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SYMPTOM SEVERITY AND IMPORTANCE IN METASTATIC BREAST CANCER

PATIENTS: AN EXAMINATION OF COGNITIVE COMPLAINTS AND RELATED

SYMPTOMS

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TABLE OF CONTENTS

ABSTRACT

Tometich, Danielle B. M.S., Purdue University, August 2016. Symptom Severity and Importance in Metastatic Breast Cancer Survivors: An Examination of Cognitive Complaints and Related Symptoms. Major Professor: Catherine Mosher.

Cognitive changes associated with cancer and its treatment have been well documented. However, the majority of research on cognitive symptoms in cancer has been conducted with early-stage breast cancer patients or survivors in remission. Little is known about cognitive symptoms in patients with late-stage or metastatic cancers. To address this gap in the literature, this study examines cognitive and related symptoms among metastatic breast cancer patients enrolled in a parent study of perceptions of symptom importance and interference. Eighty metastatic breast cancer patients were recruited from the Indiana University Simon Cancer Center to participate in this cross-sectional telephone interview study. The interview consisted of self-report measures, including measures of symptom severity, distress, and the importance of seeing improvement in specific symptoms post-treatment. I hypothesized that cognitive complaints would cluster with fatigue, sleep disturbance, depressive symptoms, anxiety, and pain. This hypothesis was tested using cluster analysis and was partially supported. Cognitive complaints were found to cluster with fatigue, sleep disturbance, depressive symptoms, and anxiety, but not pain. In addition, the extent to which ratings of symptom importance for cognitive symptoms

differed from those of other symptoms (i.e., pain, fatigue, sleep problems, depressive

symptoms, anxiety, nausea, lymphedema, hot flashes, and neuropathy) was explored

using ANOVA and Tukey's HSD tests. Cognitive complaints were rated as significantly

more important than anxiety, depressive symptoms, neuropathy, swelling, nausea, and

hot flashes. Importance ratings for cognitive complaints, pain, fatigue, and sleep

problems were not significantly different. Developing patient-centered treatment

approaches that take into account symptom clustering and patients' treatment priorities

may increase treatment adherence and optimize healthcare quality.

CHAPTER 1. INTRODUCTION

1.1   Introduction

Cognitive changes have been associated with cancer and its treatment in early-stage

breast cancer patients (Ahles, Schagen, & Vardy, 2012; Hurria, Somlo, & Ahles, 2007;

Ono et al., 2015), but a paucity of research has examined cognitive changes in patients

with metastatic cancers. Cognitive difficulties are typically viewed as a survivorship

issue affecting functional capacity (Hede, 2008; Von Ah, 2015). The majority of

research in this area has been conducted with early-stage breast cancer patients and

survivors in remission due to their large numbers and high likelihood of long-term

survival (Ahles, Schagen, et al., 2012; Newman, 2009; Von Ah, 2015). It is estimated

that 2.9 million women were living with a breast cancer diagnosis of any stage in the

United States in 2012 (Howlader et al., 2015), and 17-75% of breast cancer survivors

have some degree of cognitive dysfunction (Ahles, Root, & Ryan, 2012; Von Ah, 2015).

Survivorship issues, including cognitive changes, are becoming increasingly

relevant for patients with late-stage disease as recent advances in treatment have

increased longevity (Mayer, 2010; Reed, Simmonds, Haviland, & Corner, 2012). After a

diagnosis of metastatic breast cancer, survival can range from a few months to more than

five years, and the median survival time is approximately three years (Smerage et al.,

2014). Between 2005-2011, 5-year survival rates for metastatic breast cancer were

estimated to be 25.9% (Howlader et al., 2015). Thus, metastatic breast cancer patients may live for years with cognitive impairment which affects their daily activities and quality of life, but little is known regarding their cognitive symptoms. This study begins to address this gap by examining cognitive symptoms' relationship to other symptoms in this population. In addition, patient ratings of the importance of seeing improvement in cognitive symptoms following symptom-focused treatment were compared to those for other common symptoms.

First, I will discuss the evidence for a relationship between cancer and its treatment and cognitive symptoms and current theoretical models of this relationship. Next, I will describe the available literature on cognitive symptoms in metastatic breast cancer patients. Finally, I will provide a rationale for characterizing symptom clusters and patient perceptions of symptom importance in cancer patients. Following this review, I will present my hypotheses, study methods, and results and discuss the implications and limitations of my findings.

<div align="center">1.2 Cognitive Symptoms in Cancer</div>

History, terminology, and definitions. Medical and psychological scientists have known about the association between chemotherapy treatments for cancer and cognitive impairment for more than 40 years (Silberfarb, 1983; Weiss, Walker, & Wiernik, 1974). The first reviews exploring the neurotoxic effects of chemotherapy were published in the 1970s, and they acknowledged neurological symptoms such as somnolence and encephalopathy in cancer patients with primary central nervous system (CNS) disease or CNS metastases (Pochedly, 1977; Weiss et al., 1974). Shortly thereafter, reviews described the possibility of CNS toxicities due to cancer treatment in

patients without CNS disease (Allen, 1978; Silberfarb, 1983). The colloquial terms "chemobrain" and "chemofog" were coined in the 1990s to describe the cognitive symptoms that appeared to be related to chemotherapy (Ahles, Schagen, et al., 2012). It later became apparent that numerous factors besides chemotherapy can contribute to cognitive symptoms; thus, the terms "chemobrain" and "chemofog" have been replaced with "cancer- or cancer treatment-associated cognitive change" (Hurria et al., 2007).

The terminology for describing cancer patients' cognitive performance on neuropsychological tests is also controversial. The term "cognitive impairment" is often used in cross-sectional studies comparing patients treated with chemotherapy to non-chemotherapy controls, and the term "cognitive decline" is used in longitudinal studies of chemotherapy-treated patients (Ono et al., 2015). Ahles and colleagues (2008) question whether it is appropriate to label cognitive problems in cancer patients as "impairment" when they are typically subtle and often within the normal range. Instead, these researchers describe the cognitive deficits found in a subset of their study participants as "lower than expected cognitive performance" (Ahles et al., 2008, p. 144).

Currently, little consensus exists regarding the definition of cognitive impairment/decline in cancer populations, and clinically significant cognitive impairment/decline has no established cut-off point or statistical convention (Ono et al., 2015). Ahles and colleagues (2008) define "lower than expected cognitive performance" as two neurocognitive domains that are 1.5 standard deviations below the mean of published norms or one domain that is 2 standard deviations below the mean. Cognitive decline in longitudinal studies has often been defined as a 1 to 2 standard deviation decrease in scores on one or more cognitive domains from pre- to post-chemotherapy

(Hurria et al., 2006; Ono et al., 2015; Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005; A. Stewart et al., 2008; Vearncombe et al., 2009). Cognitive impairment in some cross-sectional studies has been defined as 2 standard deviations below the mean performance of a healthy comparison group or published norm (de Ruiter et al., 2011; Deprez et al., 2011; Donovan et al., 2005; Ono et al., 2015; Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001; Schagen et al., 1999; Schilder et al., 2009). Cognitive impairment has also been classified by degrees from mild (1 standard deviation below the norm) to moderate impairment (2 standard deviations below the norm) (Hermelink et al., 2007; Ono et al., 2015).

Evidence suggests that, in general, breast cancer patients treated with chemotherapy have worse performance on objective cognitive tests than control groups, but impairment is not consistently found in specific neurocognitive domains (Jim et al., 2012; Ono et al., 2015). A recent meta-analysis examined cross-sectional and prospective longitudinal studies of cognitive functioning among non-metastatic breast cancer patients treated with adjuvant chemotherapy (Ono et al., 2015). Analyses of cross-sectional data revealed statistically significant cognitive impairment in five of the eight examined neurocognitive domains: processing speed (d = -0.25), executive function (d = -0.19), attention (d = -0.16), motor function (d = -0.16), and short-term memory (d = -0.15). Effect sizes were non-significant for the domains of language, long-term memory, and visuospatial function (Ono et al., 2015). These results are partially consistent with those of prior meta-analyses (see Table 1). Two of the four prior meta-analyses found significant deficits in executive function (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; A. Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006),

one found a significant deficit in processing speed (Jansen et al., 2005), and another found significant deficits in motor speed, and short-term memory (A. Stewart et al., 2006). However, three of the four prior meta-analyses also found significant deficits in language (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Jim et al., 2012; A. Stewart et al., 2006), two found significant deficits in spatial function (Falleti et al., 2005; Jim et al., 2012), and one found significant deficits in long-term memory (A. Stewart et al., 2006).

Findings are also inconsistent with respect to moderators of cognitive performance in breast cancer patients post-chemotherapy. An earlier meta-analysis of cross-sectional studies found that age and time since chemotherapy treatment moderated the magnitude of cognitive impairment post-treatment (Falleti et al., 2005), whereas more recent meta-analyses did not replicate these findings (Jim et al., 2012; Ono et al., 2015). Instead, the type of control group and level of education were significant moderators (Jim et al., 2012; Ono et al., 2015). Specifically, in cross-sectional studies, breast cancer patients who had received chemotherapy had significant cognitive impairment when compared to healthy controls, but not when compared to breast cancer patients without a history of chemotherapy treatment (Ono et al., 2015). In addition, breast cancer patients with fewer years of education showed a greater degree of cognitive impairment (Ono et al., 2015). Age was also a significant moderator of cognitive change in a meta-analysis of prospective longitudinal studies, with older age being associated with greater cognitive decline post-chemotherapy (Ono et al., 2015).

Another key finding from prospective longitudinal studies is that breast cancer patients show improved cognitive function in certain domains from pre- to post-

chemotherapy (Falleti et al., 2005; Ono et al., 2015; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). One meta-analysis of these studies found that long-term memory significantly improved following chemotherapy ($d = 0.41$); however, other cognitive domains did not significantly change, with effect sizes ranging from $d = -0.29$ for visuospatial function to $d = 0.26$ for language (Ono et al., 2015). Conversely, an older prospective longitudinal study of breast cancer patients found improved attention ($d = 1.09$), executive function ($d = 0.39$), memory ($d = 0.36$), spatial ability ($d = 0.31$), and motor function ($d = 0.11$) post-chemotherapy (Falleti et al., 2005; Wefel et al., 2004).

Researchers have proposed multiple explanations for breast cancer patients' improved cognitive function from pre- to post-chemotherapy. One explanation focuses on psychological factors (e.g., anxiety, depressive symptoms) associated with a cancer diagnosis and impending treatment that may affect cognitive performance; specifically, performance is expected to improve after chemotherapy as patients psychologically adjust to their medical situation (Falleti et al., 2005; Ono et al., 2015). Thus, pre-treatment assessments of cognitive functioning may not provide an accurate estimate of premorbid functioning, complicating examination of post-chemotherapy changes in cognition. This theory is supported by findings that greater pretreatment worry in breast cancer patients is associated with altered brain activation on an fMRI, worse objective performance in verbal working memory, and subjective cognitive dysfunction (Berman et al., 2014). Alternatively, improvement in cognitive performance from pre- to post-chemotherapy may be due to practice effects, although this is less likely because studies regularly control for practice effects with alternative test forms or statistical controls (Falleti et al., 2005; Ono et al., 2015). Lastly, meta-analyses of cognitive impairment in

breast cancer patients treated with adjuvant chemotherapy have not separately analyzed results from recognition and recall tests (Falleti et al., 2005; Jansen et al., 2005; Jim et al., 2012; Ono et al., 2015; A. Stewart et al., 2006). Recognition memory tests are not sensitive to subtle cognitive deficits (Welsh, Butters, Hughes, Mohs, & Heyman, 1992); thus, collapsing recall and recognition memory performance into one cognitive domain may be underestimating memory deficits and limit researchers' ability to draw accurate conclusions from the data (F.W. Unverzagt, personal communication, March 17, 2015).

Models of cognitive symptoms in cancer. Cognitive impairment in cancer patients is most commonly associated with adjuvant chemotherapy treatments for breast cancer (Bender et al., 2006; Schagen et al., 1999; van Dam et al., 1998), but it has also been associated with endocrine or hormone therapy for breast cancer (Jenkins, Shilling, Fallowfield, Howell, & Hutton, 2004; Zwart, Terra, Linn, & Schagen, 2015) and radiation therapy for primary CNS cancer or CNS metastases (Dietrich, Monje, Wefel, & Meyers, 2008). Furthermore, some studies have found cognitive impairment in breast cancer patients after surgery, but before any hormone, radiation, or chemotherapy treatment (Ahles et al., 2008; Berman et al., 2014). This suggests that surgery, the disease, or psychological reactions to the disease may be sufficient precipitants of cognitive sequelae. To date, no systematic review has been conducted to compare the cognitive effects of different cancer treatments. Sufficient data are not available for this analysis because many cancer patients receive multiple treatment types, some of which are concurrently administered (Hurria et al., 2007).

A number of models have been proposed to characterize the multiple, interactive factors that may result in cognitive symptoms in cancer patients (Ahles, Root, et al.,

2012; Mandelblatt et al., 2013; Meyers & Perry, 2008; Wefel, Collins, & Kayl, 2008).

One conceptual model of cognitive dysfunction in cancer is analogous to the interaction

between soil, seed, and pesticides (Figure 1). The soil represents host factors (e.g.,

genetics, cognitive reserve), the seed, disease-related factors (e.g., cytokines, tumor

genetic mutations), and the pesticides, treatment-related factors (e.g., chemotherapy,

radiation, hormonal therapy) (Meyers & Perry, 2008). As soil, seed, and pesticides all

contribute to the health of a plant, so do host, disease, and treatment factors all contribute

to the cognitive health of a cancer patient.

Host factors are generally present prior to cancer treatment and include age,

genetics, cognitive reserve, and psychological factors. Older age is associated with

greater cognitive decline in prospective longitudinal studies of breast cancer patients

treated with chemotherapy (Bender et al., 2006; Collins, Mackenzie, Stewart, Bielajew,

& Verma, 2009; Debess, Riis, Engebjerg, & Ewertz, 2010; Falleti et al., 2005; Hermelink

et al., 2007; Hurria et al., 2006; Jansen, Cooper, Dodd, & Miaskowski, 2011; Jenkins et

al., 2006; Ono et al., 2015; Shilling et al., 2005; A. Stewart et al., 2008; Vearncombe et

al., 2009; Wefel et al., 2004). Genetic factors related to cognitive decline in aging and

cancer include apolipoprotein E (*APOE*) and catechol-o-methyl transferase (*COMT*)

(Ahles, Root, et al., 2012; Ahles et al., 2003; Harris & Deary, 2011; Small et al., 2011).

Genetic and environmental variables (e.g., education, occupation) contribute to cognitive

reserve, or the capacity for cognitive function (Ahles et al., 2010; Stern, 2002). People

with lower levels of cognitive reserve are at higher risk for neurodegenerative diseases

such as Alzheimer's disease (Ahles et al., 2010; Whalley, Deary, Appleton, & Starr,

2004) and are more susceptible to poorer cognitive outcomes after exposure to

neurotoxins compared to those with higher levels of cognitive reserve (Ahles et al., 2010; Bleecker, Ford, Celio, Vaughan, & Lindgren, 2007). Age, cognitive reserve, and receipt of chemotherapy were found to have an interactive effect on cognitive functioning in non-metastatic breast cancer patients; specifically, older patients who had lower levels of cognitive reserve and had been exposed to chemotherapy were impaired on processing speed compared to other groups (e.g., younger patients, patients with higher levels of cognitive reserve, patients not exposed to chemotherapy, healthy controls) (Ahles et al., 2010). Processing speed was the only examined outcome because previous research has found it to be sensitive to the effects of cancer treatment (Ahles et al., 2010; Correa & Ahles, 2008).

The host factors of anxiety, depression, fatigue, and sleep disturbance have been inconsistently associated with cognitive symptoms in cancer patients (Ahles & Saykin, 2001, 2002; Ono et al., 2015; Schagen, Muller, Boogerd, & van Dam, 2002; Valentine & Meyers, 2001; Vearncombe et al., 2009). These factors are more often related to subjective cognitive complaints than objective cognitive impairment (Jim et al., 2012; Ono et al., 2015; van Dam et al., 1998). These four constructs are frequently characterized as "psychological factors" in research on cognitive difficulties in cancer and are either statistically or methodologically controlled (Ahles, Root, et al., 2012; Hurria et al., 2007; Ono et al., 2015). Other researchers argue that they are also symptoms of cancer and its treatment (Miaskowski, Dodd, & Lee, 2004).

Disease-related factors possibly involved in cognitive change in cancer patients include genetic mutations and DNA damage, neurotoxic cytokines, and disease stage (Ahles, Root, et al., 2012; Meyers & Perry, 2008). Even prior to chemotherapy, it is

estimated that 20-30% of non-metastatic breast cancer patients have some degree of cognitive impairment compared to age- and education-adjusted norms, and this does not appear to be due to depressive symptoms, anxiety, fatigue, or surgery (Ahles, Root, et al., 2012; Ahles et al., 2008). Ahles and colleagues (2012) have presented two non-mutually exclusive hypotheses for direct effects of disease-related factors on cognitive symptoms in cancer: 1) there may be common risk factors for breast cancer and age-related cognitive decline; and 2) the biology of cancer affects cognitive performance. Both of these hypotheses have correlational support. Genetic mutations preventing repair of damaged DNA have been associated with increased risk for developing breast cancer, and deficient DNA repair has also been associated with neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (Ahles & Saykin, 2007).

Regarding the second hypothesis, one way that the biology of cancer can impact cognition is through an inflammatory response that activates neurotoxic cytokines (Ahles, Root, et al., 2012; Ahles & Saykin, 2007). Cytokine dysregulation has been associated with neurodegenerative disorders, cognitive disorders, fatigue, and depression (Ahles & Saykin, 2007). Recent findings show a significant relationship between elevated cytokine levels and poorer cognitive performance in breast cancer patients prior to treatment after controlling for other factors related to cognitive decline, such as age, education, and mood (Patel et al., 2015).

Cancer stage is another disease-related factor that may contribute to cognitive impairment. One study found that prior to chemotherapy, breast cancer patients with invasive disease were more likely than breast cancer patients with noninvasive disease to have decrements in cognitive performance compared to published norms, and these

patient groups did not differ on depressive symptoms, anxiety, or fatigue (Ahles et al., 2008). Unfortunately, disease stage is often confounded with treatment type in prospective longitudinal studies examining cognitive changes in cancer, which limits the conclusions that may be drawn (McDonald, Conroy, Ahles, West, & Saykin, 2010).

Treatment-related factors that may contribute to cognitive changes in cancer patients include chemotherapy, endocrine or hormone therapy, and radiation therapy. Evidence suggests that chemotherapy may cause changes in brain structure for at least a subgroup of cancer patients (Ahles, Root, et al., 2012; Hurria et al., 2007; Ono et al., 2015; A. Stewart et al., 2006). For example, imaging studies with breast cancer patients showed decreased grey matter in frontal, temporal, and cerebellar regions and the right thalamus at one month post-chemotherapy, whereas non-chemotherapy treated patients only showed decreased grey matter in cerebellar regions and healthy controls showed no significant structural changes (McDonald et al., 2010). These structural changes have not been associated with objective cognitive impairment, although chemotherapy-treated patients showed a non-significant decline in high-load working memory performance from baseline to one month post-chemotherapy along with compensatory hyperactivation in frontal cortices on fMRI (McDonald, Conroy, Ahles, West, & Saykin, 2012). Chemotherapy-treated patients showed only partial recovery of grey matter density at 1-year follow-up (McDonald et al., 2010). The mechanism by which chemotherapy affects cognition is still unknown (Ahles, Root, et al., 2012), although there are several theories. Animal models suggest that chemotherapy agents that cross the blood-brain barrier can reduce blood flow to the brain, cause DNA and white matter damage, inhibit the growth

of neurons in the hippocampus, and decrease activation in the hypothalamic-pituitary-adrenal (HPA) axis (Ahles, Root, et al., 2012; Seigers & Fardell, 2011).

Knowledge of the effects of hormonal and radiation therapy on cognition in cancer patients has been growing in recent years. Regarding hormonal therapy, results of several randomized trials suggest that tamoxifen is associated with cognitive impairment in breast cancer patients, whereas aromatase inhibitors (e.g., exemestane, anastrozole) are not (Zwart et al., 2015). Although radiation therapy to the brain and spinal cord has long been associated with cognitive and neurological symptoms in cancer patients (Crossen, Garwood, Glatstein, & Neuwelt, 1994; Dietrich et al., 2008; Keime-Guibert, Napolitano, & Delattre, 1998; Perry & Schmidt, 2006), emerging evidence suggests non-CNS radiation therapy is also associated with objective and subjective cognitive change in patients with several cancer types (Geinitz et al., 2001; Janaki et al., 2010; Jim et al., 2009; Kohli et al., 2007; Marchand et al., 2010; Noal et al., 2011; Phillips et al., 2012; Quesnel, Savard, & Ivers, 2009; Schagen et al., 2008; Shibayama et al., 2014). However, the evidence is inconsistent: one study found no relationship between radiation therapy and cognitive complaints (Browall et al., 2008), a few showed rapid reductions in cognitive complaints after treatment (Geinitz et al., 2001; Janaki et al., 2010; Marchand et al., 2010), and others found objective and subjective cognitive symptoms lasting months to years after treatment (Jim et al., 2009; Kohli et al., 2007; Noal et al., 2011; Phillips et al., 2012; Quesnel et al., 2009; Schagen et al., 2008; Shibayama et al., 2014). Methodological differences may explain some of the inconsistent findings (Shibayama et al., 2014). Some studies only assessed subjective cognitive complaints (Browall et al., 2008; Geinitz et al., 2001; Janaki et al., 2010; Kohli et al., 2007; Marchand et al., 2010),

whereas others also measured objective cognitive performance (Jim et al., 2009; Noal et al., 2011; Phillips et al., 2012; Quesnel et al., 2009; Schagen et al., 2008; Shibayama et al., 2014). Control groups also differed (Shibayama et al., 2014); some studies only used healthy comparison groups (Jim et al., 2009; Phillips et al., 2012; Quesnel et al., 2009), and several did not include a comparison group (Browall et al., 2008; Geinitz et al., 2001; Janaki et al., 2010; Marchand et al., 2010; Noal et al., 2011). Shibayama and colleagues (2014) explored a possible mechanism for the effect of non-CNS radiation therapy on cognition in early-stage breast cancer patients. Specifically, elevated levels of proinflammatory cytokine IL-6 were found to significantly mediate the relationship between receipt of radiation treatment and worse cognitive performance.

