinical Trial. *Sleep, 40*(4). doi:10.1093/sleep/zsx019

Carpenter, J. S., & Andrykowski, M. A. (1998). Psychometric evaluation of the Pittsburgh Sleep Quality Index. *Journal of psychosomatic research, 45*(1), 5. doi:S0022-3999(97)00298-5

Cella, D., Lai, J. S., Chang, C. H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer, 94*(2), 528-538. doi:10.1002/cncr.10245

Chee, M. W., Chuah, L. Y., Venkatraman, V., Chan, W. Y., Philip, P., & Dinges, D. F. (2006). Functional imaging of working memory following normal sleep and after 24 and 35 h of sleep deprivation: Correlations of fronto-parietal activation with performance. *Neuroimage, 31*(1), 419-428. doi:10.1016/j.neuroimage.2005.12.001

Cifu, G., Power, M. C., Shomstein, S., & Arem, H. (2018). Mindfulness-based interventions and cognitive function among breast cancer survivors: a systematic review. *BMC Cancer, 18*(1), 1163. doi:10.1186/s12885-018-5065-3

Cimprich, B., So, H., Ronis, D. L., & Trask, C. (2005). Pre-treatment factors related to cognitive functioning in women newly diagnosed with breast cancer. *Psycho-oncology, 14*(1), 70-78. doi:10.1002/pon.821

Cole, R. J., Kripke, D. F., Gruen, W., Mullaney, D. J., & Gillin, J. C. (1992). Automatic sleep/wake identification from wrist activity. *Sleep, 15*(5), 461-469. doi:10.1093/sleep/15.5.461

Conroy, S. K., McDonald, B. C., Smith, D. J., Moser, L. R., West, J. D., Kamendulis, L. M., . . . Saykin, A. J. (2013). Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. *Breast cancer research and treatment, 137*(2), 493. doi:10.1007/s10549-012-2385-x [doi]

Crosswell, A. D., Lockwood, K. G., Ganz, P. A., & Bower, J. E. (2014). Low heart rate variability and cancer-related fatigue in breast cancer survivors. *Psychoneuroendocrinology, 45*, 58-66. doi:10.1016/j.psyneuen.2014.03.011

Croyle, R. T., & Rowland, J. H. (2003). Mood disorders and cancer: a National Cancer Institute perspective. *Biol Psychiatry, 54*(3), 191-194. doi:10.1016/s0006-3223(03)00427-x

Curtis, E., Quale, C., Haggstrom, D., & Smith-Bindman, R. (2008). Racial and ethnic differences in breast cancer survival: how much is explained by screening, tumor severity, biology, treatment, comorbidities, and demographics? *Cancer, 112*(1), 171-180. doi:10.1002/cncr.23131

Damholdt, M. F., Mehlsen, M., O'Toole, M. S., Andreasen, R. K., Pedersen, A. D., & Zachariae, R. (2016). Web-based cognitive training for breast cancer survivors with cognitive complaints-a randomized controlled trial. *Psycho-oncology, 25*(11), 1293-1300. doi:10.1002/pon.4058

Davidson, J. R., MacLean, A. W., Brundage, M. D., & Schulze, K. (2002). Sleep disturbance in cancer patients. *Soc Sci Med, 54*(9), 1309-1321. doi:10.1016/s0277-9536(01)00043-0

de Lima, F. D., Bottaro, M., de Oliveira Valeriano, R., Cruz, L., Battaglini, C. L., Vieira, C. A., & de Oliveira, R. J. (2017). Cancer-Related Fatigue and Muscle Quality in Hodgkin's Lymphoma Survivors. *Integrative cancer therapies*, 1534735417712009. doi:10.1177/1534735417712009 [doi]

Derry, H. M., Jaremka, L. M., Bennett, J. M., Peng, J., Andridge, R., Shapiro, C., . . . Kiecolt-Glaser, J. K. (2015). Yoga and self-reported cognitive problems in breast cancer survivors: a randomized controlled trial. *Psycho-oncology, 24*(8), 958-966. doi:10.1002/pon.3707

Di Iulio, F., Cravello, L., Shofany, J., Paolucci, S., Caltagirone, C., & Morone, G. (2019). Neuropsychological disorders in non-central nervous system cancer: a review of objective cognitive impairment, depression, and related rehabilitation options. *Neurol Sci, 40*(9), 1759-1774. doi:10.1007/s10072-019-03898-0

Donovan, K. A., Small, B. J., Andrykowski, M. A., Munster, P., & Jacobsen, P. B. (2007). Utility of a cognitive-behavioral model to predict fatigue following breast cancer treatment. *Health Psychol, 26*(4), 464-472. doi:10.1037/0278-6133.26.4.464

Downie, F. P., Mar Fan, H. G., Houede-Tchen, N., Yi, Q., & Tannock, I. F. (2006). Cognitive function, fatigue, and menopausal symptoms in breast cancer patients receiving adjuvant

