SYMPTOM CLUSTERS IN BREAST CANCER SURVIVORS:
PREVALENCE, PREDICTORS, AND CONSEQUENCES

By

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To my husband, children, and mentor for their encouragement and endless support

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LIST OF ABBREVIATIONS

ACS   American Cancer Society

NIH   National Institutes of Health

PROMIS   Patient Reported Outcomes Measurement Information System

Abstract of Dissertation Presented to the Graduate School
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There are currently 2.9 million women survivors of breast cancer in the United

States. Many breast cancer survivors report experiencing multiple simultaneous

symptoms. The majority of research, however, has focused on single symptoms. Thus,

the purpose of this study was to investigate symptom clusters, their demographic

predictors and functional consequences, among women survivors of breast cancer. The

following aims were addressed: (1) To describe the prevalence and number of self-

reported physical (pain, fatigue) and mental (depression/anxiety/anger) health

symptoms. (2) To determine whether and how symptoms combine to create identifiable

clusters. (3) To investigate the relationships between background characteristics and

symptom clusters. (4) To investigate the relationships between symptom clusters and

functional outcomes (physical function, social role function).

The research aims were investigated using a descriptive, exploratory, cross-

sectional, secondary analysis study design. Data from 103 women breast cancer

survivors from the Patient Reported Outcomes Measurement Information System

(PROMIS) from the National Institutes of Health were analyzed. The women in this

sample were mainly White, highly educated, partnered, employed, with a mean age of

60.4 years (Range = 30-85). Data were analyzed with descriptive and non-parametric

bivariate analyses. Symptom clusters were analyzed with correlation and cluster

analysis.

The majority of women survivors of breast cancer in this sample reported

experiencing symptoms: 67% pain, 62% fatigue, and 63% depression/anxiety/anger.

Most women (n=68, 66%) experienced two or three mildly severe symptoms

concurrently. Three symptom clusters were identified: Cluster 1 (All Minimal

Symptoms) (n=53), Cluster 2 (All Mild Symptoms) (n=42), and Cluster 3 (All Moderate

Symptoms) (n=8). The background characteristic predictors revealed no significant

relationships with symptom clusters. There was a trend that women in the more

symptomatic clusters were younger. Symptom clusters were significantly associated

with the physical and social role functional outcomes. Women in the more symptomatic

clusters had lower physical and social role function.

Symptoms do cluster and differ based on symptom intensity. Women in clusters

with even mild to moderate intensity symptoms reported worse physical and social role

functioning. Practitioners need to recognize that even mild, concurrent symptoms may

require treatment for optimal daily functioning of women survivors of breast cancer.

CHAPTER 1

BACKGROUND AND SIGNIFICANCE AND THEORETICAL FRAMEWORK

Introduction

Cancer survivors are growing in numbers and surviving longer. Cancer occurs predominantly in older women, with breast cancer among the most common. One in eight women in the United States develops breast cancer in their lifetime. Most cancer survivors report simultaneous occurrence of multiple symptoms which may negatively impact their health outcomes and daily functioning. The majority of symptom management research, however, has focused on single symptoms. Thus, it is relevant that more research be done to understand the prevalence, predictors, and consequences of multiple symptoms, or symptom clusters for women survivors of breast cancer. Any new knowledge acquired may be used by healthcare providers to resolve symptoms and facilitate more positive daily physical and social functioning. The following sections present the background and significance of the problem, the theoretical framework for the study, the purpose statement, and the research aims.

Background and Significance

Over 13 million Americans are cancer survivors (ACS, 2012b). Cancer occurs predominantly in the older adult: 75% of people who develop cancer are age 55 or older, and 60% of newly diagnosed cancers occur in adults over the age of 65 (Bond, 2010a). Breast cancer is the most common cancer diagnosis for women in the United States, excluding skin cancer (ACS, 2012a). Over 2.9 million women in the United States are living with breast cancer, as they have a 90% five-year overall survival rate from diagnosis (ACS, 2012a; ACS, 2012b).

In the oncology literature, the emphasis has been on investigating single symptoms. Single symptom research in oncology has focused on pain, fatigue, depression, anxiety, and sleep disturbance. There is growing recognition that symptoms do not occur in isolation. People diagnosed with cancer present with multiple symptoms and/or develop symptoms while undergoing treatment, which may negatively impact their health outcomes and daily functioning (Barsevick, 2007a; Barsevick, 2007b; Dodd, Cho, Cooper, & Miaskowski, 2010; Miaskowski, Aouizerat, Dodd, & Cooper, 2007; Xiao, 2010). Reduction of these symptoms may positively affect a person's quality of life, adjustment to the cancer diagnosis, functional status, and survival (Brant, Beck, & Miaskowski, 2010).

Pervasive in the nursing literature is the need to define and clarify the symptom cluster concept, determine etiologies, determine consequences, and develop appropriate interventions to advance the science (Barsevick, 2007a; Barsevick, 2007b; Dodd et al., 2010; Dodd, Miaskowski, & Lee, 2004: Fan, Filipczak, & Chow, 2007; Gift, 2007; Kim, Barsevick, Tulman, & McDermott, 2008; Kim, McGuire, Tulman, & Barsevick, 2005; Miaskowski et al., 2007; Xiao, 2010). The gap in the literature identified for this study is the need to first examine the symptom experience by identifying if symptoms interact to form symptom clusters in women survivors of breast cancer. Background characteristics, primarily age as a risk factor for women survivors of breast cancer, can be investigated to determine if age impacts the symptom experience. The symptom experience and/or the symptom clusters identified can be studied to ascertain if relationships exist between the symptoms and physical or social functioning outcomes. This research is needed to determine if there are discernable

symptom clusters, so that the symptom experience and/or symptom clusters can be treated simultaneously with treatment strategies implemented by healthcare providers to positively impact physical and social functioning as women deal with breast cancer survivorship.

Conceptual Issues

There are a number of conceptual issues inherent in this work. These include the definition of a survivor, the designation of younger versus older age, and the number of symptoms that designate a symptom cluster. These conceptual issues are discussed in the following section.

Definition of a Survivor

The definition of a survivor of breast cancer is debatable. The National Cancer Institute defines a person as a cancer survivor at the time of diagnosis and discusses survival based on how long people live after diagnosis (Howlader et al., 2012). American Cancer Society (2011) discusses breast cancer survival as relative survival rates from diagnosis. Investigators in this area of inquiry studying women with breast cancer define a survivor as a woman who has been diagnosed with breast cancer (Grunfeld, 2009; Knobf, 2007). For this study, women survivors of breast cancer will be operationally defined as women from the time of diagnosis and continuing throughout their lives, consistent with the current literature review.