While some models describe potential contributors to cognitive symptoms in cancer patients, other models describe the trajectory of cognitive changes. The phase shift hypothesis assumes stable decrements in cognition in cancer patients compared to healthy individuals without a cancer history, such that cognitive dysfunction in cancer patients parallels normal aging (Figure 2) (Ahles, Root, et al., 2012; Mandelblatt et al., 2013). Conversely, the accelerated aging hypothesis suggests that the slope of cognitive decline over time is steeper for cancer patients compared to healthy individuals without a cancer history (Figure 2) (Ahles, Root, et al., 2012; Mandelblatt et al., 2013). Further longitudinal research is needed to determine which hypothesis is correct, or if both are correct, but for different patient populations. For example, it is possible that younger patients with greater cognitive reserve show a phase shift pattern, whereas older patients with less cognitive reserve show accelerated aging (Ahles, 2012).

Ahles and colleagues (2012) hypothesize that aging and cancer affect cognition in two ways: 1) the initial impact of cancer treatments has a domino effect on several biological systems that results in progressive cognitive decline with aging, or 2) a treatment might not result in enough initial biological damage to affect cognition immediately, but there may be a delayed effect with increasing age. These patterns are supported by evidence from a longitudinal study of non-metastatic breast cancer patients treated with chemotherapy (Wefel, Saleeba, Buzdar, & Meyers, 2010). The following patterns of cognitive functioning were found: 1) cognitive decline immediately post-treatment and continued decline one year post-treatment; 2) cognitive decline immediately post-treatment and stable cognitive functioning at one year; and 3) no cognitive decline immediately post-treatment and new cognitive decline at one year post-treatment (Ahles, Root, et al., 2012; Wefel et al., 2010). Clinical, mood, and demographic variables did not significantly differentiate patients with acute or late cognitive decline, but there were non-significant trends suggesting that older age and baseline cognitive impairment may be risk factors for acute and late decline (Wefel et al., 2010). The authors suggested that diminished cognitive reserve pre-treatment may contribute to late cognitive decline or prevent recovery from acute impairment.

To summarize, evidence suggests that host, disease, and treatment factors are directly and indirectly associated with cognitive impairment in cancer patients (Ahles, Root, et al., 2012; Ahles & Saykin, 2007; Ahles et al., 2003; Berman et al., 2014; Conroy et al., 2013; McDonald et al., 2010; Meyers & Perry, 2008; Ono et al., 2015; Patel et al., 2015; Zwart et al., 2015). However, a number of gaps in this literature remain, especially with respect to the impact of psychological factors and disease variables on cognition.

The model of trajectories of aging and cognitive decline in cancer is theoretically sound and has support from one longitudinal study (Ahles, Root, et al., 2012; Mandelblatt et al., 2013; Wefel et al., 2010). Taken together, models of cognition in cancer inform research and treatment by suggesting testable pathways by which various factors may impact cognition within the broader context of aging (Ahles, Root, et al., 2012; Mandelblatt et al., 2013; Meyers & Perry, 2008).

Cognitive complaints in cancer. Although substantial evidence supports cognitive change associated with cancer and its treatment (Ahles, Root, et al., 2012; Hurria et al., 2007; Ono et al., 2015; Von Ah, 2015), the relationship between objective and subjective cognitive impairment in cancer patients is less clear. Objective cognitive impairment as measured by neuropsychological tests is often found to have little to no correlation with subjective cognitive impairment or cognitive complaints (Ahles & Saykin, 2002; Hurria et al., 2007; Schagen et al., 2002; Schagen et al., 1999). One explanation for this finding is that brief neuropsychological tests commonly used in research are not sufficiently sensitive to detect the subtle cognitive deficits associated with cancer and its treatment (Hurria et al., 2007). An fMRI neuroimaging study found support for this hypothesis; during a working memory task, breast cancer patients did not show objective impairment compared to controls, yet they had hyperactivation of brain areas associated with executive function (McDonald et al., 2012). These findings suggest that the brains of breast cancer patients engage in compensatory processes (McDonald et al., 2012); thus, patients may find tasks to be more effortful while showing little to no objective impairment. Some researchers have concluded that cognitive complaints represent subtle changes in cognitive function that should be a focus of research and

clinical efforts (Pullens, De Vries, Van Warmerdam, Van De Wal, & Roukema, 2013; Von Ah & Tallman, 2015).

An alternative explanation for the small to non-existent correlation between subjective and objective cognitive impairment is that cognitive complaints are more indicative of psychological distress than cognitive dysfunction (Jansen, 2013; Jenkins et al., 2006; Kibiger, Kirsh, Wall, & Passik, 2003; Poppelreuter et al., 2004; Pullens, De Vries, & Roukema, 2010; Shilling & Jenkins, 2007; Von Ah & Tallman, 2015). Multiple studies have found a significant, moderate to strong positive relationship between depressive symptoms and cognitive complaints (Cimprich, So, Ronis, & Trask, 2005; Jenkins et al., 2006; Pullens et al., 2013; Shilling & Jenkins, 2007; Weis, Poppelreuter, & Bartsch, 2009). Some researchers have suggested that depressive symptoms are more likely to impair cognitive functioning in everyday life than during controlled neuropsychological testing; thus, cancer patients with depressive symptoms may report difficulty performing routine tasks while still performing normally on objective tests (Shilling & Jenkins, 2007; Weis et al., 2009). Others argue that although psychological factors may directly increase cognitive complaints, they may also contribute to subtle deficits in cognitive function that may not be detectable with objective tests (Jean-Pierre, Johnson-Greene, & Burish, 2014). Indeed, depression has been associated with structural and functional changes in brain regions responsible for attention and memory (Bird & Burgess, 2008; Jean-Pierre et al., 2014; Milne, MacQueen, & Hall, 2012; Sievers et al., 2012). Depression has also been associated with proinflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)-alpha (Schiepers, Wichers, & Maes,

2005), which have been related to objective and subjective cognitive symptoms in cancer patients (Ganz et al., 2013; Seruga, Zhang, Bernstein, & Tannock, 2008).

Subjective cognitive function may also be influenced by patients' expectations. One study found that breast cancer patients who were primed with a letter explaining cognitive changes associated with cancer and its treatment were more likely to report cognitive complaints during an interview about their symptoms compared to those who did not receive the letter (Schagen, Das, & van Dam, 2009). The priming effect was present for both patients who had and had not been previously treated with chemotherapy, although it was stronger for patients with no prior chemotherapy treatment (Schagen et al., 2009). This discrepant priming effect may be explained by ceiling effects for the chemotherapy-treated patients. That is, chemotherapy-naive patients may be more vulnerable to priming because they are unable to draw upon personal experience with effects of chemotherapy (Schagen et al., 2009). The same group of researchers later conducted a similar priming study that produced comparable expectancy effects with respect to cognitive complaints and objective test performance; however, the effects were stronger for chemotherapy-treated patients than chemotherapy-naïve patients (Schagen, Das, & Vermeulen, 2012). Prior knowledge of the possible effect of chemotherapy on cognition may be important for priming to take place; only about half of patients in the first study had pre-study knowledge of the relationship between chemotherapy and cognition, whereas the majority of the patients in the second study had that knowledge (Schagen et al., 2012). The researchers concluded that providing information about cognitive symptoms to patients treated with chemotherapy induces a stereotype threat which can affect both objective and subjective cognitive outcomes (Schagen et al., 2012).

Although cognitive complaints have been variously characterized as subtle cognitive deficits, psychological distress, and expectancy effects, assessment of these complaints uniquely informs our understanding of patients' experiences. Some researchers argue that perceived cognitive impairment is as important to assess as objective impairment due to its association with patients' functional status and quality of life (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Shilling & Jenkins, 2007). Greater cognitive complaints are associated with greater depressive symptoms, anxiety, and fatigue and poorer quality of life in cancer patients (Hutchinson et al., 2012; Pullens et al., 2010). Continued assessment of patients' self-reported cognitive symptoms is warranted to understand symptom experiences from the patients' perspective (Pullens et al., 2010) and inform patient-centered treatment approaches.

1.3   Cognitive Symptoms in Metastatic Breast Cancer

Although most research on cognitive symptoms has focused on early-stage breast cancer patients, a few studies have documented self-reported cognitive symptoms in metastatic breast cancer patients (Aranda et al., 2005; Bender, Ergÿn, Rosenzweig, Cohen, & Sereika, 2005; Mayer, 2010; Mayer & Grober, 2006). One study found that cognitive dysfunction was only reported by 8% of 105 metastatic breast cancer patients on the 2-item cognitive subscale of the EORTC QLQ-30 (Aranda et al., 2005). Conversely, another survey of metastatic breast cancer patients found that 60% of 618 patients reported cognitive problems on an author-constructed item (Mayer, 2010). Differences in findings across studies may reflect differential measurement of cognitive symptoms and sample characteristics: the first study consisted of patients from four urban hospitals in Australia (61% response rate) (Aranda et al., 2005), whereas the second study

was an online survey of patients from 13 countries (unknown response rate) (Mayer, 2010; Mayer & Grober, 2006). Given limitations of the research to date, the prevalence of cognitive symptoms in metastatic breast cancer patients is unclear.

Another study found that one cognitive symptom (i.e., loss of concentration) tended to cluster with fatigue, increased weakness, and mood problems in metastatic breast cancer patients; however, the analysis was limited to symptoms related to menopause (Bender et al., 2005). This symptom cluster has also been found in early-stage breast cancer patients and patients with other common cancers (Ahles & Saykin, 2002; Fan, Filipczak, & Chow, 2007; Ono et al., 2015). To my knowledge, further studies have not documented objective or subjective cognitive symptoms or symptom clusters in metastatic breast cancer patients. Standardized assessment of cognitive and other symptoms would contribute to our understanding of the symptom experience of this population.

1.4   Symptom Clusters

Research on symptom clusters in cancer and non-cancer populations is limited by a lack of consensus regarding their conceptual or methodological definition (Dong, Butow, Costa, Lovell, & Agar, 2014). A symptom cluster was originally defined by Dodd and colleagues (2001) as "three or more concurrent symptoms" that are related in some way (Dodd, Miaskowski, & Paul, 2001). A more recent definition is that two or more symptoms form a cluster if they predictably occur together in a stable group and are more strongly associated with each other than with symptoms in separate clusters (Aktas, Walsh, & Rybicki, 2010; Dong et al., 2014; Fan et al., 2007; Kim, McGuire, Tulman, & Barsevick, 2005). However, a recent systematic review of the symptom cluster literature

on patients with advanced cancer found clusters to be generally unstable both longitudinally and methodologically (Dong et al., 2014). It is also challenging to replicate clusters across studies due to a lack of consensus regarding appropriate assessment tools, symptom domains, and statistical methodologies (Aktas et al., 2010; Dong et al., 2014). For example, a systematic review found that several studies of advanced cancer patients used author-developed symptom checklists with unknown psychometric properties, and other studies with this population did not comprehensively assess common symptoms (Dong et al., 2014). Additionally, studies using different approaches to statistically derive symptom clusters within the same data set found poor stability of clusters between statistical methods (Dong et al., 2014). However, clusters derived with principal component analysis (PCA) and hierarchical cluster analysis (HCA) were more strongly correlated than clusters derived with exploratory factor analysis (EFA) (Chen et al., 2013; Chen et al., 2012; Dong et al., 2014; Khan et al., 2013).

Despite methodological and conceptual challenges, symptom clusters are especially important to examine in cancer patients for several reasons. First, when multiple symptoms occur together in cancer patients, they often have a compounding effect which may impair functional status and decrease quality of life (Cleeland, 2007; Cleeland et al., 2003; Dodd, Cho, Cooper, & Miaskowski, 2010; Dodd et al., 2001; Kurzrock, 2001; Valentine & Meyers, 2001). Second, on average, cancer patients concurrently experience 11-13 symptoms (Chang, Hwang, Feuerman, & Kasimis, 2000; Fan et al., 2007; Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar, Coyle, et al., 1994); thus, assessing and treating one symptom at a time is unlikely to have a large impact on patients' distress or quality of life (Miaskowski et al., 2004).

Furthermore, identifying symptom clusters informs research and treatment by pointing to common mechanisms—both biological and psychological—that may underlie various symptoms (Kim, Barsevick, Fang, & Miaskowski, 2012; Miaskowski et al., 2004). For example, in cancer patients with various disease sites, pain has been shown to cluster with cognitive problems (Fan et al., 2007). Although this relationship may be explained by analgesic medication use, an alternative explanation is that pain demands attention, resulting in cognitive deficits when limited attentional resources are focused on pain (Eccleston & Crombez, 1999; Grisart & Van der Linden, 2001; Moriarty, McGuire, & Finn, 2011).

Recently, researchers have suggested that cognitive symptoms, pain, fatigue, sleep problems, anxiety, and depressive symptoms form a psychoneurological symptom cluster with several interacting psychological and biological mechanisms (Kim et al., 2012; Starkweather et al., 2013; Wood & Weymann, 2013). Inflammation is an example of a possible biological mechanism underlying the psychoneurological symptom cluster (Dong et al., 2014). Elevated proinflammatory cytokines have been associated with greater overall symptom severity in lung cancer patients (Wang et al., 2010) and fatigue and cognitive dysfunction in breast cancer patients prior to chemotherapy (Patel et al., 2015). Whether inflammation is a cause or an outcome of symptom burden is currently unclear, but it appears to be one of many interactive factors influencing symptom outcomes (Dong et al., 2014; Kim et al., 2012). Another common biological mechanism that may interact with factors such as inflammation is HPA axis dysregulation (Kim et al., 2012). Animal models suggest that some chemotherapy treatments lead to HPA axis dysregulation (Seigers & Fardell, 2011), and stress associated with having cancer may

also be associated with this outcome (Kim et al., 2012). Even after completing treatment, breast cancer survivors with chronic fatigue have shown dysregulation of HPA axis responsiveness with significantly blunted cortisol response to laboratory stressors (Bower, Ganz, & Aziz, 2005). HPA axis dysregulation has also been found to be significantly associated with more sleep disturbance, pain, and depressive symptoms among metastatic breast cancer patients (Koopman et al., 2002). Exploring symptoms clusters in metastatic breast cancer patients may inform future research regarding common mechanisms of these symptoms such as stress, inflammation, and HPA axis dysregulation.

<div align="center">1.5   Patient Perceptions of Symptom Importance</div>

Research on symptoms in cancer patients has largely focused on symptom severity, frequency, and distress. Assessing patients' perceptions of symptom importance—how important it is for them to see improvement in a symptom after it is treated—would also inform patient-centered treatment approaches. The goals of patient-centered treatment are to enhance communication and collaboration between patients and clinicians and respect patients' autonomy (Epstein, Fiscella, Lesser, & Stange, 2010). Some evidence suggests that patient-centered treatment improves quality of care, health outcomes, and patient satisfaction while reducing financial costs of health care (Epstein et al., 2010; Epstein et al., 2005; Fiscella et al., 2004; Little et al., 2001; Mallinger, Griggs, & Shields, 2005; Mead & Bower, 2002; Rao, Anderson, Inui, & Frankel, 2007; Safran et al., 2006; M. Stewart et al., 2000). However, a patient-centered approach has not been adopted in symptom research with cancer patients; studies have not examined patients' perceptions of the importance of reducing specific symptoms.

Perceptions of symptom importance have been examined in research on patients with chronic pain conditions. This research found subgroups of patients who had differential perceptions of the importance of improving specific symptoms; some patients focused on pain as the most important symptom, whereas others equally valued improvement in various symptoms (M. E. Robinson et al., 2005; Yi, Kim, Ha, & Lim, 2014; Zeppieri et al., 2012). Evidence suggests that patients with chronic pain who rate all symptoms as highly important have increased depressive and anxiety symptoms (Yi et al., 2014; Zeppieri et al., 2012). One study of patients with Parkinson's disease found that they either rated all or none of their symptoms as highly important (Nisenzon et al., 2011). Although disease and treatment factors were unrelated to symptom importance ratings, low importance ratings were associated with more formal education (Nisenzon et al., 2011).

Treating symptoms such as pain, fatigue, and sleep disturbance may be a greater priority for advanced cancer patients than maintaining their cognitive functioning. For example, treating pain with narcotics often results in temporary cognitive impairment (Bruera, Macmillan, Hanson, & MacDonald, 1989), and some advanced cancer patients may consider pain treatment to be a higher priority than maintaining optimal cognitive function. Yet other patients, especially those with cognitively demanding jobs, may find cognitive deficits to be more distressing than other symptoms. Many metastatic breast cancer patients are living for years with this disease and have high levels of functioning (Mayer, 2010; Reed et al., 2012). Despite this population's increased longevity and functional capacity, their cognitive symptoms have received scarce research attention. Understanding cognitive symptoms in the context of metastatic breast cancer patients'

symptom treatment priorities informs patient-centered care for this highly burdened and prevalent, yet understudied population.

1.6   The Present Study

To address gaps in our understanding of metastatic breast cancer patients' cognitive symptoms, the present study has two specific aims:

Aim 1: Examine the extent to which cognitive complaints cluster with other common symptoms (i.e., fatigue, sleep disturbance, depressive symptoms, anxiety, pain, hot flashes, lymphedema, neuropathy, and nausea) in metastatic breast cancer patients.

Hypothesis 1: Cognitive complaints will cluster with fatigue, sleep disturbance, depressive symptoms, anxiety, and pain in metastatic breast cancer patients.

This hypothesis is illustrated in Figure 3 and is based on limited evidence from two studies suggesting that fatigue, sleep disturbance, and mood disturbance are associated with cognitive complaints in metastatic breast cancer patients (Aranda et al., 2005; Bender et al., 2005). One of these studies did not perform a cluster analysis on reported symptoms (Aranda et al., 2005). In the study that included a cluster analysis of symptoms, only single-item measures of menopausal symptoms were analyzed (Bender et al., 2005). In the current study, multi-item symptom assessments developed by the NIH and validated in cancer populations were used in order to provide a more reliable estimate of cognitive and other symptoms in metastatic breast cancer patients.

This hypothesis is also based on research suggesting that pain tends to cluster with cognitive problems in other cancer populations (Fan et al., 2007). It is estimated that 70-90% of patients with advanced cancer have chronic pain (Irvin, Muss, & Mayer, 2011; Portenoy & Lesage, 1999). Although the prevalence of chronic pain in metastatic

breast cancer patients is unknown, it is estimated that 44-64% of breast cancer patients at any stage (excluding survivors with no evidence of disease) have chronic pain (Van den Beuken-van Everdingen et al., 2007). Thus, it is important to examine whether pain tends to cluster with cognitive complaints in metastatic breast cancer patients.

Finally, this hypothesis is based on theory and empirical research suggesting that a psychoneurological symptom cluster may have common biological and psychological mechanisms (Kim et al., 2012; Miaskowski et al., 2004). Elevated proinflammatory cytokines may be one biological mechanism underlying symptom clusters, as they have been associated with greater overall symptom severity in lung cancer patients (Dong et al., 2014; Wang et al., 2010) and fatigue and cognitive dysfunction in breast cancer patients prior to chemotherapy (Patel et al., 2015). HPA axis dysregulation is another possible common mechanism underlying symptoms such as cognitive symptoms, sleep problems, fatigue, pain, anxiety, and depressive symptoms (Bower et al., 2005; Kim et al., 2012; Koopman et al., 2002; Seigers & Fardell, 2011).

Exploratory Aim: To compare metastatic breast cancer patient ratings of symptom importance for cognitive symptoms to those of other symptoms (i.e., pain, fatigue, sleep disturbance, depression, anxiety, nausea, lymphedema, hot flashes, and neuropathy).

This aim is exploratory due to the absence of prior research and theorizing on cancer patient ratings of symptom importance.

CHAPTER 2. METHOD

This study examines a portion of the data from a Walther-funded study on metastatic breast cancer patients' perceptions of symptom importance and interference. The Indiana University Institutional Review Board and IU Simon Cancer Center Scientific Review Committee approved all study procedures. This study complies with the Health Insurance Portability and Accountability Act (HIPAA).

2.1   Participants

Eighty metastatic breast cancer patients were recruited from the IU Simon Cancer Center to participate in a telephone survey. Eligible participants met the following inclusion criteria: female, diagnosis of stage IV breast cancer, at least 18 years old, able to speak and read English, and no evidence of cognitive impairment that may limit their capacity to give informed consent or participate in the study. This degree of cognitive impairment was based on investigator judgment or exceeding a clinical cutpoint (i.e., 3 or more errors) on a validated cognitive screening measure (Callahan, Unverzagt, Hui, Perkins, & Hendrie, 2002).

2.2   Procedure

IU Simon Cancer Center medical records were screened to identify patients with stage IV breast cancer, and their treating oncologists were contacted to verify eligibility

for the current study. Eligible patients were then mailed an introductory letter signed by

the PI and the patient's oncologist along with consent and HIPAA authorization forms.

The letter included an option to call or email the research assistant to decline further

contact. Within approximately 1 to 2 weeks after the mailing, the research assistant

called patients who had not opted-out to describe the study, answer any questions,

administer a brief cognitive screening assessment (Callahan et al., 2002), and obtain

verbal informed consent. Patients who declined study participation were asked to

provide their reason for study refusal as well as age and race to assess for possible

selection biases. If the patient verbally consented to participate, a 45-minute telephone

assessment was scheduled. The assessment was administered by a trained research

assistant and included questions regarding demographic information, medical history, and

symptom severity and importance. A subsample of 25 participants with one or more

symptoms of at least moderate severity (i.e., sleep problems, pain, anxiety, sadness, or

fatigue) were invited to participate in a separate qualitative phone interview, but the

qualitative data were not analyzed in the present study. Participants received a $40

Target gift card for the first assessment, and those who participated in the qualitative

interview received an additional $50 Target gift card, for a possible total of $90 in gift

cards.

<div align="center">2.3   Measures</div>

The following sections describe measures analyzed in the current study and time

points for data collection.

Brief screening measure for probable dementia. The cognitive screener was a

6-item assessment of global cognitive functioning. The 6 items were taken from the

Mini-Mental State Examination, a commonly used and validated measure (Cockrell & Folstein, 2002). Three items assess orientation to time, which increase the measure's specificity for assessing probable dementia (Callahan et al., 2002). The other 3 items assess short-term word recall, which increase the measure's sensitivity because deficits in short-term word recall are highly indicative of cognitive impairment (Callahan et al., 2002). Patients were ineligible if they missed 3 or more items on this measure, as this suggested that they lacked the capacity to provide consent and accurate responses to study questions. A cutoff score of 3 or more errors has been shown to have 88.7% sensitivity and 88.0% specificity for a diagnosis of dementia (Callahan et al., 2002). Although including this screener limited the range of cognitive abilities of study participants, mild to moderate cognitive symptoms that were not confounded with a diagnosis of dementia were the focus of this study.

Demographics. Participants were asked to report their marital status, race, ethnicity, education, income, and employment status. Age was assessed via medical record review.