chemotherapy: evaluation with patient interview after formal assessment. *Psycho-oncology, 15*(10), 921. doi:10.1002/pon.1035 [doi]
Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Seminars in neurology, 25*(1), 117. doi:10.1055/s-2005-867080 [doi]
FACITQuestionnaires. (2020). FACIT Questionnaires: FACT-Cog Scoring and Interpretation Materials. Retrieved from https://www.facit.org/facitorg/questionnaires
Fleming, L., Randell, K., Stewart, E., Espie, C. A., Morrison, D. S., Lawless, C., & Paul, J. (2019). Insomnia in breast cancer: a prospective observational study. *Sleep, 42*(3). doi:10.1093/sleep/zsy245
Flournoy, J. (2020). riclpmr: Generate lavaan syntax for RI-CLPM. R package version 0.1.0.9000. In.
Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198. doi:10.1016/0022-3956(75)90026-6
Fontes, F., Pereira, S., Costa, A. R., Goncalves, M., & Lunet, N. (2017). The impact of breast cancer treatments on sleep quality 1 year after cancer diagnosis. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer, 25*(11), 3529. doi:10.1007/s00520-017-3777-6 [doi]
Fortier-Brochu, E., Beaulieu-Bonneau, S., Ivers, H., & Morin, C. M. (2012). Insomnia and daytime cognitive performance: a meta-analysis. *Sleep medicine reviews, 16*(1), 83-94. doi:10.1016/j.smrv.2011.03.008 [doi]
Garland, S. N., Barg, F. K., Cakouros, B., Gehrman, P., DuHamel, K. N., & Mao, J. J. (2018). A qualitative examination of the factors related to the development and maintenance of insomnia in cancer survivors. *Palliative & supportive care*, 1. doi:10.1017/S1478951518000135 [doi]
Garland, S. N., Johnson, J. A., Savard, J., Gehrman, P., Perlis, M., Carlson, L., & Campbell, T. (2014). Sleeping well with cancer: a systematic review of cognitive behavioral therapy for insomnia in cancer patients. *Neuropsychiatric disease and treatment, 10*, 1113. doi:10.2147/NDT.S47790 [doi]
Gerend, M. A., & Pai, M. (2008). Social determinants of Black-White disparities in breast cancer mortality: a review. *Cancer Epidemiol Biomarkers Prev, 17*(11), 2913-2923. doi:10.1158/1055-9965.epi-07-0633
Gobin, C. M., Banks, J. B., Fins, A. I., & Tartar, J. L. (2015). Poor sleep quality is associated with a negative cognitive bias and decreased sustained attention. *J Sleep Res, 24*(5), 535-542. doi:10.1111/jsr.12302
Goedendorp, M. M., Gielissen, M. F., Verhagen, C. A., & Bleijenberg, G. (2013). Development of fatigue in cancer survivors: a prospective follow-up study from diagnosis into the year after treatment. *Journal of pain and symptom management, 45*(2), 213-222. doi:10.1016/j.jpainsymman.2012.02.009 [doi]
Goel, N., Rao, H., Durmer, J. S., & Dinges, D. F. (2009). Neurocognitive consequences of sleep deprivation. *Seminars in neurology, 29*(4), 320. doi:10.1055/s-0029-1237117 [doi]
Gokal, K., Munir, F., Ahmed, S., Kancherla, K., & Wallis, D. (2018). Does walking protect against decline in cognitive functioning among breast cancer patients undergoing chemotherapy? Results from a small randomised controlled trial. *PLoS One, 13*(11), e0206874. doi:10.1371/journal.pone.0206874

Gosain, R., & Miller, K. (2013). Symptoms and symptom management in long-term cancer survivors. *Cancer journal (Sudbury, Mass.), 19*(5), 405. doi:10.1097/01.PPO.0000434391.11187.c3 [doi]

Gullett, J. M., Cohen, R. A., Yang, G. S., Menzies, V. S., Fieo, R. A., Kelly, D. L., . . . Lyon, D. E. (2019). Relationship of fatigue with cognitive performance in women with early-stage breast cancer over 2 years. *Psycho-oncology, 28*(5), 997-1003. doi:10.1002/pon.5028

Guo, H., Wei, M., & Ding, W. (2017). Changes in Cognitive Function in Patients with Primary Insomnia. *Shanghai archives of psychiatry, 29*(3), 137. doi:10.11919/j.issn.1002-0829.216097 [doi]

Hamaker, E. L., Kuiper, R. M., & Grasman, R. P. (2015). A critique of the cross-lagged panel model. *Psychol Methods, 20*(1), 102-116. doi:10.1037/a0038889

Hartman, S. J., Nelson, S. H., Myers, E., Natarajan, L., Sears, D. D., Palmer, B. W., . . . Patterson, R. E. (2018). Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: The memory & motion study. *Cancer cytopathology, 124*(1), 192. doi:10.1002/cncr.30987 [doi]

Havekes, R., Vecsey, C. G., & Abel, T. (2012). The impact of sleep deprivation on neuronal and glial signaling pathways important for memory and synaptic plasticity. *Cell Signal, 24*(6), 1251-1260. doi:10.1016/j.cellsig.2012.02.010

Hermelink, K., Untch, M., Lux, M. P., Kreienberg, R., Beck, T., Bauerfeind, I., & Munzel, K. (2007). Cognitive function during neoadjuvant chemotherapy for breast cancer: results of a prospective, multicenter, longitudinal study. *Cancer, 109*(9), 1905-1913. doi:10.1002/cncr.22610

Hofman, M., Ryan, J. L., Figueroa-Moseley, C. D., Jean-Pierre, P., & Morrow, G. R. (2007). Cancer-related fatigue: the scale of the problem. *The oncologist, 12 Suppl 1*, 4-10. doi:12/suppl_1/4 [pii]

Hooper, D., Coughlan, J., & Mullen, M. (2008). Structural Equation Modelling: Guidelines for Determining Model Fit. *Electronic Journal of Business Research Methods, 6*, 53-60.

Hormozi, M., Hashemi, S. M., & Shahraki, S. (2019). Investigating Relationship between Pre- and Post- Chemotherapy Cognitive Performance with Levels of Depression and Anxiety in Breast Cancer Patients: A Cross-Sectional Study. *Asian Pac J Cancer Prev, 20*(12), 3831-3837. doi:10.31557/apjcp.2019.20.12.3831

Huang, H. P., Wen, F. H., Yang, T. Y., Lin, Y. C., Tsai, J. C., Shun, S. C., . . . Chen, M. L. (2019). The effect of a 12-week home-based walking program on reducing fatigue in women with breast cancer undergoing chemotherapy: A randomized controlled study. *Int J Nurs Stud, 99*, 103376. doi:10.1016/j.ijnurstu.2019.06.007

Hutchinson, A. D., Hosking, J. R., Kichenadasse, G., Mattiske, J. K., & Wilson, C. (2012). Objective and subjective cognitive impairment following chemotherapy for cancer: a systematic review. *Cancer Treat Rev, 38*(7), 926-934. doi:10.1016/j.ctrv.2012.05.002