Definition of Age: Younger Versus Older for Women Survivors of Breast Cancer

Another conceptual issue arises with the term age and the definition of older versus younger. Being female is the greatest risk factor for breast cancer, with increasing age being the second greatest risk factor for a diagnosis of breast cancer (ACS, 2012a). The lifetime risk of a breast cancer diagnosis for a woman living in the

United States has increased from 1 in 11 in the 1970s to 1 in 8 currently (ACS, 2011).

This is a 12.15% lifetime risk for women to develop breast cancer (ACS, 2011). The

American Cancer Society (2011) discusses breast cancer incidence as increasing with

age, with 95% of new cases occurring in women age 40 or older. The median age for a

breast cancer diagnosis is 61 years, with women in the last half of their seventieth

decade having the highest breast cancer incidence (ACS, 2011).

Age definitions regarding younger or older women with breast cancer varies

between studies. Some researchers use age 50 as the cut-off due to this being the

average age for menopausal onset (Howard, Anderson, Ganz, Bower, & Stanton,

2012), while others use age 65 based on retirement age set by Social Security (Albert &

Freedman, 2010). Bond (2010b) calls for considering physiological age rather than

chronological age. The National Cancer Institute (Howlader et al., 2012) relays data for

breast cancer for age ranges of under 20, 20 to 34, and then 10-year age ranges of 35

to 44, 45 to 54, 55-64, 65 to 74, 75 to 84, and 85 and above. Data tables by the

National Cancer Institute also give information comparing under age 65 to age 65 and

older, as well as other tables comparing under age 50 to age 50 and older. No rationale

is given for the age differentiations. The American Cancer Society (2011) relays data

on women with breast cancer using age 50 as the cut-point for older versus younger

women. In the United States, full Social Security benefits are awarded at age 65 and

this chronological age is often used as a marker for old age (Albert & Freedman, 2010;

Quadagno, 2008). Social gerontologists frequently split older people into categories of

young-old age 65 to 74, middle-old age 75 to 84, and oldest-old age 85 and older

(Quadagno, 2008). The PROMIS datasets use the age groupings of 18 to 29, 30 to 39,

40 to 49, 50 to 59, 60 to 64, 65 to 84, and 85 and older. Thus, there are inconsistencies in how young versus older age are defined.

The literature review on oncology and breast cancer revealed ten articles that specifically addressed younger or older patients with cancer or breast cancer. Six of these ten articles gave no rationale or used the median age of the sample for defining younger and older cancer patients (Berger, Visovsky, Hertzog, Holtz, & Loberiza, 2012; Fabro et al., 2012; Kenefick, 2006; Khan, Amatya, Pallant, & Rajapaksa, 2012; Miaskowski et al., 2006; Palesh et al., 2010). Two articles referenced age 65 as older due to the increased occurrence of cancer in this population (Bond, 2010a; Yeom & Heidrich, 2009). One article used age 60 as the cut-off for older versus younger, but gave no rationale for the designation (Cheung, Le, Gagliese, & Zimmermann, 2011). The final article used age 50 as the division between older based on menopausal status (e.g., mean age of menopause is 50) (Howard, Anderson, Ganz, Bower, & Stanton, 2012). Many other research articles on women breast cancer survivors included age as part of the background characteristics but made no reference to any delineation based on age. For this study, women will be operationally defined as younger if they are below age 50, and as older if age 50 or older. This definition correlates with the American Cancer Society, many of the datasets of the National Institutes of Health, and many breast cancer research articles that relay the age background characteristic related to menopausal onset. The PROMIS dataset fits well with this definition. If the sample has enough older women, then there will also be a comparison based on social gerontology of age 65 to 84 as the young and middle old to those age 85 and older as the oldest old. This comparison could provide additional clarification regarding older

age categories and the symptom experience since age is second only to being a woman as the greatest risk factor for a breast cancer diagnosis.

Definition of a Symptom Cluster

The nursing literature began to investigate the association between symptoms, especially in oncology, in the 1990s, but did not label these coexisting symptoms as a "cluster" (Kim et al., 2005; Lenz, Pugh, Milligan, Gift, & Suppe, 1997). Dodd, Miaskowski, and Paul (2001) are recognized as the first authors in the nursing literature to identify the concept of a symptom cluster in oncology (Kim et al., 2005; Xiao, 2010). A symptom cluster was defined as having three or more coexisting symptoms with some relationship to each other, with or without the same etiology (Dodd, Miaskowski, et al., 2001). The original authors of the symptom cluster concept did not elucidate the nature, intensity, or temporal aspect of the concurrent symptoms. An alternate definition of a symptom cluster of two or more symptoms that have a relationship to each other, occur simultaneously, remain constant, are somewhat autonomous, and may show precise core characteristics, with or without the same etiology was proposed by others (Kim et al., 2005).

Because there has only been a decade of research in this area, symptom cluster research is in its infancy. The operational definition of a symptom cluster needs further development and clarification as a means to assist in assessment and management of symptoms among cancer survivors (Dodd et al., 2004; Fan et al., 2007; Xiao, 2010).

For this study, the symptom prevalence, the number of symptoms, and the symptom experience were examined to ascertain if symptom interactions occur in any identifiable pattern to form symptom clusters. A cluster was operationally identified as having two or more symptoms based on the most recent definition. The symptom

experience was examined to determine any relationships between this experience and background characteristics, primarily age, as well as physical and social functioning outcomes. These proposed relationships were explored using theory.

Theory

Theory is a methodical expression of a set of statements articulated to communicate reality with the intent of describing, explaining, or predicting associations or outcomes (Meleis, 2007). The New Symptom Management Model was used to guide the proposed research (Brant, Beck, & Miaskowski, 2010). This model incorporates multifaceted characteristics of symptom interactions allowing for symptom cluster analysis. Figure 1-1 is a diagram of the original model (Brant et al., 2010) showing symptom interactions over time, antecedents, and consequences of symptom clusters. The New Symptom Management Model was adapted by the investigator to explore a subset of constructs. Specifically, an adapted version of this model was used to explore the constructs of the symptom experience (symptom clusters), antecedents (background characteristics), and consequences (function) among women survivors of breast cancer (see Figure 1-2). The constructs of antecedents, symptom experience, and consequences were theoretically conceptualized as background characteristics (age, ethnicity, education, relationship status, employment status, comorbid conditions), symptom clusters (physical health symptoms: pain, fatigue and mental health symptom: depression/ anxiety/anger), and function (physical, social role). The relationships between the constructs, theoretical concepts, and the empirical indicators are shown in Table 1-1.

Purpose

The purpose of this study was to investigate the symptom experience, demographic predictors, and functional consequences, among women survivors of breast cancer. This study will increase the body of knowledge of the symptom experience in women survivors of breast cancer by identifying if there is clustering of two or more symptoms, by describing relationships of symptoms or clustering of symptoms and function, and by investigating the impact of background characteristics on the symptom experience. The following aims will be addressed.

Research Aims

- Aim 1: To describe the prevalence and number of self-reported physical health symptoms (pain, fatigue) and mental health symptom (depression/anxiety/anger) among women survivors of breast cancer.