Medical information. The following information was collected from the medical record after informed consent: diagnosis date and cancer treatment history (i.e. surgeries, chemotherapy, radiation, hormone therapy, targeted therapy, bisphosphonates, and other treatment).

Medical comorbidities. A self-report measure of 9 medical conditions was used to assess the presence of comorbid conditions that were diagnosed or treated within the last 3 years (Kroenke et al., 2009). This measure has been used in NIH-funded research

with cancer patients (Kroenke et al., 2009). Reliability and validity of this measure have not been established, as this is a checklist rather than a scale (Kroenke et al., 2009).

Cognitive complaints. General cognitive concerns were assessed with a 4-item Patient Reported Outcomes Information System (PROMIS) measure (Cella et al., 2010). Patients were asked to rate the frequency of their cognitive complaints (e.g., "My thinking has been slow…") over the past 7 days on a scale from 1 (*never*) to 5 (*very often*).

The development of PROMIS measures was funded by the NIH to create a standardized way to reliably assess patient-reported health outcomes (Cella et al., 2010; Cella et al., 2007). Standardized T scores with a mean of 50 and a standard deviation of 10 can be used to compare scores to population norms. Cancer patients were involved in focus groups to develop items for PROMIS measures (Garcia et al., 2007), and several publications have demonstrated the PROMIS measures' reliability and validity in cancer populations with early to late-stage disease (Baum, Basen-Engquist, Swartz, Parker, & Carmack, 2014; Stachler, Schultz, Nerenz, & Yaremchuk, 2014; Wagner et al., 2015; Yost, Eton, Garcia, & Cella, 2011). Initial development of PROMIS short-forms showed excellent internal consistency reliability of each of the symptom measures and strong correlations between short forms and item banks ($r > .96$) (Cella et al., 2010). PROMIS items also have good convergent validity, as evidenced by moderate to strong correlations between these items and similar legacy measures (r ranges from .69 to .96) (Cella et al., 2010).

Other physical and psychological symptoms. Nine additional physical and psychological symptoms were selected for assessment in the current study due to their

high prevalence in metastatic breast cancer patients (Aranda et al., 2005; Bender et al., 2005; Carpenter et al., 1998; Given et al., 2008; Grabsch et al., 2006; Holmes et al., 1991; Ozaslan & Kuru, 2004; Palesh et al., 2007). PROMIS measures (Cella et al., 2010) were used to assess some of these symptoms. Specifically, 4-item PROMIS measures were used to assess four of these symptoms during the past week, including depressive symptoms and anxiety on a scale from 1 (*never*) to 5 (*always*), fatigue on a scale from 1 (*not at all*) to 5 (*very much*), and sleep disturbance with the first item (i.e., "My sleep quality was…") rated on a scale from 1 (*very poor*) to 5 (*very good*) and subsequent items rated on a scale from 1 (*not at all*) to 5 (*very much*). A 3-item PROMIS measure was used to assess pain intensity over the past week on a scale from 1 (*no pain*) to 5 (*very severe*).

No PROMIS measures have been developed to assess nausea, hot flashes, lymphedema, or neuropathy. Thus, these symptoms were assessed with other validated measures. Items from the Memorial Symptom Assessment Scale (MSAS) (Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar, Kiyasu, et al., 1994) were used to measure nausea, peripheral neuropathy, and lymphedema. Patients were asked to indicate whether they had experienced the symptom in the past week, and those who answered yes were asked to rate the frequency of the symptom over the past week on a scale from 1 (*rarely*) to 4 (*almost constantly*). In addition, patients reported usual symptom severity over the past week on a scale from 1 (*slight*) to 4 (*very severe*) and the extent to which the symptom was distressing on a scale from 0 (*not at all*) to 4 (*very much*). Lymphedema symptom assessment does not include a question about frequency because it is not relevant for this symptom (Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar,

Kiyasu, et al., 1994). In research with cancer patients, the MSAS had moderate to high

internal consistency for physical symptom assessment (Cronbach's α ranges from 0.58 to

0.88) and showed evidence of convergent and discriminant validity (Portenoy, Thaler,

Kornblith, Lepore, Friedlander-Klar, Kiyasu, et al., 1994). For example, it was highly

correlated with other measures of clinical status and quality of life (e.g., *r* ranges from -

0.52 to -0.75 for MSAS physical symptoms and the Functional Living Index-Cancer)

(Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar, Kiyasu, et al., 1994).

The MSAS does not include an assessment of hot flashes; thus, this symptom was

assessed with a brief measure developed to assess hot flashes in breast cancer patients

treated with hormone therapy (Carpenter et al., 1998). Similar to the MSAS, patients

were first asked to indicate whether they had experienced hot flashes, and those who

answered yes were asked to rate their severity on a scale from 0 (*not at all*) to 4

(*extremely*) and the extent to which they were bothersome on a scale from 0 (*not at all*

bothered) to 10 (*extremely bothered*). Unlike the MSAS, patients were asked if they have

experienced hot flashes over the past two weeks rather than one week. This time period

is similar to that of prior research (Brambilla, Mckinlay, & Johannes, 1994; Carpenter et

al., 1998; Hemminki, Topo, & Kangas, 1995). Hot flashes tend to be periodic

(Kronenberg, 1990); thus, limiting the assessment time period to one week may

significantly decrease the sensitivity of the measure.

Perceptions of symptom importance. Patient perceptions of symptom

importance were assessed with the Patient Centered Outcomes Questionnaire (PCOQ)

(Robinson et al., 2005), which was modified to include the symptoms described above.

The modified PCOQ consists of four sections, whereas the original PCOQ had five

sections. We omitted the section on desired level of symptom severity because ideal outcomes were likely to be "none" for the majority of patients. This section was omitted in another study using a modified version of the PCOQ with a different medical population (Nisenzon et al., 2011). In the first section of the modified PCOQ in the current study, patients were asked to report their usual level of symptom severity over the past week on a scale of 0 (*none*) to 10 (*worst imaginable*) for each of the 10 symptoms (i.e. pain, fatigue, anxiety, sadness, numbness/tingling in hands/feet, swelling of arms or legs, nausea, hot flashes, sleep problems, attention/thinking/memory problems). In the second section, patients were asked to report for each symptom the level of symptom severity that they would consider a treatment success on a scale of 0 (*none*) to 10 (*worst imaginable*). In the third section, patients were asked to report for each symptom their expected symptom severity following treatment of the symptom on a scale of 0 (*none*) to 10 (*worst imaginable*). In the fourth and final section, patients were asked to rate the importance of experiencing improvement in each of their symptoms on a scale of 0 (*not at all important*) to 10 (*most important*). Because an aim of this study was to compare metastatic breast cancer patient ratings of symptom importance for cognitive symptoms to those of other symptoms, analysis of this measure focused exclusively on the fourth section.

The PCOQ was originally developed for patients with chronic pain, and the original version showed adequate test-retest reliability over a 48 hour period (values ranging from 0.84 to 0.90) and good convergent validity with other standardized measures of pain, emotional distress, and disability (*r* values ranging from 0.52 to 0.75) (Brown et al., 2008).

2.4   Data Analysis

Data were analyzed with SPSS (IBM SPSS Statistics for Windows, Version 23.0; Armonk, NY, USA) and R (R Foundation for Statistical Computing, Version 3.2.3; Vienna, Austria) statistical software. Minimal missing data were expected; thus, listwise deletion would have been employed (i.e., all cases with missing data would be excluded from analyses). However, none of the data were missing. To examine symptoms on the same metric, scores for all measures of symptom severity (i.e., PROMIS measures, MSAS subscales, and the hot flashes assessment) were converted to z scores. Data were then examined for possible outliers, and Winsorization transformation was employed in order to reduce the influence of any extreme values by modifying scores to equate to z-scores with an absolute value of 3.0 (i.e., to 3 standard deviations of the mean) (Tukey, 1962). The assumption of normality was examined by computing skewness and kurtosis indices, which should be less than the absolute values of 3.0 and 8.0, respectively (Kline, 2011). If the assumption of normality was violated, the appropriate variable transformation (i.e., log or square root) would have been employed based on the characteristics of the violation, and sensitivity analyses would have been performed to determine differential effects of data transformations. Frequencies, means, and standard deviations were computed to characterize patient demographics, medical information, and symptom levels (i.e. cognitive complaints, hot flashes, nausea, lymphedema, neuropathy, depression, anxiety, sleep disturbance, fatigue, and pain) as well as ratings of symptom importance for each of the 10 symptoms. Chronbach's alphas were computed for multi-item assessments.

To test the hypothesis that cognitive complaints would cluster with fatigue, sleep disturbance, depressive symptoms, and anxiety, an agglomerative hierarchical cluster analysis was performed on the z scores for the 10 symptoms. This provided subgroups of co-occurring symptoms, allowing me to determine which symptoms tended to cluster with cognitive complaints. Squared Euclidian distances were used in the proximities matrix, and weighted average linkage was used as the clustering method (Everitt, Landau, & Leese, 2001; McQuitty, 1966). This cluster analysis method is frequently used in symptom cluster research with cancer patients (Bender et al., 2005; Dodd et al., 2010; Glaus et al., 2006; Miaskowski et al., 2006; Ridner, 2005). There is no reason to expect similar subgroup sizes; thus, this clustering method is preferable to Ward's method— another commonly used cluster analysis method—which forms spherical clusters, forcing the clusters to have similar sizes (Everitt et al., 2001). Because cluster analysis is an exploratory method of examining multivariate relationships, no formal power analysis based on sample size is feasible (Everitt et al., 2001; Kozachik, 2006).

To test the exploratory aim, a within-factors ANOVA was performed to compare patient ratings of the importance of symptom improvement for cognitive symptoms to those of nine other symptoms (i.e., pain, fatigue, sleep disturbance, depression, anxiety, nausea, lymphedema, hot flashes, and neuropathy). Planned simple contrasts were then performed to compare importance ratings between all symptom pairs while preventing alpha inflation. We estimated the statistical power to detect a difference between importance ratings with the G*Power statistical power analysis program (Faul, Erdfelder, Lang, & Buchner, 2007). A sensitivity power analysis for a within-factors ANOVA was performed. With a sample size of 80 and an alpha of 0.05, we had 80% power to detect a

small effect size ($f = 0.10$). Prior research using the PCOQ has not compared the importance ratings for different symptoms; thus, we do not have an empirical basis for estimating the effect size.

CHAPTER 3. RESULTS

3.1   Preliminary Analyses

Descriptive statistics. Participant characteristics are shown in Table 2. On average, participants were 55.5 years of age ($SD = 11.26$), had 15.03 years of education ($SD = 2.42$), and were 3.93 years from their stage IV breast cancer diagnosis ($SD = 3.64$). The majority of participants were Caucasian (91.3%), married or partnered (66.3%), and earning an annual household income of $51,000 or higher (55.1%). Regarding cancer treatment history, the majority of participants had received chemotherapy (86.3%), hormonal therapy (85.0%), radiation (65.0%), and a mastectomy (66.3%). The most prevalent medical comorbidities reported by participants were hypertension (32.5%) and arthritis (25.0%). There was an 87% acceptance rate for study participation (83 patients consented to participate out of 95 contacted by phone), and a 96% completion rate for those who consented to participate (see Figure 4).

Following Winsorization transformation of four outliers in the main study variables to 3 standard deviations of the mean, their means, standard deviations, and ranges were examined (see Table 4). All values were within the ranges expected for the measures. Cronbach's alphas for symptom assessments also were examined (see Table 4). Internal consistency reliability was good for PROMIS-measured symptoms (αs = 0.83 to 0.95) and MSAS-measured symptoms (αs = 0.89 to 0.95), and adequate for the

hot flashes assessment ($\alpha = 0.75$). The limited information regarding metastatic breast cancer patients' symptom experiences precludes comparisons of the current mean symptom levels of nausea, neuropathy, swelling, and hot flashes to prior literature. Total scores for symptoms measured with PROMIS instruments (i.e., pain, fatigue, sleep problems, cognitive problems, anxiety, and depressive symptoms) were uploaded to the scoring service on the PROMIS assessment center website (www.assessmentcenter.net), and T-scores were derived for each symptom. The scoring service returned spreadsheets for each symptom with each participant's calibrated T-scores. These T-scores were calibrated to the cancer sample when available (i.e., anxiety, cognitive concerns, depressive symptoms, and fatigue). For measures of pain and sleep disturbance, data from a cancer sample were unavailable; thus, T-scores were calibrated to the wave 1 general population sample.

The cancer calibration sample consisted of 1,754 participants that completed PROMIS measures on a web-based polling platform and self-reported a cancer diagnosis (Cella et al., 2010). The cancer stage of participants in the cancer population sample has not been reported. The wave 1 general population sample consisted of 21,133 participants (including clinical samples such as those who reported cancer) who were 52% female with a mean age of 50 years, and this sample has been shown to be representative of the general U.S. population (Cella et al., 2010; Liu et al., 2010). The means and standard deviations for the current sample's calibrated T-scores for PROMIS symptom measures are reported in Table 5. Mean calibrated T-scores for all PROMIS symptom measures were within one standard deviation of 50 (i.e., the average for the respective calibration sample). Additionally, unpublished results from a study of 634

metastatic breast cancer patients showed average T-scores for PROMIS measures of pain, fatigue, sleep disturbance, anxiety, depressive symptoms, and cognitive function within 1 standard deviation of those reported in the current sample (R. Jensen, personal communication, April 8, 2016). Regarding symptom importance ratings, there are no prior reports in cancer patients to serve as a comparison.

Tests of assumptions of cluster analysis and ANOVA. None of the data were missing. Data were screened for outliers (i.e., z-scores +/- 3), and Winsorization transformation was employed on four outliers to reduce the influence of these extreme values while still representing the sample distribution (Tukey, 1962) (see Table 3). After Winsorization, the normality of symptom ratings and symptom importance ratings was examined with skewness and kurtosis indices (see Table 4). Skewness and kurtosis indices were all less than the absolute values of 3.0 and 8.0 respectively; therefore, the data were normally distributed (Kline, 2011). The assumption of sphericity for a repeated-measures ANOVA on ratings of the importance of the ten symptoms was examined with Mauchly's test of sphericity. Mauchly's test was significant ($W = 0.06$, $\chi^2(44, N = 80) = 213.75$, $p < 0.05$); therefore, the assumption of sphericity for a repeated-measures ANOVA was violated. In other words, the variances of the differences between symptom importance ratings were not equal. This violation is common when there are more than three repeated measures, and patients rated the importance of ten symptoms. When the assumption of sphericity is violated, the F-ratio should be interpreted with caution, and the appropriate correction to the degrees of freedom should be employed (Warner, 2013). The Greenhouse-Geisser correction to degrees of freedom was appropriate because $\varepsilon < 0.75$ (Girden, 1992).

3.2   Analyses for Aim 1

To examine symptoms that co-occurred with cognitive complaints in metastatic breast cancer patients, a hierarchical agglomerative cluster analysis was performed with squared Euclidean distance and weighted average linkage. Results of this cluster analysis are shown in Figures 5 and 6. The number of clusters may be determined by examining the dendrogram (see Figure 5) and determining the "best cut" at the height of the dendrogram below which the changes in fusion levels are smaller relative to the changes above the cut (Everitt et al., 2001). The best cut for the current cluster analysis is approximately at a height of 115 on the dendrogram (see Figure 6). Findings partially supported my hypothesis that cognitive symptoms would cluster with fatigue, sleep problems, anxiety, depressive symptoms, and pain. Specifically, cognitive symptoms clustered with all of these symptoms except for pain. Another cluster consisted of pain, neuropathy, and nausea. Hot flashes and swelling failed to cluster with other symptoms.

There were three outlying symptom scores that were Winsorized prior to the cluster analysis. A sensitivity analysis was performed such that another hierarchical agglomerative cluster analysis with squared Euclidean distance and weighted average linkage was conducted with the non-Winsorized values. Results of this cluster analysis are shown in Figures 7 and 8. Without reducing the influence of extreme values for swelling, anxiety, and depressive symptoms, the cluster of symptoms co-occurring with cognitive complaints did not change. However, swelling clustered with pain, neuropathy, and nausea. Hot flashes again failed to cluster with other symptoms.

3.3   Analyses for Aim 2

To assess differences between importance ratings for the ten examined symptoms, a repeated-measures ANOVA was performed. Because the assumption of sphericity was violated, the Greenhouse-Geisser correction to the degrees of freedom was employed. Results of the repeated-measures ANOVA are shown in Table 6. Symptom importance ratings were significantly different among the ten symptoms, $F(5.8, 457.97) = 13.77$, $p < 0.001$; the corresponding effect size for this difference was an η^2 of 0.15. It is noteworthy that after the Greenhouse-Geisser correction was applied to the degrees of freedom for F, the obtained F remained statistically significant.

Planned simple contrasts were conducted to compare mean symptom importance for cognitive symptoms (i.e., thinking problems) to each of the nine other symptoms (see Table 7 and Figure 9). The importance of cognitive symptoms was significantly greater than anxiety ($MD = 1.11$, $p < 0.05$), depressive symptoms (i.e., sadness) ($MD = 1.33$, $p < 0.05$), neuropathy ($MD = 1.98$, $p < 0.05$), swelling ($MD = 2.76$, $p < 0.05$), nausea ($MD = 1.44$, $p < 0.05$), and hot flashes ($MD = 2.28$, $p < 0.05$). There were no significant differences in importance for cognitive symptoms, pain, fatigue, and sleep problems.

There was one outlying symptom importance value that was Winsorized prior to the repeated-measures ANOVA and planned contrasts. A sensitivity analysis was performed with the non-Winsorized value, and the results did not change.

CHAPTER 4. DISCUSSION

Broadly, the purpose of this study was to characterize metastatic breast cancer patients' symptom experiences and treatment priorities with respect to cognitive and other symptoms. Because recent advances in treatment have resulted in increased longevity for metastatic breast cancer patients, these patients may live for years with cognitive problems affecting their quality of life and functional capacity. However, little research has examined cognitive symptoms in metastatic breast cancer patients and their co-occurrence with other common symptoms. Additionally, symptom importance, or the degree to which symptoms are viewed as treatment priorities, has not been examined in any cancer population. Understanding metastatic breast cancer patients' symptom experiences and treatment priorities is a crucial step in developing patient-centered approaches to symptom management. Such approaches may improve the quality and cost of care as well as patients' adherence to treatment recommendations.

4.1   Symptom Cluster Findings

The first aim of the study was to examine the extent to which cognitive complaints cluster with other common symptoms (i.e., fatigue, sleep disturbance, depressive symptoms, anxiety, pain, hot flashes, lymphedema, neuropathy, and nausea) in metastatic breast cancer patients. I hypothesized that cognitive complaints would cluster with fatigue, sleep disturbance, depressive symptoms, anxiety, and pain. This hypothesis

was informed by limited evidence from prior studies of metastatic breast cancer patients'

symptom experiences (Aranda et al., 2005; Bender et al., 2005), the finding that pain

tends to cluster with cognitive complaints in people with other cancer types (Fan et al.,

2007), and theoretical and empirical support for common psychological and biological

mechanisms underlying a psychoneurological symptom cluster (Bower et al., 2005; Dong

et al., 2014; Kim et al., 2012; Koopman et al., 2002; Miaskowski et al., 2004; Patel et al.,

2015; Seigers & Fardell, 2011; Wang et al., 2010). Findings from the current study

partially supported my hypothesis. Cognitive complaints were found to cluster with

fatigue, sleep disturbance, depressive symptoms, and anxiety. A separate symptom

cluster consisted of pain, neuropathy, and nausea. Hot flashes and swelling failed to

cluster.

The symptom clusters found in the current study are partially consistent with

findings from the symptom cluster literature with various cancer populations (Bender et

al., 2005; Bruera, 2013; Chen et al., 2013; Fan et al., 2007; Jiménez et al., 2011). To my

knowledge, only one prior study has examined cognitive symptoms and symptom clusters

in metastatic breast cancer patients, and findings indicated that loss of concentration

clustered with anxiety, depressive symptoms, fatigue, and decreased physical strength

(Bender et al., 2005). Sleep disturbance was also assessed in this prior study, but failed

to cluster. When examining the symptom cluster literature on advanced cancer patients,

anxiety and depressive symptoms appear to be the most consistently obtained symptom

cluster (Bender et al., 2005; Bruera, 2013; Cheung, Le, & Zimmermann, 2009; Edward

Chow, Fan, Hadi, & Filipczak, 2007; E Chow et al., 2008; Dong et al., 2014; Fan et al.,

2007; Hird et al., 2010; Jiménez et al., 2011; Kirkova, Aktas, Walsh, Rybicki, & Davis,

2010; Walsh & Rybicki, 2006; Yennurajalingam et al., 2013). Occasionally, anxiety and depressive symptoms have also been found to cluster with other symptoms such as sleep problems (Jiménez et al., 2011; Walsh & Rybicki, 2006) and fatigue (Chen et al., 2013) in advanced cancer patients. Regarding cognitive symptoms, memory difficulties have been found to cluster with pain, fatigue, sleep problems, sadness, and neuropathy in several studies examining the validity of the M.D. Anderson Symptom Inventory among medically and ethnically diverse cancer patients (Cleeland et al., 2000; Fan et al., 2007; Okuyama et al., 2003; Wang et al., 2006; Wang et al., 2004). In addition, a study of non-metastatic breast cancer patients receiving chemotherapy or radiation found a psychoneurological symptom cluster consisting of cognitive symptoms, depressed mood, fatigue, insomnia, and pain (Kim, Barsevick, Tulman, & McDermott, 2008).

Recently, biological and psychological mechanisms underlying the psychoneurological symptom cluster in non-metastatic breast cancer patients have been explored. These mechanisms include oxidative stress, telomere shortening, DNA damage, proinflammatory cytokines, HPA axis dysfunction, and perceived stress (Kim et al., 2012; Starkweather et al., 2013; Wood & Weymann, 2013). Oxidative stress and telomere shortening—two factors involved in DNA damage—have been shown to be associated with cancer and chemotherapy treatment (Calado & Young, 2012), memory impairments and decreased grey matter density in breast cancer survivors (Conroy et al., 2013), muscle weakness and fatigue in patients with various cancer types (Gilliam & St. Clair, 2011), and major depressive disorder in non-cancer populations (Wolkowitz et al., 2011). Elevated proinflammatory cytokines have been associated with fatigue and cognitive symptoms in breast cancer patients (Patel et al., 2015), greater symptom burden

in lung cancer patients (Wang et al., 2010), and depressive symptoms in patients with various cancer types (Dunn et al., 2013). HPA axis dysregulation has also been found to be significantly associated with chronic fatigue in breast cancer survivors (Bower et al., 2005), and more sleep disturbance, pain, and depressive symptoms in metastatic breast cancer patients (Koopman et al., 2002) . Chronic perceived stress associated with the diagnosis and management of cancer has been correlated with increased proinflammatory cytokines, HPA axis dysregulation, fatigue, sleep disturbance, and pain in patients with metastatic breast cancer and other cancer types (Bower et al., 2009; Koopman et al., 2002).