Jacobs, S. R., Jacobsen, P. B., Booth-Jones, M., Wagner, L. I., & Anasetti, C. (2007). Evaluation of the functional assessment of cancer therapy cognitive scale with hematopoietic stem cell transplant patients. *Journal of pain and symptom management, 33*(1), 13-23. doi:S0885-3924(06)00548-3 [pii]

Janelsins, M. C., Heckler, C. E., Peppone, L. J., Ahles, T. A., Mohile, S. G., Mustian, K. M., . . . Morrow, G. R. (2018). Longitudinal Trajectory and Characterization of Cancer-Related

Cognitive Impairment in a Nationwide Cohort Study. *J Clin Oncol*, Jco2018786624. doi:10.1200/jco.2018.78.6624

Janelsins, M. C., Heckler, C. E., Peppone, L. J., Kamen, C., Mustian, K. M., Mohile, S. G., . . . Morrow, G. R. (2017). Cognitive Complaints in Survivors of Breast Cancer After Chemotherapy Compared With Age-Matched Controls: An Analysis From a Nationwide, Multicenter, Prospective Longitudinal Study. *J Clin Oncol, 35*(5), 506-514. doi:10.1200/jco.2016.68.5826

Janelsins, M. C., Kesler, S. R., Ahles, T. A., & Morrow, G. R. (2014). Prevalence, mechanisms, and management of cancer-related cognitive impairment. *International review of psychiatry (Abingdon, England), 26*(1), 102-113. doi:10.3109/09540261.2013.864260 [doi]

Jansen, C. E. (2013). Cognitive changes associated with cancer and cancer therapy: patient assessment and education. *Semin Oncol Nurs, 29*(4), 270-279. doi:10.1016/j.soncn.2013.08.007

Jarrett, B. L. (2018). *Chemotherapy induced deficits in cognition and affective behavior.* ProQuest Information & Learning, Us. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,url,uid&db=psyh&AN=2017-29366-005&site=ehost-live&scope=site Available from Ebsco (9-)

Jenkins, V., Shilling, V., Deutsch, G., Bloomfield, D., Morris, R., Allan, S., . . . Winstanley, J. (2006). A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *Br J Cancer, 94*(6), 828-834. doi:10.1038/sj.bjc.6603029

Joly, F., Giffard, B., Rigal, O., De Ruiter, M. B., Small, B. J., Dubois, M., . . . Castel, H. (2015). Impact of Cancer and Its Treatments on Cognitive Function: Advances in Research From the Paris International Cognition and Cancer Task Force Symposium and Update Since 2012. *Journal of pain and symptom management, 50*(6), 830-841. doi:10.1016/j.jpainsymman.2015.06.019

Joly, F., Lange, M., Dos Santos, M., Vaz-Luis, I., & Di Meglio, A. (2019). Long-Term Fatigue and Cognitive Disorders in Breast Cancer Survivors. *Cancers (Basel), 11*(12). doi:10.3390/cancers11121896

Jung, M. S., Zhang, M., Askren, M. K., Berman, M. G., Peltier, S., Hayes, D. F., . . . Cimprich, B. (2017). Cognitive dysfunction and symptom burden in women treated for breast cancer: A prospective behavioral and fMRI analysis. *Brain Imaging and Behavior, 11*(1), 86. doi:10.1007/s11682-016-9507-8

Juvet, L. K., Thune, I., Elvsaas, I., Fors, E. A., Lundgren, S., Bertheussen, G., . . . Oldervoll, L. M. (2017). The effect of exercise on fatigue and physical functioning in breast cancer patients during and after treatment and at 6 months follow-up: A meta-analysis. *Breast (Edinburgh, Scotland), 33*, 166-177. doi:10.1016/j.breast.2017.04.003

Kaiser, J., Dietrich, J., Amiri, M., Ruschel, I., Akbaba, H., Hantke, N., . . . Bledowski, C. (2019). Cognitive Performance and Psychological Distress in Breast Cancer Patients at Disease Onset. *Front Psychol, 10*, 2584. doi:10.3389/fpsyg.2019.02584

Kamen, C., Garland, S. N., Heckler, C. E., Peoples, A. R., Kleckner, I. R., Cole, C. L., . . . Roscoe, J. A. (2019). Social Support, Insomnia, and Adherence to Cognitive Behavioral Therapy for Insomnia After Cancer Treatment. *Behav Sleep Med, 17*(1), 70-80. doi:10.1080/15402002.2016.1276019

Kendell, C., Decker, K. M., Groome, P. A., McBride, M. L., Jiang, L., Krzyzanowska, M. K., . . . Canadian Team to Improve Community-Based Cancer Care Along the, C. (2017). Use of physician services during the survivorship phase: a multi-province study of women diagnosed with breast cancer. *Current oncology (Toronto, Ont.), 24*(2), 81. doi:10.3747/co.24.3454 [doi]

Kim, H. J., Jung, S. O., Kim, H., & Abraham, I. (2020). Systematic review of longitudinal studies on chemotherapy-associated subjective cognitive impairment in cancer patients. *Psycho-oncology*. doi:10.1002/pon.5339

Klemp, J. R., Myers, J. S., Fabian, C. J., Kimler, B. F., Khan, Q. J., Sereika, S. M., & Stanton, A. L. (2018). Cognitive functioning and quality of life following chemotherapy in pre- and peri-menopausal women with breast cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 26*(2), 575. doi:10.1007/s00520-017-3869-3 [doi]

Koffel, E. A., Koffel, J. B., & Gehrman, P. R. (2015). A meta-analysis of group cognitive behavioral therapy for insomnia. *Sleep Med Rev, 19*, 6-16. doi:10.1016/j.smrv.2014.05.001

Koppelmans, V., Breteler, M. M., Boogerd, W., Seynaeve, C., Gundy, C., & Schagen, S. B. (2012). Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 30*(10), 1080. doi:10.1200/JCO.2011.37.0189 [doi]