- Aim 2: To determine whether and how symptoms combine to create identifiable clusters in a sample of women survivors of breast cancer.

- Aim 3: To investigate the relationships between background characteristics (age, ethnicity, education, relationship status, employment status, comorbid conditions) and symptom clusters.

- Aim 4: To investigate the relationships between symptom clusters and the functional outcomes (physical function, social role function).
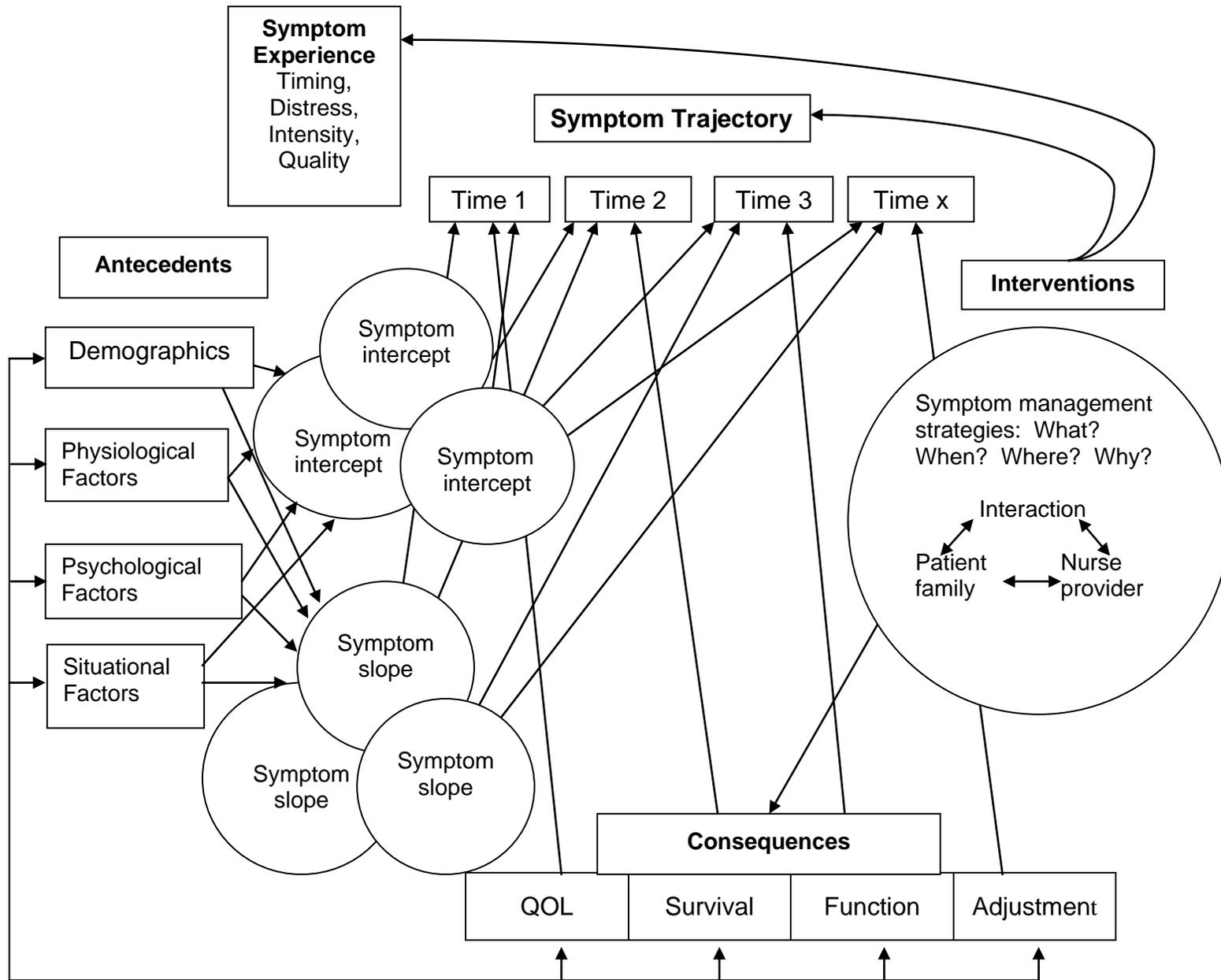
Figure 1-1. Diagram of the New Symptom Management Model (Brant et al., 2010)

Antecedents	Symptom Experience	Consequences

Background Characteristics

Primary
➢ Age
Secondary
➢ Ethnicity
➢ Education
➢ Relationship Status
➢ Employment Status
➢ Comorbid Conditions

Symptom Clusters

Physical Health Symptoms
➢ Pain
➢ Fatigue

Mental Health Symptoms
➢ Depression
➢ Anxiety
➢ Anger

Function

➢ Physical
➢ Social Role
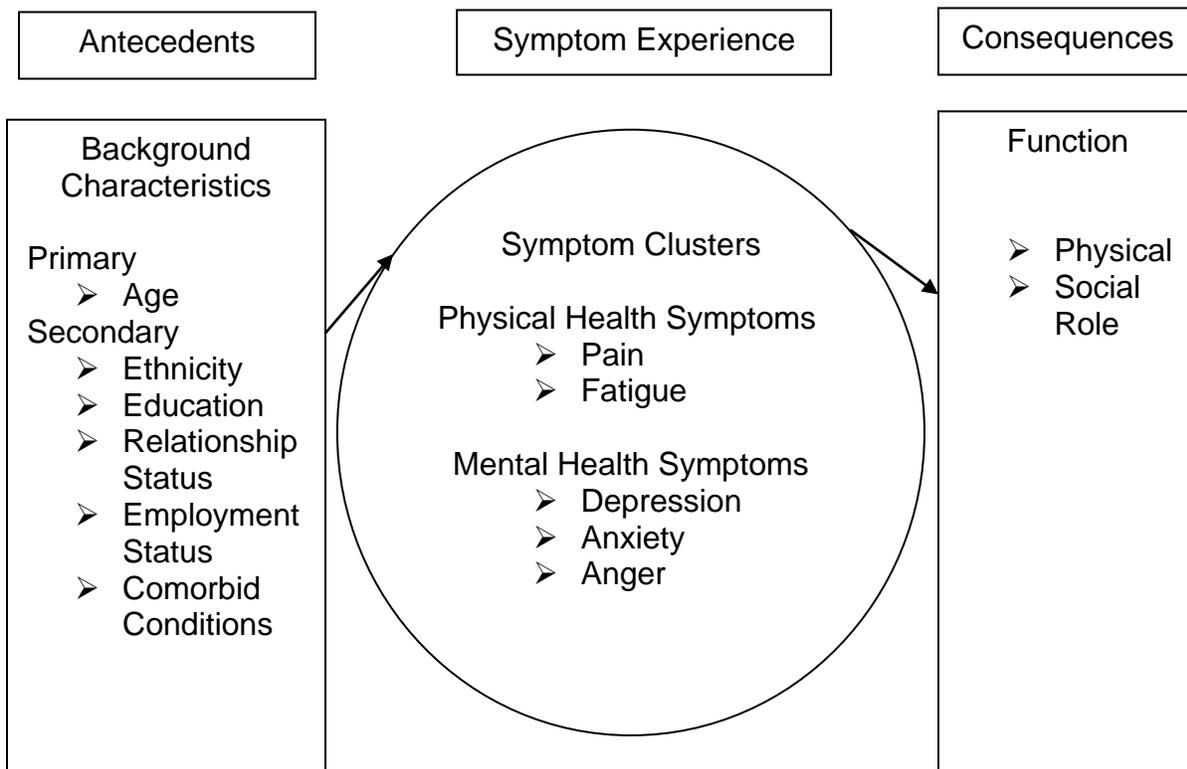
Figure 1-2. Adapted version of the New Symptom Management Model