In the present study, the cluster of symptoms including cognitive complaints (i.e., cognitive complaints, fatigue, sleep problems, anxiety, and depressive symptoms) seems to be consistent with a psychoneurological symptom cluster. Pain may not have clustered with the other psychoneurological symptoms due to differences in measurement, as pain was assessed with a 3-item PROMIS measure and the other symptoms in the psychoneurological symptom cluster were assessed with 4-item PROMIS measures. Instead, pain clustered with symptoms that were assessed with 3-item MSAS measures. However, differences in variance between pain and the symptoms assessed with the 4-item PROMIS measures were small (i.e., 3-13 for pain, 4-20 for fatigue, sleep problems, and cognitive problems, and 4-16 for anxiety and depressive symptoms) and MSAS assessments had smaller ranges (i.e., 0-3 for nausea and 0-3.67 for neuropathy). Also, z scores were computed for each of the symptom scores prior to the cluster analysis in order to place the symptom scores on the same metric.

Alternatively, pain may have clustered with neuropathy instead of the other psychoneurological symptoms because participants may have been experiencing neuropathic pain. In non-metastatic breast cancer patients treated with certain chemotherapies (i.e., taxanes), the numbness and tingling sensations of neuropathy predict later development of neuropathic pain (Reyes-Gibby, Morrow, Buzdar, & Shete, 2009). The progression of neuropathy to neuropathic pain increases with multiple lines of chemotherapy (Swain & Arezzo, 2008), and some metastatic breast cancer patients in our sample may have received multiple lines of chemotherapy. In addition, nausea may have clustered with neuropathy and pain because it is also a common side effect of chemotherapies (Hesketh 2008). However, taxane chemotherapies that are often associated with neuropathy are less emetogenic than other types of chemotherapies (Ghersi et al., 2015). Future research may benefit from exploring relationships between symptom clusters and types of ongoing chemotherapy treatments as well as other ongoing treatments among metastatic breast cancer patients. In addition, assessing pain types (e.g., neuropathic pain) would extend the current findings.

With the exception of sleep problems, the symptoms that clustered with cognitive complaints are consistent with findings from the only other published study to conduct a cluster analysis on symptoms in metastatic breast cancer patients (Bender et al., 2005). Findings from the symptom cluster literature are often slightly inconsistent; for instance, symptom clusters derived with different statistical methodologies—even from the same sample—are found to be unstable (Dong et al., 2014). Because cluster analysis is a data-driven exploratory statistical approach, current findings of symptoms clusters may be specific to this sample and should be replicated in future research. Differences in

measurement can also contribute to differential findings across studies. Most symptoms in the current study were assessed with validated measures, while single-item measures of menopausal symptoms were used in the prior study of symptom clusters in metastatic breast cancer patients (Bender et al., 2005).

<div align="center">4.2   Symptom Importance Findings</div>

Whereas findings from the first aim provide information about co-occurring symptoms, findings from the second aim increase our understanding of metastatic breast cancer patients' treatment priorities. Specifically, the second aim was to compare patient ratings of symptom importance for cognitive symptoms to those of other symptoms (i.e., pain, fatigue, sleep disturbance, depression, anxiety, nausea, lymphedema, hot flashes, and neuropathy). There was no empirical or theoretical basis for a hypothesis; therefore, this aim was exploratory. Patients were found to rate cognitive symptoms as significantly more important than anxiety, depressive symptoms, neuropathy, swelling, nausea, and hot flashes. Importance ratings for cognitive symptoms, pain, fatigue, and sleep problems were not significantly different.

The current study was the first to statistically compare ratings of symptom importance for different symptoms in any medical population. Rather than comparing importance ratings, prior research on symptom importance in certain medical populations (i.e., patients with chronic pain and Parkinson's disease) has found subgroups of patients based on their ratings of symptom importance (Nisenzon et al., 2011; M. E. Robinson et al., 2005). These subgroups typically consist of patients who rate all symptoms as high, moderate, or low in importance. In patients with chronic pain, researchers have also found subgroups of patients who consider pain to be most important (M. E. Robinson et

al., 2005). Thus, significant differences in symptom importance ratings in the current study converge with chronic pain research indicating that some symptoms are considered more important than others.

Several factors may explain the current findings regarding ratings of symptom importance. First, metastatic breast cancer patients may have been more comfortable giving a higher importance rating to cognitive symptoms than anxiety and depressive symptoms because emotional disturbances among cancer patients may be stigmatizing (Holland, 2002; Holland, Kelly, & Weinberger, 2010; Knowles, Chew-Graham, Adeyemi, Coupe, & Coventry, 2015). There are several lines of evidence pointing to stigma associated with emotional disturbances, including cancer patients' underuse of psychosocial support services (Abbott et al., 2013); one study found that only 14% of a heterogeneous sample of cancer patients reported using psychosocial support services over a period of 6 months, and this sample was moderately distressed on average (McDowell, Occhipinti, Ferguson, & Chambers, 2011). Additionally, many cancer patients endorse barriers to support services use that may be related to stigma, such as discomfort with seeking counseling and the belief that counseling may be more upsetting than helpful (Eakin & Strycker, 2001).

Second, some of the current differences in symptom importance ratings mirrored differences in symptom severity; specifically, usual levels of cognitive complaints, pain, fatigue, and sleep problems appeared to be higher in severity than neuropathy, swelling, nausea, and hot flashes. The mean severity ratings for cognitive complaints, pain, fatigue, and sleep problems fell within 40% of the total possible range, while those for neuropathy, hot flashes, nausea, and swelling were lower and fell within 15-30% of the

total possible range. However, the clinical significance of this numerical difference is unclear.

Third, high importance ratings for pain, sleep disturbance, and fatigue as well as cognitive symptoms may reflect the distressing quality of these symptoms. Pain, sleep disturbance, and fatigue have been found to be highly prevalent and distressing symptoms among patients with various advanced cancers (Butt, Wagner, et al., 2008; Reilly et al., 2013). In addition, when cancer patients in two studies ranked symptoms according to the importance of monitoring them, fatigue was consistently ranked as most important, and pain was among the top 5-6 most important (Butt, Rosenbloom, et al., 2008; Cella et al., 2011; Reeve et al., 2014). Sleep disturbance and cognitive problems were only examined in one of these studies. Of 533 advanced cancer patients who ranked 11 symptoms on the importance of monitoring them, 48% ranked fatigue as most important (ranked 1st), 16% ranked insomnia as most important (ranked 5th), 11% ranked pain as most important (ranked 6th), and only 3% ranked cognitive problems as most important (ranked 11th) (Cella et al., 2011; Reeve et al., 2014). Further research is needed to determine the degree to which cognitive symptoms are considered a clinical priority among advanced cancer patients.

Fourth, the symptoms rated as equally important in this study (i.e., cognitive symptoms, pain, fatigue, and sleep problems) may be difficult to distinguish from one another at times. There may be common biological and psychological mechanisms involved in these symptoms such as oxidative stress, telomere shortening, DNA damage, proinflammatory cytokines, HPA axis dysfunction, and perceived stress (Kim et al., 2012; Starkweather et al., 2013; Wood & Weymann, 2013). These symptoms have also

been found to exacerbate each other and have a compounding effect on health and quality-of-life outcomes in cancer populations (Cleeland, 2007; Dodd et al., 2010; Husain, Myers, Selby, Thomson, & Chow, 2011; Miaskowski et al., 2006).

Although statistically significant differences in importance ratings were obtained in the present sample, it is unclear whether these are clinically meaningful differences. Mean importance ratings for cognitive symptoms, pain, fatigue, and sleep problems ranged from 7.23 to 7.96, whereas mean importance ratings for anxiety and depressive symptoms ranged from 6.36 to 6.58 and those for neuropathy, swelling, and hot flashes ranged from 4.93 to 5.71. There is currently no established standard for a clinically meaningful difference in symptom importance; therefore, the present findings are difficult to interpret. Future research may determine clinically meaningful differences by examining levels of symptom importance that predict patient-centered care outcomes such as adherence to treatment recommendations. Furthermore, mixed-methods designs may examine differences between patient's ratings and rankings of symptom importance and elucidate patients' decision-making processes for determining symptom importance.

4.3   Synthesis of Findings for Symptom Clusters and Importance

Overall, findings suggest that assessing symptom clusters and symptom importance provides a more comprehensive picture of symptom experiences. Interestingly, cognitive symptoms were found to cluster with anxiety, depressive symptoms, sleep disturbance, and fatigue, but cognitive symptoms were rated as significantly more important than anxiety and depressive symptoms. Therefore, the co-occurrence of symptoms in metastatic breast cancer patients does not necessarily indicate that these symptoms are perceived as equally important to treat. It is possible that

focusing treatment on physical symptoms is more palatable to some cancer patients compared to psychological symptoms because of stigma associated with anxiety and depressive symptoms (Holland, 2002; Holland et al., 2010). Alternatively, physical symptoms may be more noticeable than psychological symptoms for patients with less insight into their psychological state. Again, differences in importance ratings across symptoms should be cautiously interpreted until further studies explore the degree to which these differences are clinically meaningful.

4.4   Research and Clinical Implications

The current findings regarding symptom clusters and importance have a number of implications for future research and clinical practice. Theoretically, patient ratings of symptom importance inform patient-centered care by providing information about patients' treatment priorities (Zeppieri et al., 2012). There is some evidence that patient-centered care improves the quality and cost of care as well as patients' adherence to treatment recommendations, although findings are mixed (Rathert, Wyrwich, & Boren, 2013; J. H. Robinson, Callister, Berry, & Dearing, 2008). Increased adherence to treatment recommendations in patient-centered care may be due in part to focusing on the patients' priorities. As an example, motivational interviewing is an effective behavioral intervention for improving treatment adherence which has a focus on patients' priorities. A central component of motivational interviewing is assisting patients in generating motivation to change based on their own values—what is important to them (Rollnick & Miller, 1995). This approach from motivational interviewing may be applied to future symptom management interventions. Such interventions may assist patients in generating motivation to adhere to treatment recommendations by tailoring those

recommendations to target symptoms rated as most important. Furthermore, future research may compare adherence between patients assigned to symptom management interventions that are tailored or untailored to symptoms rated as highly important.

Another potential direction for future research is testing treatments targeting one or more symptoms that cluster with other symptoms and are rated as highly important. Symptoms in a cluster may exacerbate one another (Cleeland, 2007; Dodd et al., 2010; Husain et al., 2011; Miaskowski et al., 2006; Starkweather et al., 2013); therefore, treatment focused on one symptom rated as highly important may still provide patients some relief from the other symptoms in the cluster and enhance adherence. For example, Cognitive Behavioral Therapy for Insomnia (CBT-I) is an evidence-based treatment for insomnia (Okajima, Komada, & Inoue, 2011). If CBT-I can be used to alleviate sleep disturbance in metastatic breast cancer patients, a symptom rated as highly important, the effect of sleep disturbance on other symptoms in the cluster—including anxiety and depressive symptoms—may dissipate. However, when a sample of cancer patients has heterogeneous treatment priorities, these individual differences may lessen the effects of one treatment approach—such as CBT-I—on adherence to treatment recommendations and severity of related symptoms. Therefore, single-subject designs or micro-randomized trials may provide an avenue for tailoring treatment to patients' priorities while still maintaining experimental control.

4.5   Limitations, Strengths, and Future Directions

Limitations of the current study should be noted. With the exception of medical record data (i.e., age, diagnosis date, and cancer treatment history), all measures were self-report. Self-reported data are vulnerable to biases including a desire to comply with

study expectations, social desirability, or an inability to accurately remember symptoms and their severity. Inaccurate recall may have been a particular issue for this study because participants with cognitive complaints may have had more difficulty remembering the severity of their symptoms over the last one or two weeks. However, many of these symptoms (e.g., pain) are inherently subjective experiences with self-report as the primary method of assessment.

Another limitation is the use of multiple brief symptom assessments. Although the measures have shown adequate reliability and validity, they may not fully capture the complexity of symptom constructs. The use of multiple assessments resulting in a 45-minute interview may also be overly burdensome for some patients with metastatic cancer. However, interviews of this length have been performed successfully in prior research with metastatic breast cancer patients (Mosher & DuHamel, 2012). Furthermore, the length of the interview in the current study seemed to be feasible considering the high consent and completion rates (see Figure 4).

Our sample was primarily Caucasian and only included women recruited from one academic cancer center in the Midwest; thus our findings may not generalize to men with the same disease, ethnic minorities, or patients in other geographical or institutional settings. Also, participants in our study had attained some college education on average ($M = 15.02$ years of education), although a wide range of education was reported (11-20 years). Regarding socio-economic status, one-fifth of the sample reported the lowest (i.e., $0-$30,999 per year) and highest (i.e., $100,000 +) income levels, and the most common income category was middle class ($51,000 - $99,999). Therefore, although

this sample had a range of education and income levels, our findings may not generalize to patients of lower socioeconomic status.

Another potential limitation is the use of cluster analysis, a data driven, exploratory analytical approach; therefore, findings warrant replication. However, an exploratory approach was appropriate considering the paucity of research on symptom clusters in metastatic breast cancer patients. The analytic approach was also strengthened by using weighted average linkage as the clustering method rather than Ward's method; Ward's method forces clusters to be similar sizes and is sensitive to outliers (McQuitty, 1966; Miaskowski et al., 2006).

The cross-sectional nature of our study precludes examining change in symptom clusters or patient ratings of symptom importance, both of which may be temporally unstable. Furthermore, although we collected information on cancer treatments, unexamined factors such as contact with a physician or adherence to medications may also be related to symptom clusters and importance.

Despite limitations, the current study also has several strengths. The study sample consisted of metastatic breast cancer patients, a population which has received scarce research attention despite their high symptom burden and increased longevity. Additionally, the majority of self-report measures have demonstrated good validity and reliability. There was also a considerably high response rate, as 87% (83/95) of patients contacted by phone consented to participate, and 96% (80/83) of consenting participants completed the assessment.

Future research on symptom clusters and symptom importance in cancer populations may build upon the current findings. Longitudinal designs may track

symptom clusters and symptom importance to test the temporal stability of these constructs. Future designs may also include objective measurements of symptoms when possible (e.g., sleep disturbance) or supplement self-report measures with observer (e.g., physician, caregiver) ratings. Treatment priorities may also be assessed with other methods such as asking participants to rank order their symptoms by importance, and differences among such measurement methods may be explored. A mixed-methods approach to this research may provide quantitative information about symptoms rank-ordered by importance, and qualitative information about participants reasoning for those rankings. Finally, future research may benefit from assessing other disease and quality-of-life factors along with symptom clusters and importance to generate a model of factors influencing symptom relationships and patients' treatment priorities. Such models may change at different points in the illness trajectory (e.g., diagnosis, treatment, end of life).

CHAPTER 5. CONCLUSION

Many breast cancer patients experience cognitive symptoms related to cancer and

its treatment, but our current understanding of cognitive symptoms in metastatic breast

cancer patients is limited. The present study addresses gaps in our understanding of

symptoms co-occurring with cognitive complaints in this population and the patient-rated

importance of cognitive complaints as compared to other symptoms. In this sample,

cognitive complaints clustered with anxiety, depressive symptoms, sleep problems, and

fatigue. Additionally, cognitive symptoms were rated as significantly more important

than anxiety, depressive symptoms, neuropathy, swelling, nausea, and hot flashes, and

importance ratings did not differ among cognitive symptoms, pain, fatigue, and sleep

problems. Although pain did not cluster with cognitive symptoms, fatigue, and sleep

problems, it was still rated as equally important. Although anxiety and depressive

symptoms clustered with cognitive symptoms, fatigue, and sleep problems, they were

both rated as significantly less important. However, the differences in importance ratings

were small. Future research may provide a more comprehensive understanding of

symptom experiences and treatment priorities by using alternative and mixed methods to

assess treatment priorities, exploring how symptom clusters and symptom importance

may change over time, and developing a model of symptom experiences with other

important outcomes such as patient adherence to interventions. Developing patient-

centered approaches to symptom management based on symptom severity and treatment priorities has the potential to impact patients' quality of life as well as improve health care quality and patients' adherence to treatment recommendations.

REFERENCES

REFERENCES

Abbott, Y., Shah, N. R., Ward, K. K., McHale, M. T., Alvarez, E. A., Saenz, C. C., &
    Plaxe, S. C. (2013). Use of psychosocial services increases after a social worker–
    mediated intervention in gynecology oncology patients. *Health & Social Work,*
    38, 113-121. doi: 10.1093/hsw/hlt006

Ahles, T. A. (2012). Brain vulnerability to chemotherapy toxicities. *Psycho-Oncology,*
    21, 1141-1148. doi:10.1002/pon.3196

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, 30, 3675-3686. doi:10.1200/jco.2012.43.0116

Ahles, T. A., & Saykin, A. J. (2001). Cognitive effects of standard-dose chemotherapy in
    patients with cancer. *Cancer Investigation, 19*, 812-820. doi:10.1081/CNV-
    100107743

Ahles, T. A., & Saykin, A. J. (2002). Breast cancer chemotherapy-related cognitive
    dysfunction. *Clinical Breast Cancer, 3*, S84-S90. doi:10.3816/CBC.2002.s.018

Ahles, T. A., & Saykin, A. J. (2007). Candidate mechanisms for chemotherapy-induced
    cognitive changes. *Nature Reviews Cancer, 7*, 192-201. doi:10.1038/nrc2073

Ahles, T. A., Saykin, A. J., McDonald, B. C., Furstenberg, C. T., Cole, B. F., Hanscom, B. S., . . . Kaufman, P. A. (2008). Cognitive function in breast cancer patients prior to adjuvant treatment. *Breast Cancer Research and Treatment, 110*, 143-152. doi:10.1007/s10549-007-9686-5

Ahles, T. A., Saykin, A. J., McDonald, B. C., Li, Y., Furstenberg, C. T., Hanscom, B. S., . . . Kaufman, P. A. (2010). Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: Impact of age and cognitive reserve. *Journal of Clinical Oncology, 28*, 4434-4440. doi:10.1200/JCO.2009.27.0827

Ahles, T. A., Saykin, A. J., Noll, W. W., Furstenberg, C. T., Guerin, S., Cole, B., & Mott, L. A. (2003). The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psycho-Oncology, 12*, 612-619. doi:10.1002/pon.742

Ahles, T. A., Schagen, S., & Vardy, J. (2012). Neurocognitive effects of anticancer treatments. In L. Grassi & M. Riba (Eds.), *Clinical psycho-oncology: An international perspective* (1st ed., pp. 71-82). West Sussex, UK: John Wiley & Sons, Ltd.

Aktas, A., Walsh, D., & Rybicki, L. (2010). Symptom clusters: Myth or reality? *Palliative Medicine, 24*, 373-385. doi:10.1177/0269216310367842

Allen, J. C. (1978). The effects of cancer therapy on the nervous system. *The Journal of Pediatrics, 93*, 903-909. doi:10.1016/S0022-3476(78)81209-8

Aranda, S., Schofield, P., Weih, L., Yates, P., Milne, D., Faulkner, R., & Voudouris, N. (2005). Mapping the quality of life and unmet needs of urban women with metastatic breast cancer. *European Journal of Cancer Care, 14*, 211-222. doi:10.1111/j.1365-2354.2005.00541.x

Baum, G., Basen-Engquist, K., Swartz, M. C., Parker, P. A., & Carmack, C. L. (2014). Comparing PROMIS computer-adaptive tests to the Brief Symptom Inventory in patients with prostate cancer. *Quality of Life Research, 23*, 2031-2035. doi:10.1007/s11136-014-0647-2

Bender, C. M., Ergÿn, F. S., Rosenzweig, M. Q., Cohen, S. M., & Sereika, S. M. (2005). Symptom clusters in breast cancer across 3 phases of the disease. *Cancer Nursing, 28*, 219-225. doi:10.1097/00002820-200505000-00011

Bender, C. M., Sereika, S. M., Berga, S. L., Vogel, V. G., Brufsky, A. M., Paraska, K. K., & Ryan, C. M. (2006). Cognitive impairment associated with adjuvant therapy in breast cancer. *Psycho-Oncology, 15*, 422-430. doi:10.1002/pon.964

Berman, M. G., Askren, M. K., Jung, M., Therrien, B., Peltier, S., Noll, D. C., . . . Reuter-Lorenz, P. A. (2014). Pretreatment worry and neurocognitive responses in women with breast cancer. *Health Psychology, 33*, 222-231. doi:10.1037/a0033425

Bird, C. M., & Burgess, N. (2008). The hippocampus and memory: Insights from spatial processing. *Nature Reviews. Neuroscience, 9*, 182-194. doi:10.1038/nrn2335

Bleecker, M., Ford, D., Celio, M., Vaughan, C., & Lindgren, K. (2007). Impact of cognitive reserve on the relationship of lead exposure and neurobehavioral performance. *Neurology, 69*, 470-476. doi:10.1212/01.wnl.0000266628.43760.8c

Bower, J. E., Ganz, P. A., & Aziz, N. (2005). Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosomatic Medicine, 67*, 277-280. doi:10.1097/01.psy.0000155666.55034.c6

Bower, J. E., Ganz, P. A., Tao, M. L., Hu, W., Belin, T. R., Sepah, S., . . . Aziz, N. (2009). Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clinical Cancer Research, 15*, 5534-5540. doi:10.1158/1078-0432.CCR-08-2584

Brambilla, D. J., Mckinlay, S. M., & Johannes, C. B. (1994). Defining the perimenopause for application in epidemiologic investigations. *American Journal of Epidemiology, 140*, 1091-1095. doi:10.1016/0378-5122(95)99337-2

Browall, M., Ahlberg, K., Karlsson, P., Danielson, E., Persson, L.-O., & Gaston-Johansson, F. (2008). Health-related quality of life during adjuvant treatment for breast cancer among postmenopausal women. *European Journal of Oncology Nursing, 12*, 180-189. doi:10.1016/j.ejon.2008.01.005

Brown, J. L., Edwards, P. S., Atchison, J. W., Lafayette-Lucey, A., Wittmer, V. T., & Robinson, M. E. (2008). Defining patient-centered, multidimensional success criteria for treatment of chronic spine pain. *Pain Medicine, 9*, 851-862. doi:10.1111/j.1526-4637.2007.00357.x

Bruera, E. (2013). Consistency of symptom clusters among advanced cancer patients seen at an outpatient supportive care clinic in a tertiary cancer center. *Palliative and Supportive Care, 11*, 473-480. doi:10.1017/S1478951512000879

Bruera, E., Macmillan, K., Hanson, J., & MacDonald, R. N. (1989). The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain, 39*, 13-16. doi:10.1016/0304-3959(89)90169-3

Butt, Z., Rosenbloom, S. K., Abernethy, A. P., Beaumont, J. L., Paul, D., Hampton, D., . . . Cella, D. (2008). Fatigue is the most important symptom for advanced cancer patients who have had chemotherapy. *Journal of the National Comprehensive Cancer Network, 6*, 448-455.