Koyama, N., Matsumura, C., Morii, H., Hasegawa, C., Hira, D., Daigo, Y., . . . Yano, Y. (2017). Investigation of optimal time for starting betamethasone using fatigue scores and prognostic nutritional index in terminally ill patients with cancer-related fatigue. *The American Journal of Hospice & Palliative Care, 34*(5), 449-455. doi:10.1177/1049909116632487 [doi]

Lai, J. S., Butt, Z., Wagner, L., Sweet, J. J., Beaumont, J. L., Vardy, J., . . . Cella, D. (2009). Evaluating the dimensionality of perceived cognitive function. *J Pain Symptom Manage, 37*(6), 982-995. doi:10.1016/j.jpainsymman.2008.07.012

Lange, M., & Joly, F. (2017). How to identify and manage cognitive dysfunction after breast cancer treatment. *Journal of oncology practice, 13*(12), 784-790. doi:10.1200/JOP.2017.026286 [doi]

Lange, M., Joly, F., Vardy, J., Ahles, T., Dubois, M., Tron, L., . . . Castel, H. (2019). Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. *Ann Oncol, 30*(12), 1925-1940. doi:10.1093/annonc/mdz410

Lange, M., Licaj, I., Clarisse, B., Humbert, X., Grellard, J. M., Tron, L., & Joly, F. (2019). Cognitive complaints in cancer survivors and expectations for support: Results from a web-based survey. *Cancer Med, 8*(5), 2654-2663. doi:10.1002/cam4.2069

Lee, P. E., Tierney, M. C., Wu, W., Pritchard, K. I., & Rochon, P. A. (2016). Endocrine treatment-associated cognitive impairment in breast cancer survivors: evidence from published studies. *Breast Cancer Res Treat, 158*(3), 407-420. doi:10.1007/s10549-016-3906-9

Lemay, K. R., Tulloch, H. E., Pipe, A. L., & Reed, J. L. (2019). Establishing the Minimal Clinically Important Difference for the Hospital Anxiety and Depression Scale in Patients

With Cardiovascular Disease. *J Cardiopulm Rehabil Prev, 39*(6), E6-e11. doi:10.1097/hcr.0000000000000379

Leysen, L., Lahousse, A., Nijs, J., Adriaenssens, N., Mairesse, O., Ivakhnov, S., . . . Beckwée, D. (2019). Prevalence and risk factors of sleep disturbances in breast cancersurvivors: systematic review and meta-analyses. *Support Care Cancer, 27*(12), 4401-4433. doi:10.1007/s00520-019-04936-5

Li, J., Yu, L., Long, Z., Li, Y., & Cao, F. (2015). Perceived cognitive impairment in Chinese patients with breast cancer and its relationship with post-traumatic stress disorder symptoms and fatigue. *Psycho-oncology, 24*(6), 676-682. doi:10.1002/pon.3710

Lim, M. H., Rodebaugh, T. L., Zyphur, M. J., & Gleeson, J. F. (2016). Loneliness over time: The crucial role of social anxiety. *J Abnorm Psychol, 125*(5), 620-630. doi:10.1037/abn0000162

Lindner, O. C., Phillips, B., McCabe, M. G., Mayes, A., Wearden, A., Varese, F., & Talmi, D. (2014). A meta-analysis of cognitive impairment following adult cancer chemotherapy. *Neuropsychology, 28*(5), 726-740. doi:10.1037/neu0000064

Liou, K. T., Ahles, T. A., Garland, S. N., Li, Q. S., Bao, T., Li, Y., . . . Mao, J. J. (2019). The relationship between insomnia and cognitive impairment in breast cancer survivors. *JNCI Cancer Spectr, 3*(3), pkz041. doi:10.1093/jncics/pkz041

Liu, L., Marler, M. R., Parker, B. A., Jones, V., Johnson, S., Cohen-Zion, M., . . . Ancoli-Israel, S. (2005). The relationship between fatigue and light exposure during chemotherapy. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 13*(12), 1010. doi:10.1007/s00520-005-0824-5 [doi]

Liu, L., Rissling, M., Natarajan, L., Fiorentino, L., Mills, P. J., Dimsdale, J. E., . . . Ancoli-Israel, S. (2012). The longitudinal relationship between fatigue and sleep in breast cancer patients undergoing chemotherapy. *Sleep: Journal of Sleep and Sleep Disorders Research, 35*(2), 237. doi:10.5665/sleep.1630

Lycke, M., Pottel, L., Pottel, H., Ketelaars, L., Stellamans, K., Van Eygen, K., . . . Debruyne, P. R. (2017). Predictors of baseline cancer-related cognitive impairment in cancer patients scheduled for a curative treatment. *Psycho-oncology, 26*(5), 632-639. doi:10.1002/pon.4200

Lyon, D. E., Cohen, R., Chen, H., Kelly, D. L., Starkweather, A., Ahn, H. C., & Jackson-Cook, C. K. (2016). The relationship of cognitive performance to concurrent symptoms, cancer- and cancer-treatment-related variables in women with early-stage breast cancer: a 2-year longitudinal study. *J Cancer Res Clin Oncol, 142*(7), 1461-1474. doi:10.1007/s00432-016-2163-y

Ma, Y., Hall, D. L., Ngo, L. H., Liu, Q., Bain, P. A., & Yeh, G. Y. (2020). Efficacy of cognitive behavioral therapy for insomnia in breast cancer: A meta-analysis. *Sleep Med Rev, 55*, 101376. doi:10.1016/j.smrv.2020.101376

Maass, S. W., Roorda, C., Berendsen, A. J., Verhaak, P. F., & de Bock, G. H. (2015). The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: A systematic review. *Maturitas, 82*(1), 100-108. doi:10.1016/j.maturitas.2015.04.010

Mao, H., Bao, T., Shen, X., Li, Q., Seluzicki, C., Im, E. O., & Mao, J. J. (2018). Prevalence and risk factors for fatigue among breast cancer survivors on aromatase inhibitors. *Eur J Cancer, 101*, 47-54. doi:10.1016/j.ejca.2018.06.009