Table 1-1. Theoretical constructs, concepts, and empirical indicators for the study

Constructs	Concepts	Empirical Indicators
Antecedents Background		PROMIS Measures
Characteristics	Primary	Age in years
	Age	Age Groups
		<50
		≥ 50
	Secondary	
	Ethnicity	White
		Black
		Other
	Education	HS/Associate of Arts
		College/Advanced
		Degree
	Relationship Status	Partnered
		Not Partnered
	Employment Status	Employed
		Not Employed
	Comorbid Conditions	Number of Conditions
Symptom Experience Symptom Clusters		PROMIS Measures
	Physical Health Symptoms	
	Pain	Pain
	Fatigue	Fatigue
	Mental Health Symptom	
	Depression/Anxiety/Anger	Depression/Anxiety/Anger
Consequences Function		PROMIS Measures
	Physical Function	Physical Function
	Social Role Function	Social Role Function

CHAPTER 2
REVIEW OF LITERATURE

Introduction

Cancer occurs predominantly in the older woman, with one in eight women in the

United States developing breast cancer in their lifetime (Horner et al., 2008; Perry,

Kowalski, & Chang, 2007). People diagnosed with cancer present with multiple

symptoms and/or develop symptoms while undergoing treatment, which may negatively

impact their health outcomes and daily functioning (Barsevick, 2007a; Barsevick, 2007b;

Dodd et al., 2010; Xiao, 2010). The majority of symptom management research focuses

on a single symptom when most cancer patients report simultaneous occurrence of

multiple symptoms, indicating the need for increased symptom cluster research in

oncology to better understand survivors' symptom experience and the effect on

outcomes (Gift, 2007; Miaskowski et al., 2007).

Using an adapted New Symptom Management Model as an organizing

framework, the symptom experience of women survivors of breast cancer, potential

antecedents of background characteristics, and consequences of physical and social

role functioning are explored. First, the symptom experience in oncology will be

presented, followed by diagnosis-specific breast cancer research.

Symptom Research in the Oncology Literature

Oncology symptom prevalence and symptom research is presented. This will be

followed by a presentation and synthesis of how background characteristics relate to the

symptom experience and how this experience relates to the outcomes.

Prevalence of Symptoms in Oncology

Symptoms occurring most frequently in oncology patients are pain, fatigue, sleep

disturbance, depression, and anxiety. In a literature review containing 18 research

studies pain was reported at a prevalence of 36% in cancer patients (Kim, Dodd,

Aouizerat, Jahan, & Miaskowski, 2009). At a pain clinic, neuropathic pain was found to

occur in 59% of the 131 patients (Donovan, Taliaferro, Brock, & Bazargan, 2008).

Sixty-nine percent of 80 lung cancer patients complained of pain (Hoffman, Given, von

Eye, Gift, & Given, 2007). The most common physical symptom reported was pain in

46% of 192 patients studied experiencing this symptom (Breen et al., 2009).

Fatigue is reported in literature reviews as being the most prevalent symptom

experienced by cancer patients (Donovan & Jacobsen, 2007; Kim, Dodd, et al., 2009).

In a literature review, Donovan and Jacobsen (2007) reported a 70-100% occurrence of

fatigue regardless of where a patient was in the treatment trajectory. This literature

review also included the finding that fatigue could be managed by decreasing pain

(Donovan & Jacobsen, 2007). In 80 patients with lung cancer, 97% reported

experiencing fatigue (Hoffman et al., 2007).

Sleep disturbance is generally reported to be prevalent in 30-50% of cancer

patients by several researchers (Donovan & Jacobsen, 2007; Evangelista, & Santos,

2012; Palesh et al., 2010; Savard, Ivers, Villa, Caplett-Gingras, & Morin, 2011), with a

wider range of 23-61% by others (Bardwell et al., 2008). A lung cancer study reported

51% occurrence of sleep disturbance (Hoffman et al., 2007) with a literature review

describing a 41% occurrence (Kim, Dodd, et al., 2009). Another study found a 59%

incidence of sleep disturbance, although this result was preoperatively with the

prevalence decreasing to 36% at 18 months postoperatively (Savard et al., 2011). In a

literature review, a prevalence of 72% for sleep disturbance was reported at a pain clinic

(Fiorentino, Rissling, Liu, & Ancoli-Israel, 2011). In a study of 823 cancer patients, those with sleep disturbance had an increased incidence of depression and fatigue compared to patients without any sleep disturbance (Palesh, et al., 2010).

Depression and anxiety are considered the most common mood disturbances in cancer patients (Fiorentino et al., 2011). Depression is reported at a 10-25% prevalence rate in cancer patients, but has been reported as high as 59% (Donovan & Jacobsen, 2007). Researchers found that if depression was managed, that fatigue and sleep disturbance symptoms decreased (Donovan & Jacobsen, 2007). In a study of 192 cancer patients, depression was found to occur in 45% of the sample (Breen et al., 2009). In this same study, anxiety was prevalent in 45% of the cancer patients.

Oncology Single, Multiple, and Symptom Cluster Research

In the oncology literature, the emphasis has been on investigating isolated symptoms. A literature review examining symptom cluster research in light of symptom management research was conducted with findings confirming that the majority of clinical studies in oncology on pain, fatigue, and depression focused on only one symptom (Miaskowski, Dodd, & Lee, 2004). The authors noted that patients rarely present with just one symptom and emphasized the need to assess prevalence rates of clusters of symptoms and their effect on patient outcomes. The following year a literature review indicated the need to identify the characteristics, antecedents, and consequences of symptom clusters (Kim et al., 2005). Fan, Filipczak, and Chow (2007) reviewed cancer symptom cluster research between 1997 and 2006 and found 12 studies testing statistically for a symptom cluster. The authors noted that some publications involved symptoms of pain, fatigue, sleep disturbance, and depression or these four symptoms together, but they did not statistically validate the symptom cluster.