Butt, Z., Wagner, L. I., Beaumont, J. L., Paice, J. A., Straus, J. L., Peterman, A. H., . . . Cella, D. (2008). Longitudinal screening and management of fatigue, pain, and emotional distress associated with cancer therapy. *Supportive Care in Cancer, 16*, 151-159. doi:10.1007/s00520-007-0291-2

Calado, R., & Young, N. (2012). Telomeres in disease. *F1000 Med Rep, 4*, 1-7. doi:10.3410/M4-8

Callahan, C. M., Unverzagt, F. W., Hui, S. L., Perkins, A. J., & Hendrie, H. C. (2002). Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Medical Care, 40*, 771-781. doi:10.1097/01.MLR.0000024610.33213.C8

Carpenter, J. S., Andrykowski, M. A., Cordova, M., Cunningham, L., Studts, J., McGrath, P., . . . Munn, R. (1998). Hot flashes in postmenopausal women treated for breast carcinoma. *Cancer, 82*, 1682-1691. doi:10.1002/(SICI)1097-0142(19980501)82:9<1682::AID-CNCR14>3.0.CO;2-0

Cella, D., Riley, W., Stone, A., Rothrock, N., Reeve, B., Yount, S., . . . Choi, S. (2010). The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. *Journal of Clinical Epidemiology, 63*, 1179-1194. doi:10.1016/j.jclinepi.2010.04.011

Cella, D., Rosenbloom, S. K., Beaumont, J. L., Yount, S. E., Paul, D., Hampton, D., . . . Von Roenn, J. H. (2011). Development and validation of 11 symptom indexes to evaluate response to chemotherapy for advanced cancer. *Journal of the National Comprehensive Cancer Network, 9*, 268-278.

Cella, D., Yount, S., Rothrock, N., Gershon, R., Cook, K., Reeve, B., . . . Rose, M. (2007). The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap cooperative group during its first two years. *Medical Care, 45*, S3-S11. doi:10.1097/01.mlr.0000258615.42478.55

Chang, V. T., Hwang, S. S., Feuerman, M., & Kasimis, B. S. (2000). Symptom and quality of life survey of medical oncology patients at a veterans affairs medical center. *Cancer, 88*, 1175-1183. doi:10.1002/(SICI)1097-0142(20000301)88:5<1175::AID-CNCR30>3.0.CO;2-N

Chen, E., Khan, L., Zhang, L., Nguyen, J., Zeng, L., Bedard, G., . . . Sahgal, A. (2013). Symptom clusters in patients with brain metastases—a reanalysis comparing different statistical methods. *Journal of Radiation Oncology, 2*, 95-102. doi:10.1007/s00520-012-1403-1

Chen, E., Nguyen, J., Khan, L., Zhang, L., Cramarossa, G., Tsao, M., . . . Holden, L.
(2012). Symptom clusters in patients with advanced cancer: A reanalysis
comparing different statistical methods. *Journal of Pain and Symptom
Management, 44*, 23-32. doi:10.1016/j.jpainsymman.2011.07.011

Cheung, W. Y., Le, L. W., & Zimmermann, C. (2009). Symptom clusters in patients with
advanced cancers. *Supportive Care in Cancer, 17*, 1223-1230. doi:
10.1007/s00520-009-0577-7

Chow, E., Fan, G., Hadi, S., & Filipczak, L. (2007). Symptom clusters in cancer patients
with bone metastases. *Supportive Care in Cancer, 15*, 1035-1043.
doi:10.1007/s00520-007-0241-z

Chow, E., Fan, G., Hadi, S., Wong, J., Kirou-Mauro, A., & Filipczak, L. (2008).
Symptom clusters in cancer patients with brain metastases. *Clinical Oncology, 20*,
76-82. doi:10.1016/j.clon.2007.09.007

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*, 70-78. doi:10.1002/pon.821

Cleeland, C. S. (2007). Symptom burden: Multiple symptoms and their impact as patient-
reported outcomes. *Journal of the National Cancer Institute. Monographs, 37*, 16-
21. doi:10.1093/jncimonographs/lgm005

Cleeland, C. S., Bennett, G. J., Dantzer, R., Dougherty, P. M., Dunn, A. J., Meyers, C.
A., . . . Wang, X. S. (2003). Are the symptoms of cancer and cancer treatment due
to a shared biologic mechanism? *Cancer, 97*, 2919-2925. doi:10.1002/cncr.11382

Cleeland, C. S., Mendoza, T. R., Wang, X. S., Chou, C., Harle, M. T., Morrissey, M., & Engstrom, M. C. (2000). Assessing symptom distress in cancer patients. *Cancer, 89*, 1634-1646. doi:10.1002/1097-0142(20001001)89:7<1634::AID-CNCR29>3.0.CO;2-V

Cockrell, J. R., & Folstein, M. F. (2002). Mini-mental state examination. In J. R. Copeland, M. T. Abou-Saleh, & D. G. Blazer (Eds.), *Principles and practice of geriatric psychiatry* (2nd ed., pp. 140-141). West Sussex, UK: John Wiley & Sons, Ltd.

Collins, B., Mackenzie, J., Stewart, A., Bielajew, C., & Verma, S. (2009). Cognitive effects of chemotherapy in post-menopausal breast cancer patients 1 year after treatment. *Psycho-Oncology, 18*, 134-143. doi:10.1002/pon.1379

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*, 493-502. doi:10.1007/s10549-012-2385-x

Correa, D. D., & Ahles, T. A. (2008). Neurocognitive changes in cancer survivors. *The Cancer Journal, 14*, 396-400. doi:10.1097/PPO.0b013e31818d8769

Crossen, J. R., Garwood, D., Glatstein, E., & Neuwelt, E. A. (1994). Neurobehavioral sequelae of cranial irradiation in adults: A review of radiation-induced encephalopathy. *Journal of Clinical Oncology, 12*, 627-642.

de Ruiter, M. B., Reneman, L., Boogerd, W., Veltman, D. J., van Dam, F. S., Nederveen, A. J., . . . Schagen, S. B. (2011). Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. *Human Brain Mapping, 32*, 1206-1219. doi:10.1002/hbm.21102

Debess, J., Riis, J. Ø., Engebjerg, M. C., & Ewertz, M. (2010). Cognitive function after adjuvant treatment for early breast cancer: A population-based longitudinal study. *Breast Cancer Research and Treatment, 121*, 91-100. doi:10.1007/s10549-010-0756-8

Deprez, S., Amant, F., Yigit, R., Porke, K., Verhoeven, J., Stock, J. V. d., . . . Hecke, W. V. (2011). Chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients. *Human Brain Mapping, 32*, 480-493. doi:10.1002/hbm.21033

Dietrich, J., Monje, M., Wefel, J., & Meyers, C. (2008). Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. *The Oncologist, 13*, 1285-1295. doi:10.1634/theoncologist.2008-0130

Dodd, M. J., Cho, M. H., Cooper, B. A., & Miaskowski, C. (2010). The effect of symptom clusters on functional status and quality of life in women with breast cancer. *European Journal of Oncology Nursing, 14*, 101-110. doi:10.1016/j.ejon.2009.09.005

Dodd, M. J., Miaskowski, C., & Paul, S. M. (2001). Symptom clusters and their effect on the functional status of patients with cancer. *Oncology Nursing Forum, 28*, 465-470.

Dong, S. T., Butow, P. N., Costa, D. S., Lovell, M. R., & Agar, M. (2014). Symptom

clusters in patients with advanced cancer: A systematic review of observational

studies. *Journal of Pain and Symptom Management, 48*, 411-450.

doi:10.1016/j.jpainsymman.2013.10.027

Donovan, K. A., Small, B. J., Andrykowski, M. A., Schmitt, F. A., Munster, P., &

Jacobsen, P. B. (2005). Cognitive functioning after adjuvant chemotherapy and/or

radiotherapy for early-stage breast carcinoma. *Cancer, 104*, 2499-2507.

doi:10.1002/cncr.21482

Dunn, L. B., Aouizerat, B. E., Langford, D. J., Cooper, B. A., Dhruva, A., Cataldo, J. K.,

. . . West, C. (2013). Cytokine gene variation is associated with depressive

symptom trajectories in oncology patients and family caregivers. *European

Journal of Oncology Nursing, 17*, 346-353. doi:10.1016/j.ejon.2012.10.004

Eakin, E. G., & Strycker, L. A. (2001). Awareness and barriers to use of cancer support

and information resources by HMO patients with breast, prostate, or colon cancer:

Patient and provider perspectives. *Psycho-Oncology, 10*, 103-113.

doi:10.1002/pon.500

Eccleston, C., & Crombez, G. (1999). Pain demands attention: A cognitive–affective

model of the interruptive function of pain. *Psychological Bulletin, 125*, 356-366.

doi:10.1037/0033-2909.125.3.356

Epstein, R. M., Fiscella, K., Lesser, C. S., & Stange, K. C. (2010). Why the nation needs

a policy push on patient-centered health care. *Health Affairs, 29*, 1489-1495.

doi:10.1377/hlthaff.2009.0888

Epstein, R. M., Franks, P., Shields, C. G., Meldrum, S. C., Miller, K. N., Campbell, T. L., & Fiscella, K. (2005). Patient-centered communication and diagnostic testing. *The Annals of Family Medicine, 3*, 415-421. doi:10.1370/afm.348

Everitt, B. S., Landau, S., & Leese, M. (2001). *Cluster analysis* (4th ed.). London, UK: Arnold.

Falleti, M. G., Sanfilippo, A., Maruff, P., Weih, L., & Phillips, K.-A. (2005). The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: A meta-analysis of the current literature. *Brain and Cognition, 59*, 60-70. doi:10.1016/j.bandc.2005.05.001

Fan, G., Filipczak, L., & Chow, E. (2007). Symptom clusters in cancer patients: A review of the literature. *Current Oncology, 14*, 173-179. doi:10.3747/co.2007.145

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*, 175-191. doi:10.3758/BF03193146

Fiscella, K., Meldrum, S., Franks, P., Shields, C. G., Duberstein, P., McDaniel, S. H., & Epstein, R. M. (2004). Patient trust: Is it related to patient-centered behavior of primary care physicians? *Medical Care, 42*, 1049-1055. doi:10.1097/00005650-200411000-00003

Ganz, P. A., Bower, J., Kwan, L., Castellon, S., Silverman, D., Geist, C., . . . Cole, S. (2013). Does tumor necrosis factor-alpha (TNF-α) play a role in post-chemotherapy cerebral dysfunction? *Brain, Behavior, and Immunity, 30*, S99-S108. doi:10.1016/j.bbi.2012.07.015

Garcia, S. F., Cella, D., Clauser, S. B., Flynn, K. E., Lad, T., Lai, J.-S., . . . Weinfurt, K. (2007). Standardizing patient-reported outcomes assessment in cancer clinical trials: A patient-reported outcomes measurement information system initiative. *Journal of Clinical Oncology, 25*, 5106-5112. doi:10.1200/JCO.2007.12.2341

Geinitz, H., Zimmermann, F. B., Stoll, P., Thamm, R., Kaffenberger, W., Ansorg, K., . . . Molls, M. (2001). Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. *International Journal of Radiation Oncology* Biology* Physics, 51*, 691-698. doi:10.1016/S0360-3016(01)01657-1

Ghersi, D., Willson, M. L., Chan, M. M. K., Simes, J., Donoghue, E., & Wilcken, N. (2015). Taxane-containing regimens for metastatic breast cancer. *Cochrane Database of Systematic Reviews, 2015*, 1-170. doi:10.1002/14651858.CD003366.pub3

Gilliam, L. A., & St. Clair, D. K. (2011). Chemotherapy-induced weakness and fatigue in skeletal muscle: the role of oxidative stress. *Antioxidants and Redox Signaling, 15*, 2543-2563. doi:10.1089/ars.2011.3965

Girden, E. R. (1992). *ANOVA: Repeated measures*. Newbury Park, California: Sage Publications, Inc.

Given, B., Given, C. W., Sikorskii, A., Jeon, S., McCorkle, R., Champion, V., & Decker, D. (2008). Establishing mild, moderate, and severe scores for cancer-related symptoms: How consistent and clinically meaningful are interference-based severity cut-points? *Journal of Pain and Symptom Management, 35*, 126-135. doi:10.1016/j.jpainsymman.2007.03.012

Glaus, A., Boehme, C., Thürlimann, B., Ruhstaller, T., Schmitz, S. H., Morant, R., . . . von Moos, R. (2006). Fatigue and menopausal symptoms in women with breast cancer undergoing hormonal cancer treatment. *Annals of Oncology, 17*, 801-806. doi:10.1093/annonc/mdl030

Grabsch, B., Clarke, D. M., Love, A., McKenzie, D., Snyder, R. D., Bloch, S., . . . Kissane, D. W. (2006). Psychological morbidity and quality of life in women with advanced breast cancer: A cross-sectional survey. *Palliative & Supportive Care, 4*, 47-56. doi:10.1017/S1478951506060068

Grisart, J. M., & Van der Linden, M. (2001). Conscious and automatic uses of memory in chronic pain patients. *Pain, 94*, 305-313. doi:10.1016/S0304-3959(01)00366-9

Harris, S. E., & Deary, I. J. (2011). The genetics of cognitive ability and cognitive ageing in healthy older people. *Trends in Cognitive Sciences, 15*, 388-394. doi:10.1016/j.tics.2011.07.004

Hede, K. (2008). Chemobrain is real but may need new name. *Journal of the National Cancer Institute, 100*, 162-169. doi:10.1093/jnci/djn007

Hemminki, E., Topo, P., & Kangas, I. (1995). Experience and opinions of climacterium by Finnish women. *European Journal of Obstetrics & Gynecology and Reproductive Biology, 62*, 81-87. doi:10.1016/0301-2115(95)02118-Q

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

Hesketh , P. J. (2008). Chemotherapy-induced nausea and vomiting. *New England Journal of Medicine, 358*, 2482-2494. doi:doi:10.1056/NEJMra0706547

Hird, A., Wong, J., Zhang, L., Tsao, M., Barnes, E., Danjoux, C., & Chow, E. (2010). Exploration of symptoms clusters within cancer patients with brain metastases using the Spitzer Quality of Life Index. *Supportive Care in Cancer, 18*, 335-342. doi:10.1007/s00520-009-0657-8

Holland, J. C. (2002). History of psycho-oncology: Overcoming attitudinal and conceptual barriers. *Psychosomatic Medicine, 64*, 206-221. doi:10.1097/00006842-200203000-00004

Holland, J. C., Kelly, B. J., & Weinberger, M. I. (2010). Why psychosocial care is difficult to integrate into routine cancer care: Stigma is the elephant in the room. *Journal of the National Comprehensive Cancer Network, 8*, 362-366.

Holmes, F. A., Walters, R. S., Theriault, R. L., Buzdar, A. U., Frye, D. K., Hortobagyi, G. N., . . . Raber, M. N. (1991). Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. *Journal of the National Cancer Institute, 83*, 1797-1805. doi:10.1093/jnci/83.24.1797-a

Howlader, N., Noone, A., Krapcho, M., Garshell, J., Miller, D., Altekruse, S., . . . eds. (2015). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.

Hurria, A., Rosen, C., Hudis, C., Zuckerman, E., Panageas, K. S., Lachs, M. S., . . .
D'Andrea, G. (2006). Cognitive function of older patients receiving adjuvant
chemotherapy for breast cancer: A pilot prospective longitudinal study. *Journal of
the American Geriatrics Society, 54*, 925-931. doi:10.1111/j.1532-
5415.2006.00732.x

Hurria, A., Somlo, G., & Ahles, T. A. (2007). Renaming "chemobrain". *Cancer
Investigation, 25*, 373-377. doi:10.1080/07357900701506672

Husain, A., Myers, J., Selby, D., Thomson, B., & Chow, E. (2011). Subgroups of
advanced cancer patients clustered by their symptom profiles: Quality-of-life
outcomes. *Journal of Palliative Medicine, 14*, 1246-1253.
doi:10.1089/jpm.2011.0112

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 Treatment Reviews, 38*, 926-934.
doi:10.1016/j.ctrv.2012.05.002

Irvin, W., Muss, H. B., & Mayer, D. K. (2011). Symptom management in metastatic
breast cancer. *The Oncologist, 16*, 1203-1214. doi:10.1634/theoncologist.2011-
0159

Janaki, M., Kadam, A. R., Mukesh, S., Nirmala, S., Ponni, A., Ramesh, B., & Rajeev, A.
(2010). Magnitude of fatigue in cancer patients receiving radiotherapy and its
short term effect on quality of life. *Journal of Cancer Research and Therapeutics,
6*, 22-26. doi:10.4103/0973-1482.63566

Jansen, C. E. (2013). Cognitive changes associated with cancer and cancer therapy: Patient assessment and education. *Seminars in Oncology Nursing, 29*, 270-279. doi:10.1016/j.soncn.2013.08.007

Jansen, C. E., Cooper, B. A., Dodd, M. J., & Miaskowski, C. A. (2011). A prospective longitudinal study of chemotherapy-induced cognitive changes in breast cancer patients. *Supportive Care in Cancer, 19*, 1647-1656. doi:10.1007/s00520-010-0997-4

Jansen, C. E., Miaskowski, C., Dodd, M. J., Dowling, G., & Kramer, J. (2005). A meta analysis of studies of the effects of cancer chemotherapy on various domains of cognitive function. *Cancer, 104*, 2222-2233. doi:10.1002/cncr.21469

Jean-Pierre, P., Johnson-Greene, D., & Burish, T. G. (2014). Neuropsychological care and rehabilitation of cancer patients with chemobrain: Strategies for evaluation and intervention development. *Supportive Care in Cancer, 22*, 2251-2260. doi:10.1007/s00520-014-2162-y

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

Jenkins, V., Shilling, V., Fallowfield, L., Howell, A., & Hutton, S. (2004). Does hormone therapy for the treatment of breast cancer have a detrimental effect on memory and cognition? A pilot study. *Psycho-Oncology, 13*, 61-66. doi:10.1002/pon.709

Jim, H. S., Donovan, K. A., Small, B. J., Andrykowski, M. A., Munster, P. N., & Jacobsen, P. B. (2009). Cognitive functioning in breast cancer survivors: A controlled comparison. *Cancer, 115*, 1776-1783. doi:10.1002/cncr.24192

Jim, H. S., Phillips, K. M., Chait, S., Faul, L. A., Popa, M. A., Lee, Y.-H., . . . Small, B. J. (2012). Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *Journal of Clinical Oncology, 30*, 3578-3587. doi:10.1200/JCO.2011.39.5640

Jiménez, A., Madero, R., Alonso, A., Martínez-Marín, V., Vilches, Y., Martínez, B., . . . Feliu, J. (2011). Symptom clusters in advanced cancer. *Journal of Pain and Symptom Management, 42*, 24-31. doi:10.1016/j.jpainsymman.2010.10.266

Keime-Guibert, F., Napolitano, M., & Delattre, J.-Y. (1998). Neurological complications of radiotherapy and chemotherapy. *Journal of Neurology, 245*, 695-708. doi:10.1007/s004150050271

Khan, L., Cramarossa, G., Lemke, M., Nguyen, J., Zhang, L., Chen, E., & Chow, E. (2013). Symptom clusters using the Spitzer quality of life index in patients with brain metastases—a reanalysis comparing different statistical methods. *Supportive Care in Cancer, 21*, 467-473. doi:10.1007/s00520-012-1540-6

Kibiger, G., Kirsh, K. L., Wall, J. R., & Passik, S. D. (2003). My mind is as clear as it used to be: A pilot study illustrating the difficulties of employing a single-item subjective screen to detect cognitive impairment in outpatients with cancer. *Journal of Pain and Symptom Management, 26*, 705-715. doi:10.1016/S0885-3924(03)00237-9

Kim, H.-J., Barsevick, A. M., Fang, C. Y., & Miaskowski, C. (2012). Common biological pathways underlying the psychoneurological symptom cluster in cancer patients. *Cancer Nursing, 35*, E1-E20. doi:10.1097/NCC.0b013e318233a811

Kim, H.-J., Barsevick, A. M., Tulman, L., & McDermott, P. A. (2008). Treatment-related symptom clusters in breast cancer: A secondary analysis. *Journal of Pain and Symptom Management, 36*, 468-479. doi:10.1016/j.jpainsymman.2007.11.011

Kim, H.-J., McGuire, D. B., Tulman, L., & Barsevick, A. M. (2005). Symptom clusters: Concept analysis and clinical implications for cancer nursing. *Cancer Nursing, 28*, 270-282.

Kirkova, J., Aktas, A., Walsh, D., Rybicki, L., & Davis, M. P. (2010). Consistency of symptom clusters in advanced cancer. *American Journal of Hospice and Palliative Medicine, 27*, 342-346. doi:10.1177/1049909110369869

Kline, R. B. (2011). *Principles and practice of structural equation modeling* (3rd ed.). New York, NY, US: Guilford Press.

Knowles, S. E., Chew-Graham, C., Adeyemi, I., Coupe, N., & Coventry, P. A. (2015). Managing depression in people with multimorbidity: A qualitative evaluation of an integrated collaborative care model. *BMC Family Practice, 16*, 32-42. doi:10.1186/s12875-015-0246-5

Kohli, S., Griggs, J. J., Roscoe, J. A., Jean-Pierre, P., Bole, C., Mustian, K. M., . . . Morrow, G. R. (2007). Self-reported cognitive impairment in patients with cancer. *Journal of Oncology Practice, 3*, 54-59. doi:10.1200/JOP.0722001

Koopman, C., Nouriani, B., Erickson, V., Anupindi, R., Butler, L. D., Bachmann, M. H., . . . Spiegel, D. (2002). Sleep disturbances in women with metastatic breast cancer. *The Breast Journal, 8*, 362-370. doi:10.1046/j.1524-4741.2002.08606.x

Kozachik, S. L. (2006). *Symptom clusters in elderly cancer patients*. (Unpublished doctoral dissertation). The Johns Hopkins University, Baltimore, MD.