Martino, G., Catalano, A., Agostino, R. M., Bellone, F., Morabito, N., Lasco, C. G., . . . Feldt-Rasmussen, U. (2020). Quality of life and psychological functioning in postmenopausal women undergoing aromatase inhibitor treatment for early breast cancer. *PLoS One, 15*(3), e0230681. doi:10.1371/journal.pone.0230681

Massie, M. J. (2004). Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr*(32), 57-71. doi:10.1093/jncimonographs/lgh014

Meerlo, P., Mistlberger, R. E., Jacobs, B. L., Heller, H. C., & McGinty, D. (2009). New neurons in the adult brain: the role of sleep and consequences of sleep loss. *Sleep Med Rev, 13*(3), 187-194. doi:10.1016/j.smrv.2008.07.004

Meneses-Echávez, J. F., González-Jiménez, E., & Ramírez-Vélez, R. (2015). Effects of supervised exercise on cancer-related fatigue in breast cancer survivors: a systematic review and meta-analysis. *BMC Cancer, 15*, 77. doi:10.1186/s12885-015-1069-4

Minton, O., & Stone, P. C. (2012). A comparison of cognitive function, sleep and activity levels in disease-free breast cancer patients with or without cancer-related fatigue syndrome. *BMJ supportive & palliative care, 2*(3), 231-238. doi:10.1136/bmjspcare-2011-000172 [doi]

Mitchell, A. J., Meader, N., & Symonds, P. (2010). Diagnostic validity of the Hospital Anxiety and Depression Scale (HADS) in cancer and palliative settings: a meta-analysis. *Journal of affective disorders, 126*(3), 335-348. doi:10.1016/j.jad.2010.01.067 [doi]

Mitchell, M. D., Gehrman, P., Perlis, M., & Umscheid, C. A. (2012). Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC Fam Pract, 13*, 40. doi:10.1186/1471-2296-13-40

Morin, C. M. (1993). *Insomnia: Psychological Assessment and Management*. New York, NY, US: Guilford Press.

Mu, Q., Nahas, Z., Johnson, K. A., Yamanaka, K., Mishory, A., Koola, J., . . . George, M. S. (2005). Decreased cortical response to verbal working memory following sleep deprivation. *Sleep, 28*(1), 55-67. doi:10.1093/sleep/28.1.55

Munro Cullum, C., Hynan, L. S., Grosch, M., Parikh, M., & Weiner, M. F. (2014). Teleneuropsychology: evidence for video teleconference-based neuropsychological assessment. *J Int Neuropsychol Soc, 20*(10), 1028-1033. doi:10.1017/s1355617714000873

Myers, J. S. (2013). Cancer- and chemotherapy-related cognitive changes: the patient experience. *Seminars in oncology nursing, 29*(4), 300-307. doi:10.1016/j.soncn.2013.08.010 [doi]

Myers, J. S., Mitchell, M., Krigel, S., Steinhoff, A., Boyce-White, A., Van Goethem, K., . . . Bender, C. M. (2019). Qigong intervention for breast cancer survivors with complaints of decreased cognitive function. *Support Care Cancer, 27*(4), 1395-1403. doi:10.1007/s00520-018-4430-8

National Comprehensive Cancer Network. (2020). NCNN guidelines for supportive care. Retrieved from https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf

Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *Br J Sports Med, 52*(3), 154-160. doi:10.1136/bjsports-2016-096587

Ono, M., Ogilvie, J. M., Wilson, J. S., Green, H. J., Chambers, S. K., Ownsworth, T., & Shum, D. H. (2015). A meta-analysis of cognitive impairment and decline associated with

adjuvant chemotherapy in women with breast cancer. *Front Oncol, 5*, 59. doi:10.3389/fonc.2015.00059

Ooi, S. L., Martinez, M. E., & Li, C. I. (2011). Disparities in breast cancer characteristics and outcomes by race/ethnicity. *Breast Cancer Res Treat, 127*(3), 729-738. doi:10.1007/s10549-010-1191-6

Palesh, O., Zeitzer, J. M., Conrad, A., Giese-Davis, J., Mustian, K. M., Popek, V., . . . Spiegel, D. (2008). Vagal regulation, cortisol, and sleep disruption in women with metastatic breast cancer. *J Clin Sleep Med, 4*(5), 441-449.

Palesh, O. G., Roscoe, J. A., Mustian, K. M., Roth, T., Savard, J., Ancoli-Israel, S., . . . Morrow, G. R. (2010). Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 28*(2), 292. doi:10.1200/JCO.2009.22.5011 [doi]

Partridge, A. H., Burstein, H. J., & Winer, E. P. (2001). Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer. *Journal of the National Cancer Institute.Monographs, (30)*(30), 135.

Pendergrass, J. C., Targum, S. D., & Harrison, J. E. (2018). Cognitive impairment associated with cancer: A brief review. *Innovations in Clinical Neuroscience, 15*(1-2), 36-44. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,url,uid&db=psyh&AN=2018-08440-008&site=ehost-live&scope=site

Peoples, A. R., Garland, S. N., Pigeon, W. R., Perlis, M. L., Wolf, J. R., Heffner, K. L., . . . Roscoe, J. A. (2019). Cognitive Behavioral Therapy for Insomnia Reduces Depression in Cancer Survivors. *J Clin Sleep Med, 15*(1), 129-137. doi:10.5664/jcsm.7586

Pertl, M. M., Hevey, D., Collier, S., Lambe, K., & O'Dwyer, A. M. (2014). Predictors of fatigue in cancer patients before and after chemotherapy. *Journal of health psychology, 19*(6), 699-710. doi:10.1177/1359105313477675 [doi]

Peukert, X., Steindorf, K., Schagen, S. B., Runz, A., Meyer, P., & Zimmer, P. (2020). Hippocampus-Related Cognitive and Affective Impairments in Patients With Breast Cancer-A Systematic Review. *Front Oncol, 10*, 147. doi:10.3389/fonc.2020.00147

Pullens, M. J., De Vries, J., Van Warmerdam, L. J., Van De Wal, M. A., & Roukema, J. A. (2013). Chemotherapy and cognitive complaints in women with breast cancer. *Psycho-oncology, 22*(8), 1783-1789. doi:10.1002/pon.3214

R Core Team. (2019). R: A language and environment for statistical imputing. Version 3.6.2. In. Vienna, Austria: R Foundation for Statistical Imputing.