Pain as a single symptom was compared in male and female patients with unspecified cancer diagnoses (Donovan, Taliaferro, et al., 2008). Fatigue was reviewed in a systematic review of the literature of 55 studies (Donovan, & Jacobsen, 2010). Sleep disturbance was researched in advanced cancer patients receiving palliative care, cancer patients receiving chemotherapy, and cancer patients prior to surgery consecutively (Delgado-Guay, Yennurajalingam, Parson, Palmer, & Bruera, 2011; Palesh et al., 2010; Savard et al., 2011).

Multiple symptoms were studied in oncology with symptom distress studied in cancer patients, with a control group of non-cancer patients, with pain and fatigue identified as most severe (Cleeland et al., 2000). Symptom burden was studied as a predictor of depression and anxiety prior to chemotherapy with percentages of occurrence given for pain, sleep disturbance, depression, and anxiety (Breen et al., 2009). Donovan, Hartenback, and Method (2005) studied women with ovarian cancer specifically and reported 12 concurrent symptoms with fatigue, bowel disturbances, and peripheral neuropathies as the most prevalent. These multiple symptom studies are differentiated from studies that follow in which the authors specifically addressed symptom clusters in oncology.

Symptom clusters studied in 30 research articles reviewed by Gift (2007) revealed the need to focus on one type of cancer to delineate specific symptom clusters for a specific cancer. Gift recommended looking at the interactive or additive effects of symptoms, since relieving one symptom could reduce the burden of another co-occurring symptom. Conceptually examining symptom cluster research over a six year timeframe led to the conclusion that symptom management research was focused on

single symptoms rather than on the simultaneous occurrence of symptoms in cancer patients (Miaskowski et al., 2007). The authors proposed that symptom clusters needed to be identified within and across cancer diagnoses, treatments, and stages of disease.

Donovan and Jacobsen (2007) completed a literature review on articles published between 1998 and 2004 to try to document evidence for fatigue, sleep disturbance, and depression to be designated as a symptom cluster in cancer with multiple studies found using individual tools to measure these symptoms. Pain and fatigue were most prevalent with sleep disturbance occurring less frequently in the symptom cluster identified in patients receiving chemotherapy (Dodd, Miaskowski, & Lee, 2004; Dodd, Miaskowski, & Paul, 2001; Hoffman et al., 2007). Data were relayed in two research articles using the same dataset of oncology patients receiving radiation with symptom clusters identified as mood-cognitive, sickness-behavior, or treatment-related (Kim et al., 2009a; Kim et al., 2009b). The three clusters designated included the individual symptoms of pain, fatigue, sleep disturbance, nausea, lack of appetite, dyspnea, sweats, and urinary difficulty. Various combinations of symptom clusters were noted in advanced or metastatic cancer (Stage IV or distant stage) patients, but overall the symptom clusters dealt with pain, sleep disturbance, depression, anxiety, gastrointestinal symptoms affecting appetite, and dyspnea with no relationship to outcomes (Cheun, Le, Gagliese, & Zimmermann, 2011; Cheung, Le, & Zimmermann, 2009; Jimenez et al., 2011). Symptom cluster studies dealing with activity influenced by pain and by the support or relationships with others related to quality of life as the outcome (Hadi et al., 2008; Hird et al., 2010).

Single symptom studies may be helpful if the healthcare provider is able to extrapolate what is needed to treat individual symptoms. Since this would rarely give an integrated view of the oncology patient who is experiencing multiple symptoms, their usefulness is limited. Since cancer patients present most frequently with multiple symptoms, an examination of these symptoms in light of clustering brings a more complete picture of what a cancer patient is experiencing leading to the management of these symptoms concurrently. In addition to looking at oncology from the perspective of single, multiple, and clustering of symptoms, researchers need to be aware of the effect background characteristics have on the symptom experience as well as how symptoms relate to outcomes.

Relationship Between Background Characteristics and the Symptom Experience in Oncology

The background characteristics of age, ethnicity, education, relationship status, employment status, and comorbid conditions have been associated with the symptom experience in oncology. Age was related to pain with younger ($\leq$60) metastatic cancer patients experiencing worse pain than older ($>$60) patients (Cheun, Le, Gagliese, & Zimmermann, 2011). Outpatients undergoing treatment (N=191) were questioned regarding pain, as well as fatigue, sleep disturbance, and depression (Miaskowski et al., 2006). Subgroups were designated based on high to low occurrence of the symptoms. Those in the all high group reported a high occurrence of all four symptoms of pain, fatigue, sleep disturbance, and depression. The all low group described low occurrences of all four symptoms of pain, fatigue, sleep disturbance, and depression. The outpatients in the all high group were significantly younger at 54.4 (SD 12.8) than those in the all low group at age 62.4 (SD 12.3). Pain, fatigue, and sleep disturbance

were also assessed in a study of 80 lung cancer patients with age in this study showing no significant effect on the symptom experience (Hoffman et al. 2007). Sleep disturbance was significantly lower in older (≥58) versus younger patients (Palesh et al., 2010). A potential rationale for this finding was given that younger patients may experience an increased symptom burden as well as more aggressive tumors. In a literature review of 18 studies only two of the studies looked at the relationship of age and symptoms (Kim, Dodd, et al., 2009). The two studies revealed conflicting results, with one study noting that age was weakly correlated to distress with younger patients having greater symptom distress than older patients, while the second study found patients older than age 70 reported higher symptom distress than patients younger than age 40 (Kim, Dodd, et al., 2009). In a study looking at physical symptoms of long-term survivors (N=863) who were more than five years post diagnosis, with 73% age 50 or older, it was found that 17.6% experienced two or more symptoms with sleep disturbance the most prevalent symptom at 13.1% (Zucca, Boyes, Linden, & Girgis, 2012). In addition to looking at age in relationship to cancer symptoms, ethnicity, education, relationship status, and employment status are also presented.

Ethnicity was highlighted with a statement that being an ethnic minority was associated with the increased likelihood of having pain inadequately treated (Donovan, Taliaferro, et al., 2008). Education was noted as being associated with inadequate pain treatment (Donovan, Taliaferro, Brock, et al., 2008). Being married or partnered was associated with being in a group reporting low symptoms of pain, fatigue, sleep disturbance, and depression (Miaskowski et al., 2006). In this same study (N=191), those reporting high symptoms of pain, fatigue, sleep disturbance, and depression were

less likely to be employed than those reporting low symptoms of pain, fatigue, sleep disturbance, and depression (29% versus 36%, respectively).

Comorbid conditions need to be addressed to note any relationships between these and the symptom experience. Comorbity has been defined as a person having two or more health conditions (Albert & Freedman, 2010). In the United States, over one third of adults aged 65 to 79 and over two thirds of adults 80 and older have two or more chronic conditions (Albert & Freedman, 2010). Researchers studying pain, fatigue, and sleep disturbance assessed 80 lung cancer patients and found no difference in the symptom experience related to comorbidities (Hoffman et al., 2007).