Kroenke, K., Theobald, D., Norton, K., Sanders, R., Schlundt, S., McCalley, S., . . . Carpenter, J. S. (2009). The Indiana Cancer Pain and Depression (INCPAD) trial: Design of a telecare management intervention for cancer-related symptoms and baseline characteristics of study participants. *General Hospital Psychiatry, 31*, 240-253. doi:10.1016/j.genhosppsych.2009.01.007

Kronenberg, F. (1990). Hot flashes: Epidemiology and physiologya. *Annals of the New York Academy of Sciences, 592*, 52-86. doi:10.1111/j.1749-6632.1990.tb30316.x

Kurzrock, R. (2001). The role of cytokines in cancer-related fatigue. *Cancer, 92*, 1684-1688. doi:10.1002/1097-0142(20010915)92:6+<1684::AID-CNCR1497>3.0.CO;2-Z

Little, P., Everitt, H., Williamson, I., Warner, G., Moore, M., Gould, C., . . . Payne, S. (2001). Observational study of effect of patient centredness and positive approach on outcomes of general practice consultations. *British Medical Journal, 323*, 908-911. doi:10.1136/bmj.323.7318.908

Liu, H., Cella, D., Gershon, R., Shen, J., Morales, L. S., Riley, W., & Hays, R. D. (2010). Representativeness of the Patient-Reported Outcomes Measurement Information System internet panel. *Journal of Clinical Epidemiology, 63*, 1169-1178. doi:10.1016/j.jclinepi.2009.11.021

Mallinger, J. B., Griggs, J. J., & Shields, C. G. (2005). Patient-centered care and breast cancer survivors' satisfaction with information. *Patient Education and Counseling, 57*, 342-349. doi:10.1016/j.pec.2004.09.009

Mandelblatt, J. S., Hurria, A., McDonald, B. C., Saykin, A. J., Stern, R. A., VanMeter, J. W., . . . Turner, S. (2013). Cognitive effects of cancer and its treatments at the intersection of aging: What do we know; what do we need to know? *Seminars in Oncology, 40*, 709-725. doi:10.1053/j.seminoncol.2013.09.006

Marchand, V., Bourdin, S., Charbonnel, C., Rio, E., Munos, C., Campion, L., . . . Supiot, S. (2010). No impairment of quality of life 18 months after high-dose intensity-modulated radiotherapy for localized prostate cancer: A prospective study. *International Journal of Radiation Oncology* Biology* Physics, 77*, 1053-1059. doi:10.1016/j.ijrobp.2009.06.024

Mayer, M. (2010). Lessons learned from the metastatic breast cancer community. *Seminars in Oncology Nursing, 26*, 195-202. doi:10.1016/j.soncn.2010.05.004

Mayer, M., & Grober, S. E. (2006). Silent Voices: Women with advanced (metastatic) breast cancer share their needs and preferences for information, support and practical resources. Havorford, PA: Living Beyond Breast Cancer.

McDonald, B. C., Conroy, S. K., Ahles, T. A., West, J. D., & Saykin, A. J. (2010). Gray matter reduction associated with systemic chemotherapy for breast cancer: A prospective MRI study. *Breast Cancer Research and Treatment, 123*, 819-828. doi:10.1007/s10549-010-1088-4

McDonald, B. C., Conroy, S. K., Ahles, T. A., West, J. D., & Saykin, A. J. (2012). Alterations in brain activation during working memory processing associated with breast cancer and treatment: A prospective functional magnetic resonance imaging study. *Journal of Clinical Oncology, 30*, 2500-2508. doi:10.1200/JCO.2011.38.5674

McDowell, M. E., Occhipinti, S., Ferguson, M., & Chambers, S. K. (2011). Prospective predictors of psychosocial support service use after cancer. *Psycho-Oncology, 20*, 788-791. doi:10.1002/pon.1774

McQuitty, L. L. (1966). Similarity analysis by reciprocal pairs for discrete and continuous data. *Educational and Psychological Measurement, 26*, 825-831. doi:10.1177/001316446602600402

Mead, N., & Bower, P. (2002). Patient-centred consultations and outcomes in primary care: A review of the literature. *Patient Education and Counseling, 48*, 51-61. doi:10.1016/S0738-3991(02)00099-X

Meyers, C., & Perry, J. (Eds.). (2008). *Cognition and cancer*. Cambridge, UK: Cambridge University Press.

Miaskowski, C., Cooper, B. A., Paul, S. M., Dodd, M., Lee, K., Aouizerat, B. E., . . . Bank, A. (2006). Subgroups of patients with cancer with different symptom experiences and quality-of-life outcomes: A cluster analysis. *Oncology Nursing Forum, 33*, E79-E89. doi:10.1188/06.ONF.E79-E89

Miaskowski, C., Dodd, M., & Lee, K. (2004). Symptom clusters: The new frontier in symptom management research. *Journal of the National Cancer Institute. Monographs, 32*, 17-21. doi:10.1093/jncimonographs/lgh023

Milne, A. M., MacQueen, G. M., & Hall, G. B. (2012). Abnormal hippocampal activation in patients with extensive history of major depression: An fMRI study. *Journal of Psychiatry & Neuroscience, 37*, 28-36. doi:10.1503/jpn.110004

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: A review of clinical and preclinical research. *Progress in Neurobiology, 93*, 385-404. doi:10.1016/j.pneurobio.2011.01.002

Mosher, C. E., & DuHamel, K. N. (2012). An examination of distress, sleep, and fatigue in metastatic breast cancer patients. *Psycho-Oncology, 21*, 100-107. doi:10.1002/pon.1873

Newman, L. A. (2009). Epidemiology of locally advanced breast cancer. *Seminars in Radiation Oncology, 19*, 195-203. doi:10.1016/j.semradonc.2009.05.003

Nisenzon, A. N., Robinson, M. E., Bowers, D., Banou, E., Malaty, I., & Okun, M. S. (2011). Measurement of patient-centered outcomes in Parkinson's disease: What do patients really want from their treatment? *Parkinsonism & Related Disorders, 17*, 89-94. doi:10.1016/j.parkreldis.2010.09.005

Noal, S., Levy, C., Hardouin, A., Rieux, C., Heutte, N., Ségura, C., . . . Delcambre, C. (2011). One-year longitudinal study of fatigue, cognitive functions, and quality of life after adjuvant radiotherapy for breast cancer. *International Journal of Radiation Oncology* Biology* Physics, 81*, 795-803. doi:10.1016/j.ijrobp.2010.06.037

Okajima, I., Komada, Y., & Inoue, Y. (2011). A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. *Sleep and Biological Rhythms, 9*, 24-34. doi:10.1111/j.1479-8425.2010.00481.x

Okuyama, T., Wang, X. S., Akechi, T., Mendoza, T. R., Hosaka, T., Cleeland, C. S., & Uchitomi, Y. (2003). Japanese version of the MD Anderson Symptom Inventory: A validation study. *Journal of Pain and Symptom Management, 26*, 1093-1104. doi:10.1016/j.jpainsymman.2003.05.003

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. *Frontiers in Oncology, 5*, 1-19. doi:10.3389/fonc.2015.00059

Ozaslan, C., & Kuru, B. (2004). Lymphedema after treatment of breast cancer. *The American Journal of Surgery, 187*, 69-72. doi:10.1016/j.amjsurg.2002.12.003

Palesh, O. G., Collie, K., Batiuchok, D., Tilston, J., Koopman, C., Perlis, M. L., . . . Spiegel, D. (2007). A longitudinal study of depression, pain, and stress as predictors of sleep disturbance among women with metastatic breast cancer. *Biological Psychology, 75*, 37-44. doi:10.1016/j.biopsycho.2006.11.002

Patel, S. K., Wong, A. L., Wong, F. L., Breen, E. C., Hurria, A., Smith, M., . . . Somlo, G. (2015). Inflammatory biomarkers, comorbidity, and neurocognition in women with newly diagnosed breast cancer. *Journal of the National Cancer Institute, 107*, 1-7. doi:10.1093/jnci/djv131

Perry, A., & Schmidt, R. E. (2006). Cancer therapy-associated CNS neuropathology: An update and review of the literature. *Acta Neuropathologica, 111*, 197-212. doi:10.1007/s00401-005-0023-y

Phillips, K. M., Jim, H. S., Small, B. J., Laronga, C., Andrykowski, M. A., & Jacobsen, P. B. (2012). Cognitive functioning after cancer treatment: A 3-year longitudinal comparison of breast cancer survivors treated with chemotherapy or radiation and noncancer controls. *Cancer, 118*, 1925-1932. doi:10.1002/cncr.26432

Pochedly, C. (1977). Neurotoxicity due to CNS therapy for leukemia. *Medical and Pediatric Oncology, 3*, 101-115. doi:10.1002/mpo.2950030114

Poppelreuter, M., Weis, J., Külz, A., Tucha, O., Lange, K., & Bartsch, H. (2004). Cognitive dysfunction and subjective complaints of cancer patients: A cross-sectional study in a cancer rehabilitation centre. *European Journal of Cancer, 40*, 43-49. doi:10.1016/j.ejca.2003.08.001

Portenoy, R. K., & Lesage, P. (1999). Management of cancer pain. *The Lancet, 353*, 1695-1700. doi:10.1016/S0140-6736(99)01310-0

Portenoy, R. K., Thaler, H., Kornblith, A., Lepore, J. M., Friedlander-Klar, H., Coyle, N., . . . Hoskins, W. (1994). Symptom prevalence, characteristics and distress in a cancer population. *Quality of Life Research, 3*, 183-189. doi:10.1007/BF00435383

Portenoy, R. K., Thaler, H. T., Kornblith, A. B., Lepore, J. M., Friedlander-Klar, H., Kiyasu, E., . . . Norton, L. (1994). The Memorial Symptom Assessment Scale: An instrument for the evaluation of symptom prevalence, characteristics and distress. *European Journal of Cancer, 30*, 1326-1336. doi:10.1016/0959-8049(94)90182-1

Pullens, M. J., De Vries, J., & Roukema, J. A. (2010). Subjective cognitive dysfunction in breast cancer patients: A systematic review. *Psycho-Oncology, 19*, 1127-1138. doi:10.1002/pon.1673

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, 1783-1789. doi:10.1002/pon.3214

Quesnel, C., Savard, J., & Ivers, H. (2009). Cognitive impairments associated with breast
 cancer treatments: Results from a longitudinal study. *Breast Cancer Research and
 Treatment, 116*, 113-123. doi:10.1007/s10549-008-0114-2

Rao, J. K., Anderson, L. A., Inui, T. S., & Frankel, R. M. (2007). Communication
 interventions make a difference in conversations between physicians and patients:
 A systematic review of the evidence. *Medical Care, 45*, 340-349.
 doi:10.1097/01.mlr.0000254516.04961.d5

Rathert, C., Wyrwich, M. D., & Boren, S. A. (2013). Patient-centered care and outcomes:
 A systematic review of the literature. *Medical Care Research and Review, 70*,
 351-379. doi:10.1177/1077558712465774

Reed, E., Simmonds, P., Haviland, J., & Corner, J. (2012). Quality of life and experience
 of care in women with metastatic breast cancer: A cross-sectional survey. *Journal
 of Pain and Symptom Management, 43*, 747-758.
 doi:10.1016/j.jpainsymman.2011.05.005

Reeve, B. B., Mitchell, S. A., Dueck, A. C., Basch, E., Cella, D., Reilly, C. M., . . . Fisch,
 M. J. (2014). Recommended patient-reported core set of symptoms to measure in
 adult cancer treatment trials. *Journal of the National Cancer Institute, 106*, 1-8.
 doi:10.1093/jnci/dju129

Reilly, C. M., Bruner, D. W., Mitchell, S. A., Minasian, L. M., Basch, E., Dueck, A. C., . . . Reeve, B. B. (2013). A literature synthesis of symptom prevalence and severity in persons receiving active cancer treatment. *Supportive Care in Cancer, 21*, 1525-1550. doi:10.1007/s00520-012-1688-0

Reyes-Gibby, C. C., Morrow, P. K., Buzdar, A., & Shete, S. (2009). Chemotherapy-induced peripheral neuropathy as a predictor of neuropathic pain in breast cancer patients previously treated with paclitaxel. *The Journal of Pain, 10*, 1146-1150. doi:10.1016/j.jpain.2009.04.006

Ridner, S. H. (2005). Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. *Supportive Care in Cancer, 13*, 904-911. doi:10.1007/s00520-005-0810-y

Robinson, J. H., Callister, L. C., Berry, J. A., & Dearing, K. A. (2008). Patient-centered care and adherence: Definitions and applications to improve outcomes. *Journal of the American Academy of Nurse Practitioners, 20*, 600-607. doi:10.1111/j.1745-7599.2008.00360.x

Robinson, M. E., Brown, J. L., George, S. Z., Edwards, P. S., Atchison, J. W., Hirsh, A. T., . . . Fillingim, R. B. (2005). Multidimensional success criteria and expectations for treatment of chronic pain: The patient perspective. *Pain Medicine, 6*, 336-345. doi:10.1111/j.1526-4637.2005.00059.x

Rollnick, S., & Miller, W. R. (1995). What is motivational interviewing? *Behavioural and Cognitive Psychotherapy, 23*, 325-334. doi:10.1017/S135246580001643X

Safran, D. G., Karp, M., Coltin, K., Chang, H., Li, A., Ogren, J., & Rogers, W. H. (2006). Measuring patients' experiences with individual primary care physicians. *Journal of General Internal Medicine, 21*, 13-21. doi:10.1111/j.1525-1497.2005.00311.x

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

Schagen, S. B., Das, E., & van Dam, F. S. (2009). The influence of priming and pre-existing knowledge of chemotherapy-associated cognitive complaints on the reporting of such complaints in breast cancer patients. *Psycho-Oncology, 18*, 674-678. doi:10.1002/pon.1454

Schagen, S. B., Das, E., & Vermeulen, I. (2012). Information about chemotherapy-associated cognitive problems contributes to cognitive problems in cancer patients. *Psycho-Oncology, 21*, 1132-1135. doi:10.1002/pon.2011

Schagen, S. B., Hamburger, H. L., Muller, M. J., Boogerd, W., & van Dam, F. S. (2001). Neurophysiological evaluation of late effects of adjuvant high-dose chemotherapy on cognitive function. *Journal of Neuro-Oncology, 51*, 159-165. doi:10.1023/A:1010635229762

Schagen, S. B., Muller, M. J., Boogerd, W., & van Dam, F. S. M. (2002). Cognitive dysfunction and chemotherapy: Neuropsychological findings in perspective. *Clinical Breast Cancer, 3*, S100-S108. doi:10.3816/CBC.2002.s.020

Schagen, S. B., van Dam, F. S., Muller, M. J., Boogerd, W., Lindeboom, J., & Bruning, P. F. (1999). Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer, 85*, 640-650. doi:10.1002/(SICI)1097-0142(19990201)85:3<640::AID-CNCR14>3.0.CO;2-G

Schiepers, O. J., Wichers, M. C., & Maes, M. (2005). Cytokines and major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29*, 201-217. doi:10.1016/j.pnpbp.2004.11.003

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 Oncologica, 48*, 76-85. doi:10.1080/02841860802314738

Seigers, R., & Fardell, J. E. (2011). Neurobiological basis of chemotherapy-induced cognitive impairment: A review of rodent research. *Neuroscience and Biobehavioral Reviews, 35*, 729-741. doi:10.1016/j.neubiorev.2010.09.006

Seruga, B., Zhang, H., Bernstein, L. J., & Tannock, I. F. (2008). Cytokines and their relationship to the symptoms and outcome of cancer. *Nature Reviews. Cancer, 8*, 887-899. doi:10.1038/nrc2507

Shibayama, O., Yoshiuchi, K., Inagaki, M., Matsuoka, Y., Yoshikawa, E., Sugawara, Y., . . . Murakami, K. (2014). Association between adjuvant regional radiotherapy and cognitive function in breast cancer patients treated with conservation therapy. *Cancer Medicine, 3*, 702-709. doi:10.1002/cam4.174

Shilling, V., & Jenkins, V. (2007). Self-reported cognitive problems in women receiving adjuvant therapy for breast cancer. *European Journal of Oncology Nursing, 11*, 6-15. doi:10.1016/j.ejon.2006.02.005

Shilling, V., Jenkins, V., Morris, R., Deutsch, G., & Bloomfield, D. (2005). The effects of adjuvant chemotherapy on cognition in women with breast cancer—preliminary results of an observational longitudinal study. *The Breast, 14*, 142-150. doi:10.1016/j.breast.2004.10.004

Sievers, C., Sämann, P., Pfister, H., Dimopoulou, C., Czisch, M., Roemmler, J., . . . Zihl, J. (2012). Cognitive function in acromegaly: Description and brain volumetric correlates. *Pituitary, 15*, 350-357. doi:10.1007/s11102-011-0326-z

Silberfarb, P. M. (1983). Chemotherapy and cognitive defects in cancer patients. *Annual Review of Medicine, 34*, 35-46. doi:10.1146/annurev.me.34.020183.000343

Small, B. J., Rawson, K. S., Walsh, E., Jim, H. S., Hughes, T. F., Iser, L., . . . Jacobsen, P. B. (2011). Catechol-O-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors. *Cancer, 117*, 1369-1376. doi:10.1002/cncr.25685

Smerage, J. B., Barlow, W. E., Hortobagyi, G. N., Winer, E. P., Leyland-Jones, B., Srkalovic, G., . . . Lew, D. L. (2014). Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *Journal of Clinical Oncology, 32*, 3483-3489. doi:10.1200/JCO.2014.56.2561

Stachler, R. J., Schultz, L. R., Nerenz, D., & Yaremchuk, K. L. (2014). PROMIS
evaluation for head and neck cancer patients: A comprehensive quality-of-life
outcomes assessment tool. *The Laryngoscope, 124*, 1368-1376.
doi:10.1002/lary.23853

Starkweather, A. R., Lyon, D. E., Elswick Jr, R., Montpetit, A. J., Conley, Y., & McCain,
N. L. (2013). A conceptual model of psychoneurological symptom cluster
variation in women with breast cancer: Bringing nursing research to personalized
medicine. *Current Pharmacogenomics and Personalized Medicine, 11*, 224-230.
doi:10.2174/18756921113119990004

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the
reserve concept. *Journal of the International Neuropsychological Society, 8*, 448-
460. doi:10.1017.S1355617701020240

Stewart, A., Bielajew, C., Collins, B., Parkinson, M., & Tomiak, E. (2006). A meta-
analysis of the neuropsychological effects of adjuvant chemotherapy treatment in
women treated for breast cancer. *The Clinical Neuropsychologist, 20*, 76-89.
doi:10.1080/138540491005875

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*, 122-130. doi:10.1002/pon.1210

Stewart, M., Brown, J., Donner, A., Oates, J., Weston, W., & Jordan, J. (2000). The
impact of patient-centered care on outcomes. *The Journal of Family Practice, 49*,
796-804.

Swain, S. M., & Arezzo, J. C. (2008). Neuropathy associated with microtubule inhibitors: Diagnosis, incidence, and management. *Clinical Advances in Hematology and Oncology, 6*, 455-467.

Tukey, J. W. (1962). The future of data analysis. *The Annals of Mathematical Statistics*, 1-67.

Valentine, A. D., & Meyers, C. A. (2001). Cognitive and mood disturbance as causes and symptoms of fatigue in cancer patients. *Cancer, 92*, 1694-1698. doi:10.1002/1097-0142(20010915)92:6+<1694::AID-CNCR1499>3.0.CO;2-S

van Dam, F. S., Boogerd, W., Schagen, S. B., Muller, M. J., Fortuyn, M. E. D., vd Wall, E., & Rodenhuis, S. (1998). Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: High-dose versus standard-dose chemotherapy. *Journal of the National Cancer Institute, 90*, 210-218. doi:10.1093/jnci/90.3.210

Van den Beuken-van Everdingen, M., De Rijke, J., Kessels, A., Schouten, H., Van Kleef, M., & Patijn, J. (2007). Prevalence of pain in patients with cancer: A systematic review of the past 40 years. *Annals of Oncology, 18*, 1437-1449. doi:10.1093/annonc/mdm056

Vearncombe, K. J., Rolfe, M., Wright, M., Pachana, N. A., Andrew, B., & Beadle, G. (2009). Predictors of cognitive decline after chemotherapy in breast cancer patients. *Journal of the International Neuropsychological Society, 15*, 951-962. doi:10.1017/S1355617709990567

Von Ah, D. (2015). Cognitive changes associated with cancer and cancer treatment: State of the science. *Clinical Journal of Oncology Nursing, 19*, 47-56. doi:10.1188/15.CJON.19-01AP

Von Ah, D., & Tallman, E. F. (2015). Perceived cognitive function in breast cancer survivors: Evaluating relationships with objective cognitive performance and other symptoms using the Functional Assessment of Cancer Therapy Cognitive scale (FACT-Cog). *Journal of Pain and Symptom Management, 49*, 697-706. doi:10.1016/j.jpainsymman.2014.08.012

Wagner, L. I., Schink, J., Bass, M., Patel, S., Diaz, M. V., Rothrock, N., . . . Rosen, S. (2015). Bringing PROMIS to practice: Brief and precise symptom screening in ambulatory cancer care. *Cancer, 121*, 927-934. doi:10.1002/cncr.29104

Walsh, D., & Rybicki, L. (2006). Symptom clustering in advanced cancer. *Supportive Care in Cancer, 14*, 831-836. doi:10.1007/s00520-005-0899-z

Wang, X. S., Laudico, A. V., Guo, H., Mendoza, T. R., Matsuda, M. L., Yosuico, V. D., . . . Cleeland, C. S. (2006). Filipino version of the MD Anderson Symptom Inventory: Validation and multisymptom measurement in cancer patients. *Journal of Pain and Symptom Management, 31*, 542-552. doi:10.1016/j.jpainsymman.2005.11.011

Wang, X. S., Shi, Q., Williams, L. A., Mao, L., Cleeland, C. S., Komaki, R. R., . . . Liao, Z. (2010). Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. *Brain, Behavior, and Immunity, 24*, 968-974. doi:10.1016/j.bbi.2010.03.009

Wang, X. S., Wang, Y., Guo, H., Mendoza, T. R., Hao, X. S., & Cleeland, C. S. (2004). Chinese version of the MD Anderson symptom inventory. *Cancer, 101*, 1890-1901. doi:10.1002/cncr.20448

Warner, R. M. (2013). *Applied statistics: From bivariate to multivariate techniques* (2nd ed.). Thousand Oaks, California: Sage Publications, Inc.

Wefel, J. S., Collins, R., & Kayl, A. E. (2008). Cognitive dysfunction related to chemotherapy and biological response modifiers. In C. Meyers & J. Perry (Eds.), *Cognition and cancer.* (pp. 97-114). Cambridge, UK: Cambridge University Press.