Rabin, L. A., Roth, R. M., Isquith, P. K., Wishart, H. A., Nutter-Upham, K. E., Pare, N., . . . Saykin, A. J. (2006). Self- and informant reports of executive function on the BRIEF-A in MCI and older adults with cognitive complaints. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists, 21*(7), 721-732. doi:S0887-6177(06)00107-7 [pii]

Ramalho, M., Fontes, F., Ruano, L., Pereira, S., & Lunet, N. (2017). Cognitive impairment in the first year after breast cancer diagnosis: A prospective cohort study. *Breast (Edinburgh, Scotland), 32*, 173-178. doi:10.1016/j.breast.2017.01.018

Reuter-Lorenz, P. A., & Cimprich, B. (2013). Cognitive function and breast cancer: promise and potential insights from functional brain imaging. *Breast Cancer Res Treat, 137*(1), 33-43. doi:10.1007/s10549-012-2266-3

Riemann, D., Voderholzer, U., Spiegelhalder, K., Hornyak, M., Buysse, D. J., Nissen, C., . . . Feige, B. (2007). Chronic insomnia and MRI-measured hippocampal volumes: a pilot study. *Sleep, 30*(8), 955-958. doi:10.1093/sleep/30.8.955

Rosseel, Y. (2012). lavaan: An R Package for Structural Equation Modeling. *Journal of Statistical Software, 48*, 1-36. Retrieved from http://www.jstatsoft.org/v48/i02/

Rupp, T. L., & Balkin, T. J. (2011). Comparison of Motionlogger Watch and Actiwatch actigraphs to polysomnography for sleep/wake estimation in healthy young adults. *Behavior research methods, 43*(4), 1152-1160. doi:10.3758/s13428-011-0098-4 [doi]

Sachdev, P. S., Lipnicki, D. M., Kochan, N. A., Crawford, J. D., Thalamuthu, A., Andrews, G., . . . Santabarbara, J. (2015). The prevalence of mild cognitive impairment in diverse geographical and ethnocultural regions: the COSMIC collaboration. *PLoS One, 10*(11), e0142388. doi:10.1371/journal.pone.0142388

Sanford, S. D., Beaumont, J. L., Butt, Z., Sweet, J. J., Cella, D., & Wagner, L. I. (2014). Prospective longitudinal evaluation of a symptom cluster in breast cancer. *J Pain Symptom Manage, 47*(4), 721-730. doi:10.1016/j.jpainsymman.2013.05.010

Savard, J., Ivers, H., Villa, J., Caplette-Gingras, A., & Morin, C. M. (2011). Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. *J Clin Oncol, 29*(26), 3580-3586. doi:10.1200/jco.2010.33.2247

Savard, J., Liu, L., Natarajan, L., Rissling, M. B., Neikrug, A. B., He, F., . . . Ancoli-Israel, S. (2009). Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. *Sleep, 32*(9), 1155-1160. doi:10.1093/sleep/32.9.1155

Savard, J., & Morin, C. M. (2001). Insomnia in the context of cancer: a review of a neglected problem. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 19*(3), 895-908. doi:10.1200/JCO.2001.19.3.895 [doi]

Savard, M., Savard, J., Simard, S., & Ivers, H. (2005). Empirical validation of the Insomnia Severity Index in cancer patients. *Psycho-oncology, 14*(6), 429-441. doi:10.1002/pon.860

Savard, M. H., Savard, J., Caplette-Gingras, A., Ivers, H., & Bastien, C. (2013). Relationship between objectively recorded hot flashes and sleep disturbances among breast cancer patients: investigating hot flash characteristics other than frequency. *Menopause (New York, N.Y.), 20*(10), 997-1005. doi:10.1097/GME.0b013e3182885e31

Schagen, S. B., Boogerd, W., Muller, M. J., Huinink, W. T., Moonen, L., Meinhardt, W., & Van Dam, F. S. (2008). Cognitive complaints and cognitive impairment following BEP chemotherapy in patients with testicular cancer. *Acta Oncol, 47*(1), 63-70. doi:10.1080/02841860701518058

Schilder, C. M., Eggens, P. C., Seynaeve, C., Linn, S. C., Boogerd, W., Gundy, C. M., . . . Schagen, S. B. (2009). Neuropsychological functioning in postmenopausal breast cancer patients treated with tamoxifen or exemestane after AC-chemotherapy: cross-sectional findings from the neuropsychological TEAM-side study. *Acta Oncol, 48*(1), 76-85. doi:10.1080/02841860802314738

Schilder, C. M., & Schagen, S. B. (2007). Effects of hormonal therapy on cognitive functioning in breast cancer patients: a review of the literature. *Minerva ginecologica, 59*(4), 387.

Schilder, C. M., Seynaeve, C., Linn, S. C., Boogerd, W., Beex, L. V., Gundy, C. M., . . . Schagen, S. B. (2012). Self-reported cognitive functioning in postmenopausal breast cancer patients before and during endocrine treatment: findings from the neuropsychological TEAM side-study. *Psycho-oncology, 21*(5), 479-487. doi:10.1002/pon.1928

Schilder, C. M., Seynaeve, C., Linn, S. C., Boogerd, W., Gundy, C. M., Beex, L. V., . . . Schagen, S. B. (2010a). The impact of different definitions and reference groups on the prevalence of cognitive impairment: a study in postmenopausal breast cancer patients before the start of adjuvant systemic therapy. *Psycho-oncology, 19*(4), 415-422. doi:10.1002/pon.1595

Schilder, C. M., Seynaeve, C., Linn, S. C., Boogerd, W., Gundy, C. M., Beex, L. V., . . . Schagen, S. B. (2010b). The impact of different definitions and reference groups on the prevalence of cognitive impairment: a study in postmenopausal breast cancer patients before the start of adjuvant systemic therapy. *Psycho-oncology, 19*(4), 415-422. doi:10.1002/pon.1595