Relationship Between the Symptom Experience and Outcomes in Oncology

The most commonly studied symptoms in the oncology literature are pain, fatigue, sleep disturbance, depression, and anxiety. Pain was assessed and treated in 348 patients with metastatic bone pain with subsequent improvement in function and overall quality of life (Hadi et al., 2008). Cancer outpatients who reported low levels of pain, fatigue, sleep disturbance, and depression also reported the highest functional status and quality of life compared to outpatients who had high levels of these four symptoms (Miaskowski et al., 2006). Kim, Dodd, Aouizerat, Jahan, and Miaskowski (2009) systematically reviewed 18 studies from 1990 to 2007 that met criteria of oncology patients undergoing active treatment experiencing multiple symptoms with negative effect on patient outcomes with sample sizes ranging from 26 to 727 with results indicating that approximately 40% of the patients experienced more than one symptom. Only five of the 18 studies looked at symptoms in relationship to functional status and quality of life. Two of these five studies looked at number of symptoms related to functional status. Functional status decreased with an increase in number of

symptoms or if symptom distress increased. Four of the five studies found that poorer

quality of life was associated with reports of more symptoms or symptom distress. Xiao

(2010) reviewed oncology symptom clusters in published literature from 1950 through

January 2010. The author located 61 articles and noted that the majority of researchers

selected specific clusters and then tested for these symptoms, e.g. pain, fatigue, sleep

disturbance, and depression. Xiao (2010) indicated that most clusters identified had

two or three symptoms with functional status or quality of life as the major outcomes

researched.

Summary of Symptom Research in the Oncology Literature

The oncology research literature emphasizes the need for more symptom cluster

research since cancer patients present most frequently with multiple symptoms. If the

symptoms are treated holistically, then patients may experience greater improvement in

their overall functioning. Pain, fatigue, sleep disturbance, depression, and anxiety are

the symptoms reported to be most prevalent in the oncology literature. Across studies,

the prevalence of symptoms is as follows: pain, 36-59%; fatigue, 70-100%; sleep

disturbance, 30-50% (with reports as high as 72%); depression, 10-25% (with reports as

high as 45%); and anxiety, 45%. The study of background characteristics in relation to

symptoms is limited in the published research. Generally older patients, with older age

not consistently defined, experience less pain, less sleep disturbance, and less distress

than younger patients, but data is conflicting. Ethnic minority status and having less

education were associated with inadequate pain treatment in one study, with no other

available information in other research articles. Only one article linked relationship

status to symptoms with being married or partnered associated with fewer symptoms.

Employment was only mentioned in the same article referring to relationship status with

more women working who had lower levels of symptoms. Comorbidities were mentioned in relation to symptoms in only a few articles, showing no association to symptoms. Two articles related the need to be aware of the physiological age of older adults when considering symptoms for management of care. This is definitely a gap in the literature that the current study will address. The symptom experience related to outcomes in oncology relates symptoms to outcomes of functional status and/or quality of life and not to social role function specifically. The oncology literature notes a need for cancer-specific research. Using an adapted New Symptom Management Model as an organizing framework, the symptom experience of women survivors of breast cancer, potential antecedents of background characteristics, and consequences of physical and social role functioning are explored.

Symptom Research in the Breast Cancer Literature

Breast cancer symptom prevalence and symptom research is presented. This will be followed by a presentation and synthesis of how background characteristics relate to the symptom experience and how this experience relates to the outcomes.

Prevalence of Symptoms in Breast Cancer

Pain is reported as a symptom in 40-50% of breast cancer patients. A study (N=32) reported 54% pain prevalence one month following needle biopsy, lumpectomy, or mastectomy for women survivors of breast cancer (Starkweather, Lyon, & Schubert, 2011). In another study with a sample of 127 women with breast cancer who had undergone a mastectomy and chemotherapy, 47% reported pain (Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999). Six months following mastectomy, with or without adjuvant therapy, 52% of women survivors of breast cancer (N=174) reported pain (Fabro et al., 2012). On average at 26 months after unilateral lumpectomy or

mastectomy, with or without adjuvant therapy, 47% of women survivors of breast cancer (N=3,754) reported having pain (Gartner et al., 2009). Following lumpectomy or mastectomy, with or without adjuvant therapy, 75% of 85 women who averaged two years since a breast cancer diagnosis stated that they had pain (Khan, Amatya, Pallant, & Rajapaksa, 2012). This higher percentage for this study may possibly be explained by noting that only a visual analog scale was used to ascertain pain, whereas the other four studies used multiple questions (intensity, location, severity).

Fatigue is found to occur in 60-80% of breast cancer patients. Fatigue was found in 64% of study participants (N=103) post treatment, which consisted of surgery, with or without adjuvant therapy (Bower et al., 2011). Kenefick (2006) studied 55 women after surgery at discharge with 70% reporting fatigue. Six months later, reports of fatigue had decreased to 60% for these same women. In another study of 154 women with various stages of breast cancer having undergone surgery, with or without adjuvant therapy, 83% reported fatigue (Bender, Ergyn, Rosenzweig, Cohen, & Sereika, 2005). Fatigue was reported at 91% (N=127) by women survivors of breast cancer that had undergone surgery, with or without adjuvant therapy (Gaston-Johansson et al., 1999). This higher occurrence may be explained by the fact that fatigue was measured with a visual analog scale, with the other three studies using multiple-item questionnaires for assessment of fatigue. One study looking specifically at chronic fatigue six to 42 months off adjuvant treatment (N=304) found a much lower occurrence with 9% of women reporting fatigue six months after treatment and 13% reporting fatigue at 42 months post treatment (Andrykowski, Donovan, Laronga, & Jacobsen, 2010).

Sleep disturbance is reported to occur in 50-70% of women survivors of breast cancer (Bower et al., 2011; Fiorentino et al., 2011; Van Onselen et al., 2012). In a study of 398 patients, sleep disturbance was measured prior to surgery and monthly for six months (Van Onselen et al., 2012). Three groups were distinguishable using growth mixture modeling: high sustaining (high levels of sleep disturbance that continued throughout the time trajectory of the study); decreasing (high levels that decreased over time); and low sustaining (low levels of sleep disturbance that continued). The high sustaining group reported a 55% prevalence of continued sleep disturbance (Van Onselen et al., 2012). In a study of 103 post treatment (surgery, with or without adjuvant therapy) women breast cancer survivors, 60% reported sleep disturbances (Bower et al., 2011). Mosher and Duhamel (2010) found that 70% (N=173) of metastatic breast cancer patients had sleep disturbance. In another study of 154 women with various stages of breast cancer having undergone surgery, with or without adjuvant therapy, 89% reported sleep disturbance (Bender et al., 2005). This last study utilized an expert consensus panel to select items for a secondary analysis, which could explain the high sleep disturbance percentage, while the other three studies utilized standardized sleep disturbance psychometric scales (Pittsburgh Sleep Quality Index or the General Sleep Disturbance Scale).