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*, 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*, 3348-3356. doi:10.1002/cncr.25098

Weis, J., Poppelreuter, M., & Bartsch, H. (2009). Cognitive deficits as long-term side-effects of adjuvant therapy in breast cancer patients:'Subjective'complaints and 'objective'neuropsychological test results. *Psycho-Oncology, 18*, 775-782. doi:10.1002/pon.1472

Weiss, H. D., Walker, M. D., & Wiernik, P. H. (1974). Neurotoxicity of commonly used antineoplastic agents. *The New England Journal of Medicine, 291*, 75-81. doi:10.1056/NEJM197407112910205

Welsh, K. A., Butters, N., Hughes, J. P., Mohs, R. C., & Heyman, A. (1992). Detection and staging of dementia in alzheimer's disease: Use of the neuropsychological measures developed for the consortium to establish a registry for alzheimer's disease. *Archives of Neurology, 49*, 448-452. doi:10.1001/archneur.1992.00530290030008

Whalley, L. J., Deary, I. J., Appleton, C. L., & Starr, J. M. (2004). Cognitive reserve and the neurobiology of cognitive aging. *Ageing Research Reviews, 3*, 369-382. doi:10.1016/j.arr.2004.05.001

Wolkowitz, O. M., Mellon, S. H., Epel, E. S., Lin, J., Dhabhar, F. S., Su, Y., . . . Kupferman, E. (2011). Leukocyte telomere length in major depression: Correlations with chronicity, inflammation and oxidative stress-preliminary findings. *PloS one, 6*, 1-10. doi:10.1371/journal.pone.0017837

Wood, L. J., & Weymann, K. (2013). Inflammation and neural signaling: Etiologic mechanisms of the cancer treatment-related symptom cluster. *Current Opinion in Supportive and Palliative Care, 7*, 54-59. doi:10.1097/SPC.0b013e32835dabe3

Yennurajalingam, S., Kwon, J. H., Urbauer, D. L., Hui, D., Reyes-Gibby, C. C., & Bruera, E. (2013). Consistency of symptom clusters among advanced cancer patients seen at an outpatient supportive care clinic in a tertiary cancer center. *Palliative & Supportive Care, 11*, 473-480. doi:10.1017/s1478951512000879

Yi, T. I., Kim, B. K., Ha, S. A., & Lim, J. Y. (2014). The relationships between determination of treatment success and emotional factors in patients with chronic musculoskeletal pain. *Annals of Rehabilitation Medicine, 38*, 77-83. doi:10.5535/arm.2014.38.1.77

Yost, K. J., Eton, D. T., Garcia, S. F., & Cella, D. (2011). Minimally important
differences were estimated for six Patient-Reported Outcomes Measurement
Information System-Cancer scales in advanced-stage cancer patients. *Journal of
Clinical Epidemiology, 64*, 507-516. doi:10.1016/j.jclinepi.2010.11.018

Zeppieri, G., Lentz, T. A., Atchison, J. W., Indelicato, P. A., Moser, M. W., Vincent, K.
R., & George, S. Z. (2012). Preliminary results of patient-defined success criteria
for individuals with musculoskeletal pain in outpatient physical therapy settings.
Archives of Physical Medicine and Rehabilitation, 93, 434-440.
doi:10.1016/j.apmr.2011.10.007

Zwart, W., Terra, H., Linn, S. C., & Schagen, S. B. (2015). Cognitive effects of
endocrine therapy for breast cancer: Keep calm and carry on? *Nature Reviews
Clinical Oncology, 12*, 597-606. doi:10.1038/nrclinonc.2015.124

APPENDICES

Appendix A   Measures

Cognitive Screening for Patients

I would like to ask you some questions that ask you to use your memory. I am going to

name three objects. Please wait until I say all three words, then repeat them. Remember

what they are because I am going to ask you to name them again in a few minutes. Please

repeat these words for me: APPLE—TABLE—PENNY. (Interviewer may repeat words

3 times if necessary but repetition not scored.)

Did patient correctly repeat all three words?   *Yes*   *No*

	Incorrect	Correct
1. What year is this?	0	1
2. What month is this?	0	1
3. What day of the week?	0	1
What were the three objects I asked you to remember?		
4. *Apple* =	0	1
5. *Table* =	0	1
6. *Penny* =	0	1

Demographic Information

1. What race or ethnicity to you consider yourself to be?

    1 = non-Hispanic White

    2 = African American/Black

    3 = Asian

    4 = Hispanic

    5 = Native Hawaiian or other Pacific Islander

    6 = American Indian/Alaskan Native

    7 = Other

2. What was the last grade you completed in school?

3. What is your marital status?

    1 = Married

    2 = Living with partner

    3 = Separated

    4 = Single

    5 = Divorced

    6 = Widowed

4. Thinking about your yearly household income, before taxes, is it $21,000 or higher?

	1 = $0 - $10,999
if no, Is it $11,000 or higher?	2 = $11,000 - $20,999
if yes, Is it $31,000 or higher?	3 = $21,000 - $30,999
if yes, Is it $41,000 or higher?	4 = $31,000 - $50,999
if yes, Is it $51,000 or higher?	5 = $50,000 - $99,999
if yes, Is it $100,000 or more?	6 = $100,000 +

5. What is your current employment status?

1 = Employed full-time

2 = Employed part-time

3 = Student

4 = Homemaker

5 = Retired

6 = Unemployed, looking for paid work

7 = Unemployed due to disability

8 = Other

Information Collected from Medical Record

(1) Age: _____

(2) Date(s) of Breast Cancer Diagnosis and Disease Stage at Diagnosis:

    a. _____/_____/_____; Disease Stage (circle one): 0   1   2   3   4

    b. _____/_____/_____; Disease Stage (circle one): 0   1   2   3   4

    c. _____/_____/_____; Disease Stage (circle one): 0   1   2   3   4

Treatments for Breast Cancer (check all that have been received): 1 = yes, 0 = no

☐ Mastectomy
☐ Lumpectomy
☐ Surgery to remove metastases
☐ Bilateral oophorectomy
☐ Other surgery (specify):_____
☐ Chemotherapy
☐ Radiation
   Did the patient receive radiation to the brain? ___yes   ___no
☐ Targeted therapy (e.g., trastuzumab, bevacizumab)
☐ Hormonal therapy (e.g., Tamoxifen)
☐ Bisphosphonate/s
☐ Other (please specify): _____

Medical Conditions

I am going to read you a list of chronic health problems that some people have. Please tell me if a doctor or another health care worker has diagnosed you with or treated you for one of the following medical problems in the past 3 years.

No = 0	Yes = 1	Don't know or refused to answer = 99

1. In the past 3 years, have you been diagnosed or treated for asthma, emphysema, or chronic bronchitis
2. In the past 3 years, have you been diagnosed or treated for high blood pressure or hypertension
3. High blood sugar or diabetes
4. Arthritis or rheumatism (inflammation of the joints)
5. Angina, heart failure, or other types of heart disease
6. Stroke, seizures, Parkinson's disease, or another neurological condition
7. Liver disease
8. Kidney or renal disease
9. Cancer other than breast cancer or skin cancer

   if Yes [List types: _____]

PROMIS Applied Cognition – General Concerns

In the past 7 days…

	Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Very Often (Several times a day)
1. My thinking has been slow…	5	4	3	2	1
2. It has seemed like my brain was not working as well as usual…	5	4	3	2	1
3. I have had to work harder than usual to keep track of what I was doing…	5	4	3	2	1
4. I have had trouble shifting back and forth between different activities that require thinking…	5	4	3	2	1

PROMIS Emotional Distress – Depression

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
1. I felt worthless…	1	2	3	4	5
2. I felt helpless…	1	2	3	4	5
3. I felt depressed…	1	2	3	4	5
4. I felt hopeless…	1	2	3	4	5

PROMIS Emotional Distress – Anxiety

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
1. I felt fearful…	1	2	3	4	5
2. I found it hard to focus on anything other than my anxiety…	1	2	3	4	5

3. My worries overwhelmed me…	1	2	3	4	5
4. I felt uneasy…	1	2	3	4	5

PROMIS Fatigue

During the past 7 days…

	Not at all	A little bit	Somewhat	Quite a bit	Very much
1. I feel fatigued…	1	2	3	4	5
2. I have trouble starting things because I am tired…	1	2	3	4	5

In the past 7 days…

	Not at all	A little bit	Somewhat	Quite a bit	Very much
3. How run-down did	1	2	3	4	5

you feel on average?				
4. How fatigued were you on average?	1	2	3	4	5

PROMIS Sleep Disturbance

In the past 7 days…

1. My sleep quality was…

Very poor = 1   Poor = 2   Fair = 3   Good = 4   Very Good = 5

	Not at all	A little bit	Somewhat	Quite a bit	Very much
2. My sleep was refreshing…	1	2	3	4	5
3. I had a problem with my sleep…	1	2	3	4	5
4. I had difficulty falling asleep…	1	2	3	4	5

PROMIS Pain Intensity

In the past 7 days…

	No pain	Mild	Moderate	Severe	Very Severe
1. How intense was your pain at its worst?	1	2	3	4	5
2. How intense was your average pain?	1	2	3	4	5
3. What is your level of pain right now?	1	2	3	4	5

MSAS Selected items and Carpenter et al. (1998)

1. Have you had **nausea** in the past week?

    No = 0, skip to question 2.   Yes = 1

    how often did you have it?

      Rarely = 1   Occasionally = 2   Frequently = 3   Almost constantly = 4

    how severe was it usually?

      Slight = 1   Moderate = 2   Severe = 3   Very Severe = 4

    how much did it distress or bother you?

     Not at all = 0   A little bit = 1   Somewhat = 2   Quite a bit = 3   Very much = 4

2. Have you had **numbness/tingling in your hands/feet** in the past week?

    No = 0, skip to question 3.   Yes = 1

    how often did you have it?

      Rarely = 1   Occasionally = 2   Frequently = 3   Almost constantly = 4

    how severe was it usually?

      Slight = 1   Moderate = 2   Severe = 3   Very Severe =4

    how much did it distress or bother you?

     Not at all = 0   A little bit = 1   Somewhat = 2   Quite a bit = 3   Very much = 4

3. Have you had **swelling of arms or legs** in the past week?

    No = 0, skip to question 4.   Yes = 1

    how severe was it usually?

    Slight = 1   Moderate = 2   Severe = 3   Very Severe = 4

    how much did it distress or bother you?

    Not at all = 0   A little bit = 1   Somewhat = 2   Quite a bit = 3   Very much = 4

4. Have you experienced **hot flashes** in the past 2 weeks?

    No = 0, skip to next measure.   Yes = 1

    how severe were they usually?

    Not at all = 0   Slightly = 1   Moderately = 2   Quite a bit = 3   Extremely = 4

    how much did the hot flashes bother you on a scale from 0 to 10, 0 being not at all bothered and 10 being extremely bothered?

0	1	2	3	4	5	6	7	8	9	10

    Not at all   Extremely
    bothered   bothered

PCOQ-Revised for metastatic breast cancer

Many people experience pain, fatigue (i.e. feeling tired), anxiety, and other symptoms as a result of their medical condition. We would like to understand how you have been impacted in each of these areas. We would also like to learn more about what you want your treatment to do for you.

First, we would like to know your <u>USUAL</u> levels of pain, fatigue, anxiety, and other symptoms.

On a scale of 0 (none) to 10 (worst imaginable) please indicate your <u>usual level</u> (during the past week) of…

Pain	_____	Swelling of arms or legs	_____
Fatigue (or tiredness)	_____	Nausea	_____
Anxiety	_____	Hot flashes	_____
Sadness	_____	Sleep problems	_____
Numbness/tingling in hands/feet	_____	Attention/thinking/memory problems	_____

Patients understandably want their treatment to result in desired or ideal outcomes. Unfortunately, available treatments do not always produce desired outcomes. Therefore, it is important for us to understand what treatment outcomes you would consider sucessful.

On a scale of 0 (none) to 10 (worst imaginable) please indicate the level each of these areas would have to be at for you to consider treatment <u>SUCCESSFUL</u>.

Pain	_____	Swelling of arms or legs	_____
Fatigue (or tiredness)	_____	Nausea	_____
Anxiety	_____	Hot flashes	_____
Sadness	_____	Sleep problems	_____
Numbness/tingling in hands/feet	_____	Attention/thinking/memory problems	_____

Now, we would like to know what you <u>EXPECT</u> your treatment to do for you.

On a scale of 0 (none) to 10 (worst imaginable) please indicate the levels you expect following treatment.

Pain	_____	Swelling of arms or legs	_____
Fatigue (or tiredness)	_____	Nausea	_____
Anxiety	_____	Hot flashes	_____
Sadness	_____	Sleep problems	_____
Numbness/tingling in hands/feet	_____	Attention/thinking/memory problems	_____

Other (please specify)_____ _____

Say, "Is there any other symptom that you have experienced? What level of this symptom do you expect following treatment?"

Finally, we would like to understand how <u>IMPORTANT</u> it is for you to see improvement in your pain, fatigue, anxiety, and other symptoms following treatment.

On a scale of 0 (not at all important) to 10 (most important) please indicate how important it is for you to see improvement in your…

Pain	_____	Swelling of arms or legs	_____
Fatigue (or tiredness)	_____	Nausea	_____
Anxiety	_____	Hot flashes	_____
Sadness	_____	Sleep problems	_____
Numbness/tingling in hands/feet	_____	Attention/thinking/memory problems	_____

Appendix B   Figures
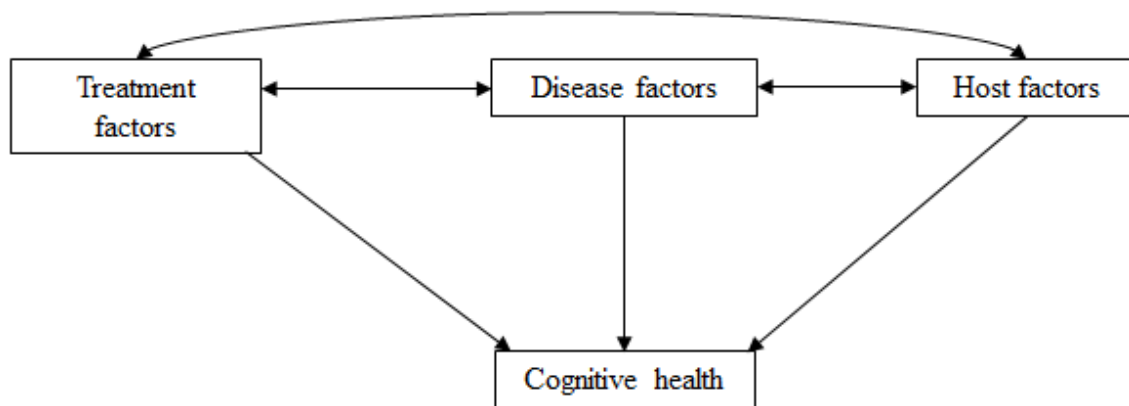
Figure 1. Model of Interacting Factors Involved in Cognitive Change Associated with

Cancer and Its Treatment.

Figure 2. Trajectories of Cognitive Change over Time. Adapted from 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, 30*, 3675-3686. doi: 10.1200/jco.2012.43.0116.

Figure 3. Hypothesized Dendrogram of a Symptom Cluster Involving Cognitive Complaints in Metastatic Breast Cancer Patients.

```
┌─────────────────────────────────────────────────────────────────────────────┐
│ Medical records screened to identify potentially eligible patients and        │
│ treating physicians contacted to confirm potential eligibility                │
└─────────────────────────────────────────────────────────────────────────────┘
                                        │
┌─────────────────────────────────────────────────────────────────────────────┐
│ Potentially eligible patients mailed an introductory letter and consent form  │
│ (N = 107)                                                                     │
└─────────────────────────────────────────────────────────────────────────────┘

┌──────────────────────────────────────┐
│ Could not be reached by phone (N = 12)│
└──────────────────────────────────────┘

┌─────────────────────────────────────────────────────────────────────────────┐
│ 1-2 weeks after mailing, RA contacted patients to describe study, administer  │
│ cognitive screener, and obtain informed consent (N = 95)                      │
└─────────────────────────────────────────────────────────────────────────────┘

┌──────────────────────────────────────┐   ┌────────────────────────────────────────────────┐
│ Those with 3+ errors on cognitive     │   │ Refused participation (N = 10)                  │
│ screener were ineligible (N = 2)       │   │ Reason:                                         │
└──────────────────────────────────────┘   │  • Too busy (N = 5)                             │
                                            │  • Too ill (N = 3)                              │
                                            │  • Already participating in another study (N = 1)│
                                            │  • Too emotionally difficult (N = 1)            │
                                            └────────────────────────────────────────────────┘

┌─────────────────────────────────────────────────────────────────────────────┐
│ 45-minute phone assessment scheduled for eligible, consenting patients (N = 83)│
└─────────────────────────────────────────────────────────────────────────────┘

┌──────────────────────────────────────┐
│ Unable to reach for interview (N = 3) │
└──────────────────────────────────────┘

                    ┌──────────────────────────────────────┐
                    │ Completed phone assessment (N = 80)   │
                    └──────────────────────────────────────┘
```
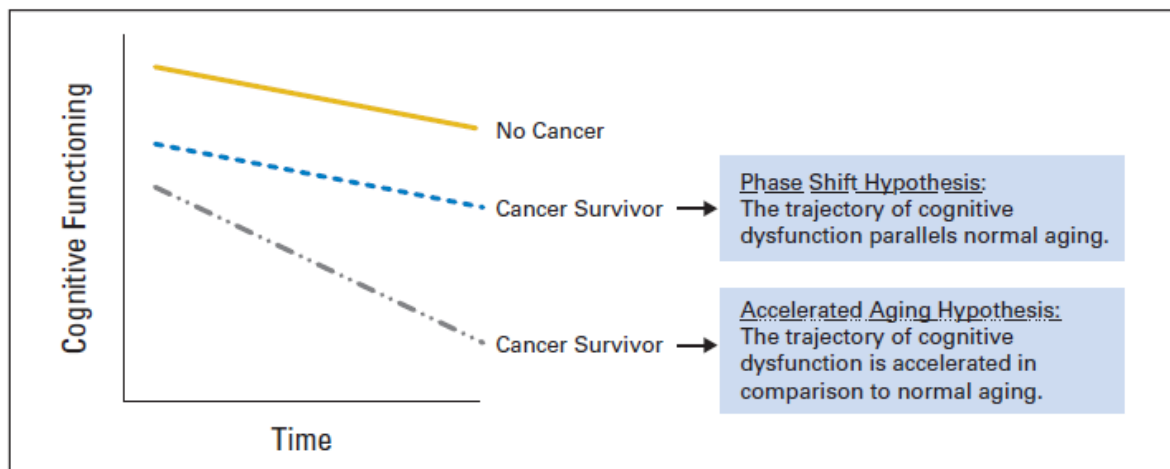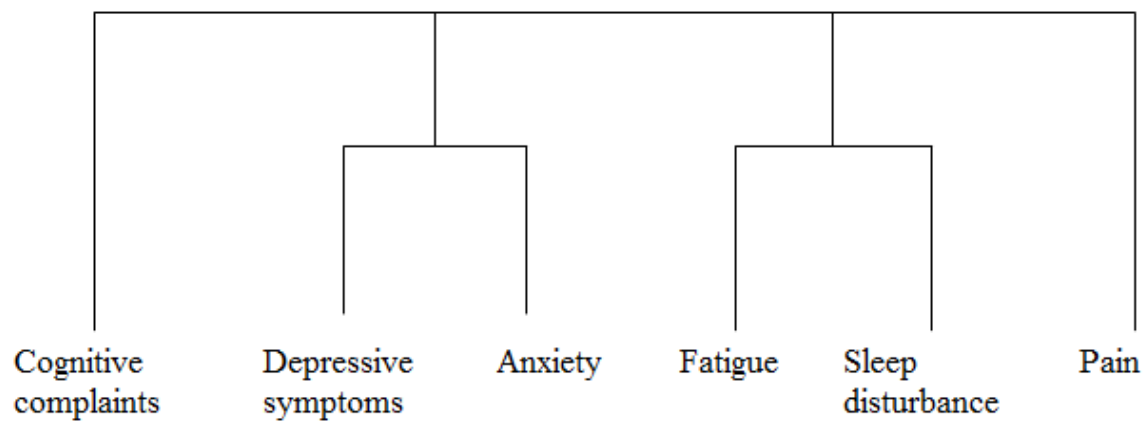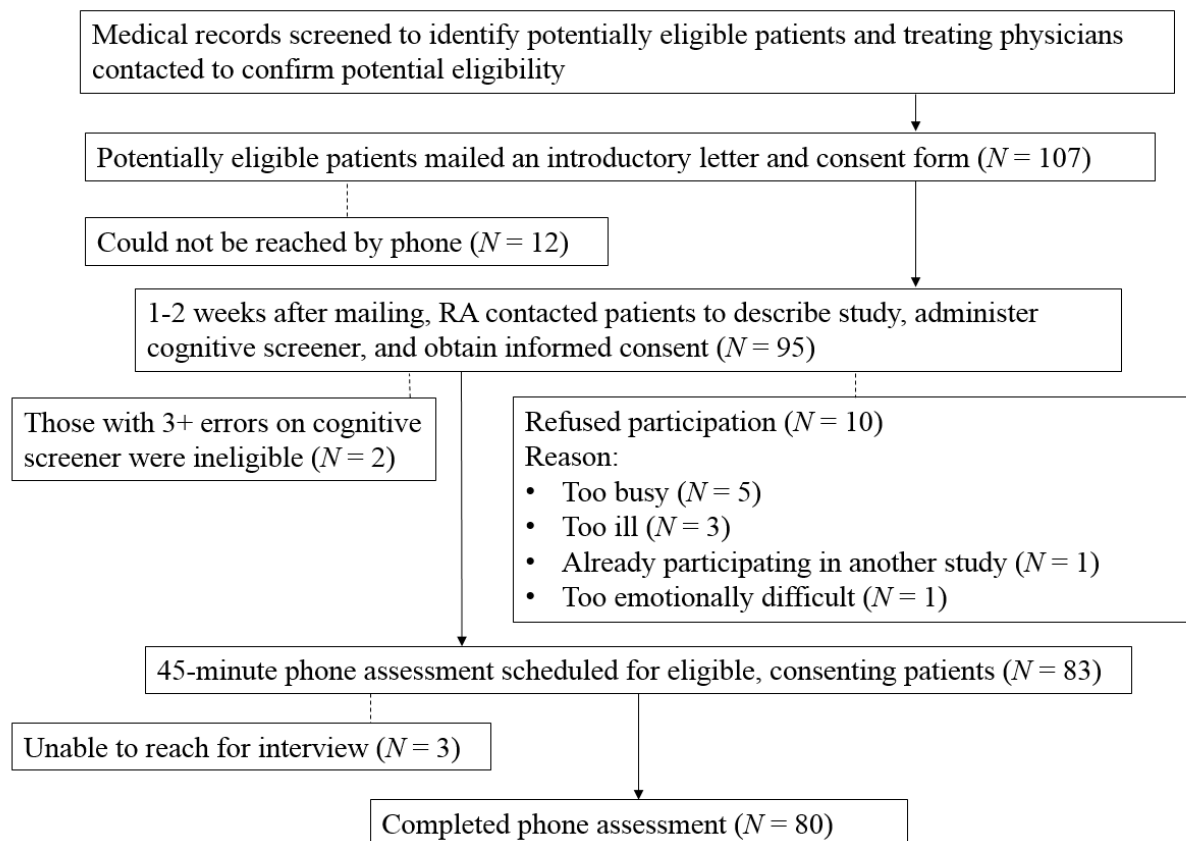
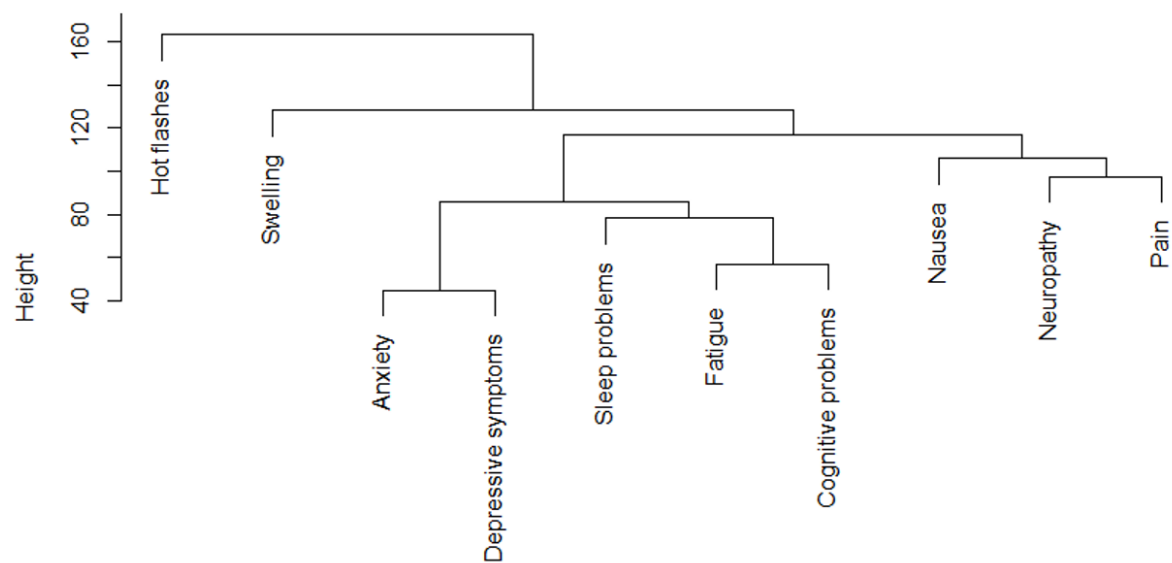Figure 4. Flow Chart of Study Procedures.