Schmidt, M. E., Wiskemann, J., Armbrust, P., Schneeweiss, A., Ulrich, C. M., & Steindorf, K. (2015). Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: A randomized controlled trial. *Int J Cancer, 137*(2), 471-480. doi:10.1002/ijc.29383

Scurrey, S., Garland, S. N., Thoms, J., & Laing, K. (2019). Evaluating the experience of rural individuals with prostate and breast cancer participating in research via telehealth. *Rural and remote health, 19*(3), 52-69. doi:10.22605/rrh5269

Small, B. J., Jim, H. S. L., Eisel, S. L., Jacobsen, P. B., & Scott, S. B. (2019). Cognitive performance of breast cancer survivors in daily life: Role of fatigue and depressed mood. *Psycho-oncology, 28*(11), 2174-2180. doi:10.1002/pon.5203

Stasi, R., Abriani, L., Beccaglia, P., Terzoli, E., & Amadori, S. (2003). Cancer-related fatigue: evolving concepts in evaluation and treatment. *Cancer, 98*(9), 1786. doi:10.1002/cncr.11742 [doi]

Statistics Canada. (2019). Cancer in Canada: Focus on lung, colorectal, breast, and prostate. *Statistics Canada Catalogue no. 82-624-X.*

Steiger, J. H. L., J. C. (1980). Statistically-based tests for the number of factors. Paper presented at the Psychometric Society. In *Psychometrika*. Iowa City, IA.

Stein, K. D., Jacobsen, P. B., Blanchard, C. M., & Thors, C. (2004). Further validation of the multidimensional fatigue symptom inventory-short form. *Journal of pain and symptom management, 27*(1), 14-23. doi:S0885392403004573 [pii]

Stewart, A., Collins, B., Mackenzie, J., Tomiak, E., Verma, S., & Bielajew, C. (2008). The cognitive effects of adjuvant chemotherapy in early stage breast cancer: a prospective study. *Psycho-oncology, 17*(2), 122-130. doi:10.1002/pon.1210

Szelenberger, W., & Niemcewicz, S. (2000). Severity of insomnia correlates with cognitive impairment. *Acta Neurobiologiae Experimentalis, 60*(3), 373.

Tabachnick, B., & Fidell, L. (2012). *Using Multivariate Statistics.* Boston: Pearson.

Tao, J. J., Visvanathan, K., & Wolff, A. C. (2015). Long term side effects of adjuvant chemotherapy in patients with early breast cancer. *Breast (Edinburgh, Scotland), 24 Suppl 2*, 149-153. doi:10.1016/j.breast.2015.07.035

Tao, L., Lin, H., Yan, Y., Xu, X., Wang, L., Zhang, J., & Yu, Y. (2017). Impairment of the executive function in breast cancer patients receiving chemotherapy treatment: a functional MRI study. *Eur J Cancer Care (Engl), 26*(6). doi:10.1111/ecc.12553

Trauer, J. M., Qian, M. Y., Doyle, J. S., Rajaratnam, S. M., & Cunnington, D. (2015). Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-analysis. *Ann Intern Med, 163*(3), 191-204. doi:10.7326/m14-2841

Tucker, L. R. L., C. (1973). A reliability coefficient for maximum likelihood factor analysis. *Psychometrika, 38*, 1-10. doi:http://dx.doi.org/10.1007/BF02291170

Turner, T. H., Horner, M. D., Vankirk, K. K., Myrick, H., & Tuerk, P. W. (2012). A pilot trial of neuropsychological evaluations conducted via telemedicine in the Veterans Health Administration. *Telemed J E Health, 18*(9), 662-667. doi:10.1089/tmj.2011.0272

Underwood, E. A., Jerzak, K. J., Lebovic, G., Rochon, P. A., Elser, C., Pritchard, K. I., & Tierney, M. C. (2019). Cognitive effects of adjuvant endocrine therapy in older women treated for early-stage breast cancer: a 1-year longitudinal study. *Support Care Cancer, 27*(8), 3035-3043. doi:10.1007/s00520-018-4603-5

van Dalfsen, J. H., & Markus, C. R. (2018). The influence of sleep on human hypothalamic-pituitary-adrenal (HPA) axis reactivity: A systematic review. *Sleep Med Rev, 39*, 187-194. doi:10.1016/j.smrv.2017.10.002

Van Dyk, K., Bower, J. E., Crespi, C. M., Petersen, L., & Ganz, P. A. (2018). Cognitive function following breast cancer treatment and associations with concurrent symptoms. *NPJ Breast Cancer, 4*, 25. doi:10.1038/s41523-018-0076-4

Van Dyk, K., Crespi, C. M., Bower, J. E., Castellon, S. A., Petersen, L., & Ganz, P. A. (2019). The cognitive effects of endocrine therapy in survivors of breast cancer: A prospective longitudinal study up to 6 years after treatment. *Cancer, 125*(5), 681-689. doi:10.1002/cncr.31858

Van Dyk, K., Hunter, A. M., Ercoli, L., Petersen, L., Leuchter, A. F., & Ganz, P. A. (2017). Evaluating cognitive complaints in breast cancer survivors with the FACT-Cog and quantitative electroencephalography. *Breast cancer research and treatment, 166*(1), 157. doi:10.1007/s10549-017-4390-6 [doi]

Vardy, J., Wong, K., Yi, Q. L., Park, A., Maruff, P., Wagner, L., & Tannock, I. F. (2006). Assessing cognitive function in cancer patients. *Support Care Cancer, 14*(11), 1111-1118. doi:10.1007/s00520-006-0037-6

Vardy, J. L., Stouten-Kemperman, M. M., Pond, G., Booth, C. M., Rourke, S. B., Dhillon, H. M., . . . Tannock, I. F. (2019). A mechanistic cohort study evaluating cognitive impairment in women treated for breast cancer. *Brain Imaging and Behavior, 13*(1), 15-26. doi:10.1007/s11682-017-9728-5