With regard to mental health symptoms, depression occurs in 20-30% of women with breast cancer (Bower et al., 2011; Knobf, 2007). In a study of 103 women who had completed treatment, 25% reported depressive symptoms (Bower et al., 2011). During treatment, 36% of 215 women with breast cancer reported being depressed (So et al., 2009). Knobf (2007) reported the occurrence of anxiety at 20-30% in a literature review

on women survivors with breast cancer. Consistent with this range, anxiety was assessed in 21% of 215 women during treatment (So et al., 2009). In 154 women there was a 79% finding of anxiety (Bender et al., 2005). This higher anxiety prevalence in this study might be explained by the use of an expert panel to select items for representation of the symptom, while the other two studies consisted of a literature review and the use of a multiple-item fatigue inventory. In women post chemotherapy, anger was found in some women and reported to be due to a preoccupation with death, a concern for recurrence of disease, and an uncertain future, but no prevalence was noted (Evangelista & Santos, 2012). Using principal component factor analysis, anger was associated with depression and fatigue.

Breast Cancer Single, Multiple, and Symptom Cluster Research

In the breast cancer literature, the emphasis has been on investigating isolated symptoms. Single symptom research in breast cancer has included research into pain, fatigue, sleep disturbance, depression, and anxiety. Anger has also been considered as a symptom. Pain was studied in women with early stage breast cancer prior to treatment (Starkweather et al., 2011) and in women post-mastectomy (Fabro et al., 2012). Fatigue was studied in women with early stage breast cancer receiving adjuvant therapy (Andrykowski, 2009; Donovan, Jacobsen, Small, Munster, & Andrykowski, 2008). Another study of fatigue in women breast cancer survivors was conducted comparing this cohort to healthy women in a control group (Andrykowski et al., 2010). Fatigue has also been studied in women breast cancer patients receiving hormonal treatment (Glaus et al., 2006). Pain and fatigue were studied individually in women awaiting surgery to determine predictors of these symptoms postoperatively (Schnur et al., 2007). Preoperative anxiety was associated with expectations of higher

postoperative pain and fatigue (Schnur et al., 2007). Older participants expected less pain, while more educated participants expected more fatigue postoperatively (Schnur et al., 2007). Three studies on sleep disturbance in women survivors of breast cancer were conducted: post treatment for Stage I to IIIA (Bardwell et al., 2008); post treatment with local or regional (Taylor et al., 2011), and post surgery (Van Onselen et al., 2012). Depression was assessed in women who were long-term survivors of breast cancer (Brunault et al., 2012). Women breast cancer survivors receiving chemotherapy were tested for depression using a questionnaire (Akin-Odanye, Chioma, & Abiodun, 2011). A study of women compared at diagnosis and at six months post diagnosis of breast cancer had results indicating a significant improvement over time in anxiety scores for women who perceived that their treatment would be effective and that their lives would return to what they considered normal pre-cancer diagnosis (McCorry et al., 2012).

In addition to single symptom research, multiple symptom research has been conducted in women survivors of breast cancer. Multiple symptoms consisting of 23 symptoms from the Memorial Symptom Assessment Scale were reported by women breast cancer survivors with Stage I or II post surgery and undergoing chemotherapy with high and low symptom prevalence groups identified, with the high prevalence symptom group reporting significantly poorer quality of life (Gwede, Small, Munster, Andrykowski, & Jacobsen, 2008). Women survivors of breast cancer were assessed post treatment with any combination of surgery, chemotherapy, and/or radiation and were found to have symptoms of fatigue, sleep disturbance, and depression (Berger, Visovsky, Hertzog, Holtz, & Loberiza, 2012; Bower et al., 2011). Mosher and DuHamel

(2010) studied women with metastatic breast cancer (Stage IV or distant stage) and assessed distress associated with fatigue, sleep disturbance, depression, and anxiety with functional impairment linked to poorer sleep quality and higher levels of fatigue and depression.

Some researchers specifically designated and studied multiple symptoms as symptom clusters in breast cancer. A literature review of 50 articles was conducted on pain, fatigue, sleep disturbance, depression, and anxiety as a symptom cluster prevalent in women survivors of breast cancer (Fiorentino et al., 2011). Percentages of occurrence of these symptoms were given for women survivors of breast cancer: pain, 52%; fatigue, 30-60%; sleep disturbance, 20-70%; depression (linked to anxiety with no percentage given); and anxiety, 33%. In the review of articles, pain was associated with sleep disturbance; fatigue was associated with pain, sleep disturbance, depression, and anxiety; sleep disturbance was associated with pain, fatigue, depression, and anxiety; and depression and anxiety were associated with each other and with sleep disturbance (Fiorentino et al., 2011). These authors concluded that breast cancer patients often have more than one symptom simultaneously or a symptom cluster. This literature review did not actually give a definitive definition of a symptom cluster nor did it confirm a specific symptom cluster, but indicated the relations between the five symptoms studied without any significance levels discussed. Three symptom clusters were identified through confirmatory factor analysis in a study of women (N=93) undergoing radiotherapy for breast cancer (Matthews, Schmiege, Cook, & Sousa, 2012). The three clusters were pain-insomnia-fatigue, cognitive disturbance-outlook, and gastrointestinal. Three stages of breast cancer were explored in patients using secondary analysis:

women with early stage; women with Stage I, II, or III, and women with Stage IV metastatic (Bender et al., 2005). The authors indicated the study was unique since symptoms in a cluster were not predetermined. A symptom cluster was defined as having three or more symptoms. Hierarchical cluster analysis identified three consistent symptoms clustering, although not at a significant level, across all stages of breast cancer: fatigue (lack of energy), cognitive impairment (memory problem or loss of concentration), and depression and anxiety (Bender et al., 2005). Individual symptoms were prevalent at a significant level, but the clustering was not at a significant level. The authors recommended future studies be completed linking this symptom cluster to functional ability and quality of life.

Pain, fatigue, and depression in advanced breast cancer patients were assessed as a symptom cluster with shared variance linking these three symptoms (Thornton, Andersen, & Blakely, 2010). The authors defined a symptom cluster as three or more concurrent indictors of physiological or psychological disturbance that relate to one another. They indicated the need to identify symptom clusters to aid in symptom management.

Recognizing that single, multiple, and symptom cluster research gives an overview of the most common symptoms exhibited by women survivors of breast cancer, the question arises of how background characteristics relate to the symptom experience of these women.

Relationship Between Background Characteristics and the Symptom Experience in Breast Cancer

The background characteristics of age, ethnicity, education, relationship status, employment status, and comorbid diseases have been associated with the symptom

experience in breast cancer. Age was related to symptoms in several research articles.