Figure 5. Cluster Dendrogram. One value each for swelling, anxiety, and depressive symptoms was Winsorized prior to this analysis.
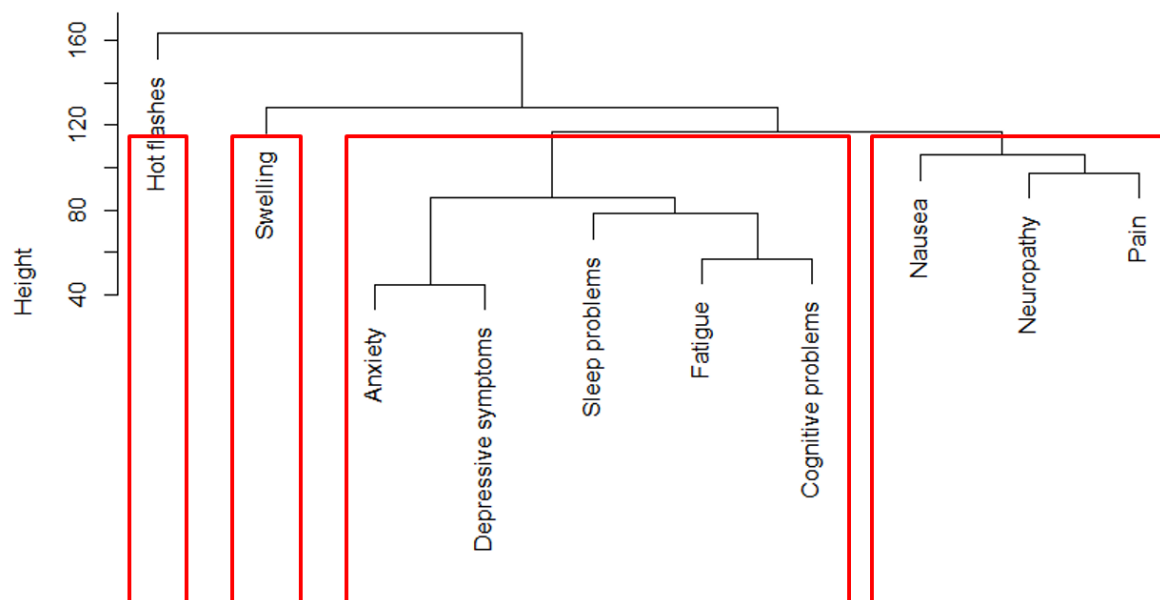
Figure 6. Cluster Dendrogram with Clusters Boxed. One value each for swelling,

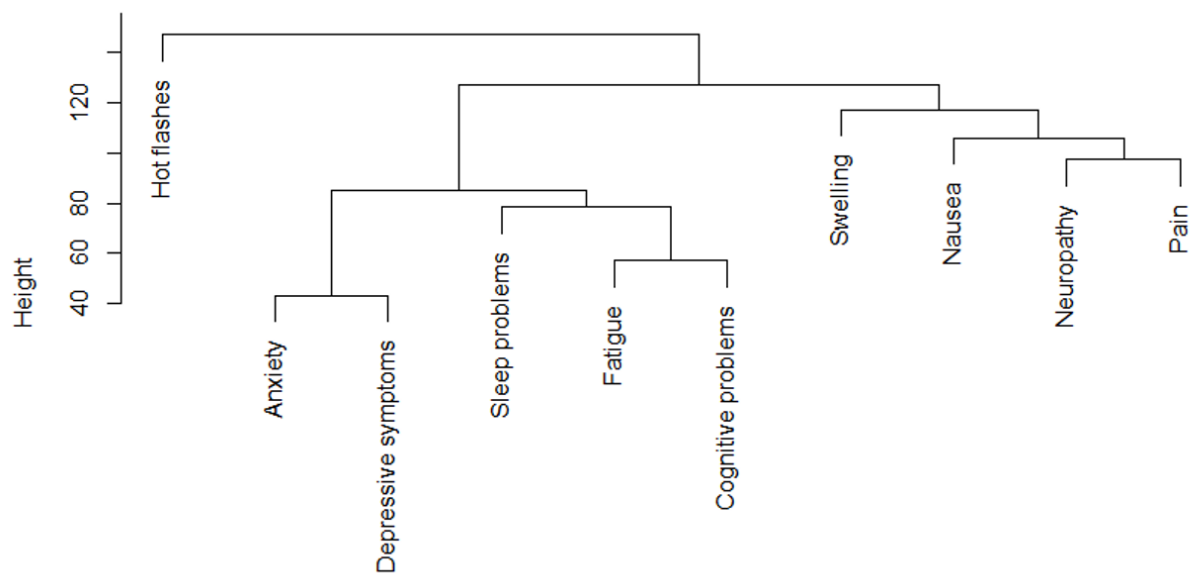anxiety, and depressive symptoms was Winsorized prior to this analysis.

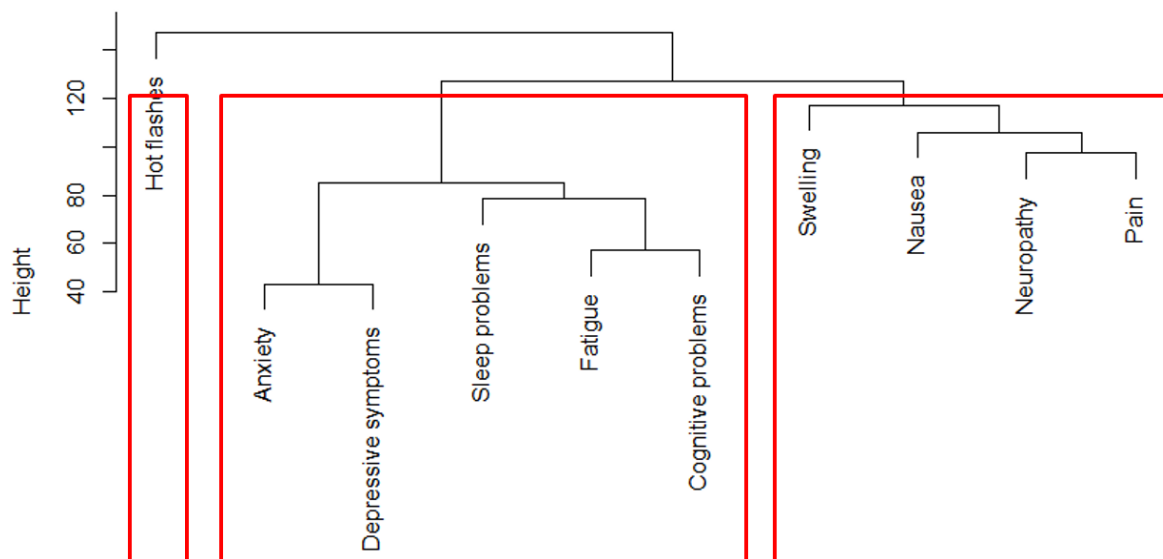Figure 7. Cluster Dendrogram using non-Winsorized Variables.

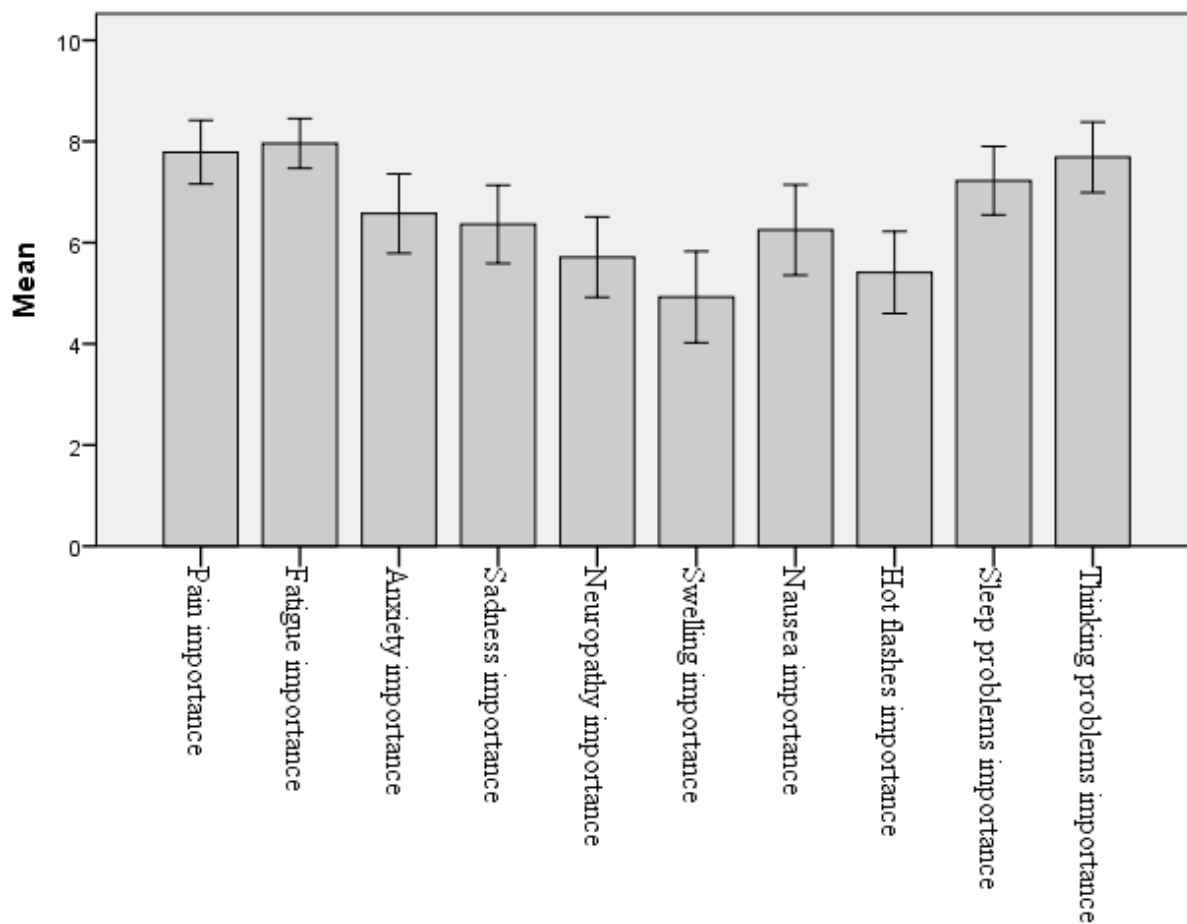Figure 8. Cluster Dendrogram using non-Winsorized Variables with Clusters Boxed.

Figure 9. Bar Graph of Mean Symptom Importance Ratings with 95% Confidence

Interval Error Bars. One value for fatigue importance was Winsorized prior to this

analysis.

Appendix C   Tables

Table 1. Cognitive Domains found to be Impaired among Breast Cancer Survivors in Meta-Analyses. *Found to be a significant deficit. Findings in red text are inconsistent with findings in the most recent meta-analysis. N/A = domain not assessed in the meta-analysis.

Ono et al. (2015)	Jim et al. (2012)	Stewart et al. (2006)	Jansen et al. (2005)	Falleti et al. (2005)
Processing speed*	Processing speed	Processing speed	Processing speed*	N/A
Executive function*	Executive function	Executive function*	Executive function*	Executive function
Attention*	Attention	Attention	Attention	Attention
Motor function*	Motor function	Motor function*	Motor function	Motor function
Short-term memory*	N/A	Short-term memory*	N/A	N/A
Language	Language*	Language*	Language	Language*
Long-term memory	N/A	Long-term memory*	N/A	N/A
Visuospatial function	Visuospatial function*	Visuospatial function	Visuospatial function	Visuospatial function*

Table 2. Participant Characteristics ($N = 80$). SD = standard deviation. [a]African

American/Black, Hispanic, and other. [b]History of bladder cancer

Characteristic	
Age	
Mean (SD)	55.5 (11.26)
Range	32-80
Years of education	
Mean (SD)	15.03 (2.42)
Range	11-20
Years since the stage IV breast cancer diagnosis	
Mean (SD)	3.93 (3.64)
Range	.21-19.46
Ethnicity, no. (%)	
Non-Hispanic White	73 (91.3%)
Other ethnicity[a]	7 (8.8%)
Married or partnered, no. (%)	53 (66.3)
Employed, no. (%)	24 (30.0)
Household Income, no. (%)	
$0 - $30,999	17 (21.8)
$31,000 - $50,999	18 (23.1)
$51,000 - $99,999	26 (33.3)
$100,000 +	17 (21.8)
Cancer treatment history, no. (%)	
Chemotherapy	69 (86.3)
Hormonal therapy	68 (85.0)
Mastectomy	53 (66.3)
Radiation	52 (65.0)
Targeted therapy	36 (45.0)
Lumpectomy	17 (21.3)
Medical comorbidities	
Hypertension	26 (32.5)
Arthritis	20 (25.0)
Diabetes	11 (13.8)
Asthma, emphysema, or chronic bronchitis	9 (11.3)
Stroke or other neurological condition	3 (3.8)
Heart disease	2 (2.5)
Liver disease	2 (2.5)
Kidney disease	2 (2.5)
Other cancers[b]	1 (1.3)

Table 3. Winsorization of Main Study Variable Outliers. [a]Memorial Symptom
Assessment Scale (MSAS) average score of symptom severity and distress.
[b]PROMIS measure total score. [c]Patient-Centered Outcomes Questionnaire (PCOQ)
symptom importance score.

Variable	Variable value	
	Original	Winsorized
Swelling[a]	4	3
Anxiety[b]	17	16
Depressive symptoms[c]	20	16
Fatigue importance[d]	0	2

Table 4. Descriptive Statistics and Normality Estimates for Main Study Variables. SD = standard deviation.

Variable	Mean	SD	Range	Skewness	Kurtosis	Cronbach's α
				Normality estimate		
Nausea	0.63	0.91	0 – 3.00	1.12	-0.07	0.95
Neuropathy	1.13	1.19	0 – 3.67	0.39	-1.44	0.89
Swelling	0.46	0.87	0 – 3.00	1.65	1.28	0.91
Hot flashes	1.64	1.92	0 – 7.00	0.75	-0.66	0.75
Pain	6.60	2.65	3 – 13	0.26	-0.76	0.83
Fatigue	11.39	4.31	4 – 20	0.20	-0.97	0.92
Sleep problems	11.10	3.90	4 – 20	0.48	-0.43	0.84
Cognitive problems	11.43	5.11	4 – 20	0.26	-1.06	0.95
Anxiety	7.33	3.14	4 – 16	0.51	-0.85	0.86
Depressive symptoms	6.65	3.20	4 – 16	1.39	1.19	0.90
Pain importance	7.79	2.83	0 – 10	-1.61	1.83	
Fatigue importance	7.96	2.21	2 – 10	-1.48	1.53	
Anxiety importance	6.58	3.53	0 – 10	-0.89	-0.61	
Sadness importance	6.36	3.48	0 – 10	-0.78	-0.72	
Neuropathy importance	5.71	3.57	0 – 10	-0.47	-1.21	
Swelling importance	4.93	4.06	0 – 10	-0.07	-1.72	
Nausea importance	6.25	4.01	0 – 10	-0.64	-1.31	
Hot flashes importance	5.41	3.65	0 – 10	-0.34	-1.34	
Sleep importance	7.23	3.04	0 – 10	-1.11	0.07	
Thinking problems importance	7.69	3.14	0 – 10	-1.52	1.10	

Table 5. T Score Means and Standard Deviations for PROMIS-Measured Symptoms.

[a]Scores from the current sample were calibrated based on scores obtained in PROMIS calibration samples. The cancer calibration sample consisted of 1,754 participants that completed PROMIS measures on a web-based polling platform and self-reported a cancer diagnosis (Cella et al., 2010). The cancer stage of participants in the cancer population sample has not been reported. The wave 1 general population sample consisted of 21,133 participants (including clinical samples such as those who reported cancer) who were 52% female with a mean age of 50 years, and this sample has been shown to be representative of the general U.S. population (Cella et al., 2010; Liu et al., 2010). Mean T score of 50 and standard deviation of 10 reflect the mean and standard deviation obtained in calibration samples.

Variable	Cancer calibration[a]		Wave 1 calibration[a]	
	Mean	SD	Mean	SD
Anxiety	51.27	8.82		
Cognitive concerns	41.16	9.97		
Depressive symptoms	50.42	8.45		
Fatigue	55.39	9.73		
Pain			43.81	8.58
Sleep disturbance			53.07	3.35

Table 6. Repeated-Measures ANOVA on Symptom Importance Ratings for Symptoms
Assessed with the Modified Patient-Centered Outcomes Questionnaire (PCOQ). [a]*df*
corrected with Greenhouse-Geisser ε for violation of sphericity assumption.

Source	*SS*	*df*[a]	*MS*	*F*	η^2	*p*
Symptom	801.75	5.80	138.30	13.77	0.15	< .001
Error	4600.66	457.97	10.05			

Table 7. Simple Contrasts Comparing the Importance of Thinking Problems to the

Importance of Other Symptoms. SE = standard error. *$p < 0.05$.

Symptom (I)	Symptom (J)	Mean Difference (I – J)	SE	p	95% Confidence Interval	
					Lower Bound	Upper Bound
	Pain	-0.10	0.41	.810	-0.92	0.72
	Fatigue	-0.28	0.28	.328	-0.83	0.28
	Anxiety	1.11*	0.37	.004	0.37	1.85
	Sadness	1.33*	0.33	.000	0.67	1.98
Thinking problems	Neuropathy	1.98*	0.43	.000	1.12	2.83
	Swelling	2.76*	0.46	.000	1.84	3.68
	Nausea	1.44*	0.49	.005	0.46	2.42
	Hot flashes	2.28*	0.36	.000	1.57	2.98
	Sleep problems	0.46	0.26	.076	-0.05	0.97

Appendix D   Syntax

R Syntax – For Cluster Analysis

```
install.packages("cluster")
library(cluster)
thesisdata = read.csv(file.choose(), header = TRUE)
#remove non-numeric column
thesisdata.use=thesisdata[, -c(1)]
thesisdata.use
#calculate the euclidean distance matrix
distance=dist(thesisdata.use, method="euclidean")
#calculate squared euclidean distance
d.sqeuc=distance^2
#run the cluster analysis
thesisdata.hclust=hclust(d.sqeuc, method="mcquitty")
#create dendrogram of cluster analysis
plot(thesisdata.hclust)
plot(thesisdata.hclust,labels=thesisdata$Symptom)
#cut the winsorized one at 110 and non-winsorized one at 120
rect.hclust(hclust(d.sqeuc, method="mcquitty"),h=110)
```

SPSS Syntax – For Repeated-Measures ANOVA

```
GLM PCOQ4pain PCOQ4fatig PCOQ4anx PCOQ4sad PCOQ4numb PCOQ4swell
PCOQ4naus PCOQ4hotf PCOQ4sleep
   PCOQ4cog
 /WSFACTOR=symptom 10 Polynomial
 /MEASURE=importance
 /METHOD=SSTYPE(3)
 /EMMEANS=TABLES(symptom) COMPARE ADJ(LSD)
 /PRINT=DESCRIPTIVE
 /CRITERIA=ALPHA(.05)
 /WSDESIGN=symptom.

DATASET ACTIVATE DataSet1.
GRAPH
 /BAR(SIMPLE)=MEAN(PCOQ4pain) MEAN(PCOQ4fatig) MEAN(PCOQ4anx)
MEAN(PCOQ4sad) MEAN(PCOQ4numb) MEAN(PCOQ4swell)
   MEAN(PCOQ4naus) MEAN(PCOQ4hotf) MEAN(PCOQ4sleep) MEAN(PCOQ4cog)
 /MISSING=LISTWISE
 /INTERVAL CI(95.0).
```