Visovatti, M. A., Reuter-Lorenz, P. A., Chang, A. E., Northouse, L., & Cimprich, B. (2016). Assessment of Cognitive Impairment and Complaints in Individuals With Colorectal Cancer. *Oncol Nurs Forum, 43*(2), 169-178. doi:10.1188/16.onf.43-02ap

Von Ah, D., Carpenter, J. S., Saykin, A., Monahan, P., Wu, J., Yu, M., . . . Unverzagt, F. (2012). Advanced cognitive training for breast cancer survivors: a randomized controlled trial. *Breast Cancer Res Treat, 135*(3), 799-809. doi:10.1007/s10549-012-2210-6

Von Ah, D., Habermann, B., Carpenter, J. S., & Schneider, B. L. (2013). Impact of perceived cognitive impairment in breast cancer survivors. *Eur J Oncol Nurs, 17*(2), 236-241. doi:10.1016/j.ejon.2012.06.002

Wagner, L. I., Gray, R. J., Sparano, J. A., Whelan, T. J., Garcia, S. F., Yanez, B., . . . Cella, D. (2020). Patient-Reported Cognitive Impairment Among Women With Early Breast Cancer Randomly Assigned to Endocrine Therapy Alone Versus Chemoendocrine Therapy: Results From TAILORx. *J Clin Oncol*, Jco1901866. doi:10.1200/jco.19.01866

Wagner, L. I., Sweet, J., Butt, Z., Lai, J. S., & Cella, D. (2009). Measuring patient self-reported cognitive function: Development of the Functional Assessment of Cancer Therapy-Cognitive Function instrument. *The Journal of Supportive Oncology*(7), 32.

Wang, L., Apple, A. C., Schroeder, M. P., Ryals, A. J., Voss, J. L., Gitelman, D., . . . Wagner, L. I. (2016). Reduced prefrontal activation during working and long-term memory tasks and impaired patient-reported cognition among cancer survivors postchemotherapy compared with healthy controls. *Cancer, 122*(2), 258-268. doi:10.1002/cncr.29737

Wang, L., Yan, Y., Wang, X., Tao, L., Chen, Q., Bian, Y., . . . Qiu, B. (2016). Executive Function Alternations of Breast Cancer Patients After Chemotherapy: Evidence From Resting-state Functional MRI. *Acad Radiol, 23*(10), 1264-1270. doi:10.1016/j.acra.2016.05.014

Wang, X. S., & Woodruff, J. F. (2015). Cancer-related and treatment-related fatigue. *Gynecologic oncology, 136*(3), 446. doi:10.1016/j.ygyno.2014.10.013 [doi]

Wardle-Pinkston, S., Slavish, D. C., & Taylor, D. J. (2019). Insomnia and cognitive performance: A systematic review and meta-analysis. *Sleep Med Rev, 48*, 101205. doi:10.1016/j.smrv.2019.07.008

Wefel, J. S., Lenzi, R., Theriault, R. L., Davis, R. N., & Meyers, C. A. (2004). The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer, 100*(11), 2292-2299. doi:10.1002/cncr.20272

Wefel, J. S., Saleeba, A. K., Buzdar, A. U., & Meyers, C. A. (2010). Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. *Cancer, 116*(14), 3348-3356. doi:10.1002/cncr.25098

Wefel, J. S., Vardy, J., Ahles, T., & Schagen, S. B. (2011). International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *The Lancet.Oncology, 12*(7), 703-708. doi:10.1016/S1470-2045(10)70294-1 [doi]

Wynne, S. C., Patel, S., Barker, R. E., Jones, S. E., Walsh, J. A., Kon, S. S., . . . Nolan, C. M. (2020). Anxiety and depression in bronchiectasis: Response to pulmonary rehabilitation and minimal clinically important difference of the Hospital Anxiety and Depression Scale. *Chron Respir Dis, 17*, 1479973120933292. doi:10.1177/1479973120933292

Xu, S., Thompson, W., Ancoli-Israel, S., Liu, L., Palmer, B., & Natarajan, L. (2017). Cognition, quality-of-life, and symptom clusters in breast cancer: Using Bayesian networks to elucidate complex relationships. *Psycho-oncology*. doi:10.1002/pon.4571 [doi]

Yamada, T. H., Denburg, N. L., Beglinger, L. J., & Schultz, S. K. (2010). Neuropsychological outcomes of older breast cancer survivors: cognitive features ten or more years after chemotherapy. *The Journal of neuropsychiatry and clinical neurosciences, 22*(1), 48. doi:10.1176/appi.neuropsych.22.1.48 [doi]

Yang, Y., & Hendrix, C. C. (2018). Cancer-Related Cognitive Impairment in Breast Cancer Patients: Influences of Psychological Variables. *Asia Pac J Oncol Nurs, 5*(3), 296-306. doi:10.4103/apjon.apjon_16_18

Yao, C., Bernstein, L. J., & Rich, J. B. (2017). Executive functioning impairment in women treated with chemotherapy for breast cancer: a systematic review. *Breast cancer research and treatment, 166*(1), 15. doi:10.1007/s10549-017-4376-4 [doi]

Zachariae, R., Amidi, A., Damholdt, M. F., Clausen, C. D. R., Dahlgaard, J., Lord, H., . . . Ritterband, L. M. (2018a). Internet-delivered cognitive-behavioral therapy for insomnia in breast cancer survivors: a randomized controlled trial. *Journal of the National Cancer Institute, 110*(8), 880-887. doi:10.1093/jnci/djx293 [doi]

Zachariae, R., Amidi, A., Damholdt, M. F., Clausen, C. D. R., Dahlgaard, J., Lord, H., . . . Ritterband, L. M. (2018b). Internet-Delivered Cognitive-Behavioral Therapy for

Insomnia in Breast Cancer Survivors: A Randomized Controlled Trial. *J Natl Cancer Inst, 110*(8), 880-887. doi:10.1093/jnci/djx293