In a study of 418 women awaiting surgery, a significant negative correlation between

age and expected pain was found with older women more likely to expect less

postoperative pain than younger women (Schnur et al., 2007). Younger women (<40) in

a sample of 174 women post mastectomy were found to have a significantly increased

risk of pain lasting beyond the expected three months healing (Fabro et al., 2012). In a

study of fatigue (N=373), with 80% of the participants ≥50 years, menopausal symptoms

related to higher levels of fatigue (Glaus et al., 2006). In a study of sleep disturbance

(N=398), women who had high levels of sleep disturbance prior to surgery and for six

months after surgery were younger at age 53 (SD 10.9) than the women at age 57.7

(SD 12.1) who had low levels of sleep disturbance throughout this same timeframe (Van

Onselen et al., 2012). Three studies reported younger women had greater depression

and anxiety than older women with ages noted for older women as over age 50

(Howard, Anderson, Ganz, Bower, & Stanton, 2012), over age 57 (Khan et al., 2012),

and no age given (Mosher & Danoff-Burg, 2005). Age was found to have no

association with depression in a study of 120 women after cancer treatment (Brunault et

al., 2012). Age was related to distress or general physical and psychological problems

in several studies. Distress was noted to be lower in older women although "older" was

not defined in one study (Matthews et al., 2012) and was defined as being age 50 or

older in two literature reviews (Knopf, 2007; Knopf, 2011). Mosher and DuHamel (2010)

found age to not be significantly associated with distress level.

Ethnicity was addressed in a few studies. In a study of 139 women post adjuvant

treatment, Hispanic women were more likely to report multiple symptoms than Black or

White women (Fu et al., 2009). Mosher and Duhamel (2010) found ethnicity was not associated with distress in 173 metastatic breast cancer patients comprised of Hispanic, Black, and White ethnic backgrounds.

Education was linked to symptoms in three studies. Lower educational level was associated with increased sleep disturbance (Bardwell et al., 2008), higher levels of depression (Akin-Odanye, Chioma, & Abiodun, 2011), and with less distress (Kenefick, 2006).

Relationship status was associated with symptoms in two studies. Being married or living with a partner produced greater symptom distress in one study (Kenefick, 2006), while marital status was not associated with depression in two other studies (Akin-Odanye et al., 2011; Brunault et al., 2012).

Employment status was discussed in three studies. Being unemployed was associated with persistent treatment-related symptoms in one study (Fu et al., 2009) and was not associated with depression in another study (Akin-Odanye et al., 2011). Being unable to return to work was independently associated with the sequelae of an advanced stage of breast cancer in a study of 96 women survivors of breast cancer (Villaverde et al., 2008).

Comorbid conditions also need to be addressed to note any relationship between these covariates and the breast cancer symptom experience. No articles were found that expressly considered any relationship.

Relationship Between the Symptom Experience and Outcomes in Breast Cancer

Several studies have looked at the relationship of symptoms to outcomes in women survivors of breast cancer. Pain, fatigue, and sleep disturbance symptoms were negatively correlated with optimism, self-transcendence, and positive mood in 93

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women receiving radiotherapy (Matthews et al., 2012). Women survivors of breast

cancer were questioned about the symptoms of pain, fatigue, sleep disturbance, and

depression and how these symptoms affected activity and life satisfaction (Berger et al.,

2012). Pain was consistently associated with severity of the other symptoms and with

lower functioning. In another study, women with breast cancer receiving chemotherapy,

with or without radiation, were assessed for pain, fatigue, sleep disturbance, and

depression related to functional status and quality of life at three time points: the week

prior to the second chemotherapy cycle, immediately following the conclusion of

chemotherapy, and one year from the initiation of chemotherapy (Dodd, Cho, Cooper, &

Miaskowski, 2010). Subgroups of mild, moderate, and all high symptoms were identified

through cluster analysis. At one year after treatment initiation, the women with all high

symptoms reported significantly poorer physical functional status and quality of life. At

the conclusion of chemotherapy women were questioned regarding pain, fatigue, and

depression with moderately, significant correlations found between these three

symptoms to each other and with pain and fatigue moderately and significantly

correlating with health status (Gaston-Johansson et al., 1999). Pain, fatigue,

depression, and anxiety were assessed related to quality of life (So et al., 2009).

Women (N=215) receiving chemotherapy had higher levels of these four symptoms with

poorer quality of life scores than those receiving radiotherapy. The authors found that

there were significant, moderate correlations to support a cluster for the four symptoms.

Pain, depression, anxiety, and stress symptoms were assessed in a study of 85

women post treatment and were associated with functional independence and well-

being (Khan et al., 2012). Women in this study reported on average two years post

treatment: breast-related pain, 75%; depression, 22%; anxiety, 19%; and stress, 19%. The majority of these women reported minimal change in their physical functioning with one third noting the highest impact on their psychological well-being.

Fatigue, sleep disturbance, and depression were studied in 90 metastatic breast cancer patients with higher levels of these symptoms resulting in greater functional impairment (Mosher & DuHamel, 2010). Fatigue, weight gain, and altered sexuality reported following chemotherapy adversely affected quality of life (Wilmoth, Coleman, Smith, & Davis, 2004). Treatment-related lymphedema symptoms in women survivors of breast cancer were assessed with a cluster identified with five symptoms including fatigue, limb sensation, loss of body confidence, decreased physical activity, and psychological distress (Ridner, 2005). Quality of life was the outcome in this study with overall poor quality of life reported.

Pain, fatigue, sleep disturbance, depression, and anxiety have been studied in various combinations, as well as with additional symptoms, in women survivors of breast cancer with anger not investigated in any detail. The outcomes of quality of life and physical functioning have been used most frequently. However, a variety of other outcomes have also been utilized.

Summary of Symptom Research in the Breast Cancer Literature

The literature review of research studies on women survivors of breast cancer illustrates the variety of symptoms that various researchers considered during diverse timeframes, various treatment modalities, and various stages of the breast cancer experience. The research to date has included studies of single symptoms and multiple symptoms. Women survivors of breast cancer most often present with multiple symptoms. Several different symptom clusters were identified in various studies. There

was no definitive number in a cluster, with cluster size ranging from two to five symptoms within the cluster. Pain, fatigue, sleep disturbance, depression, and anxiety are the symptoms reported to be most prevalent in the breast cancer research.

The relationships of background characteristics to symptoms are limited in the breast cancer research. Older women, with various ages denoted for older, were found to more likely expect less postoperative pain, have higher levels of fatigue, and less sleep disturbance, depression, and anxiety than younger women. Studies conflicted on whether distress was higher or lower in older women. Studies were few and inconsistent regarding ethnicity, education, relationship status, and employment status. Hispanic women were found to more likely report multiple symptoms than Black or White ethnicities in one study with ethnicity not associated with distress in another study. Lower educational levels were associated with increased sleep disturbance and depression but with lower distress in various studies. Being in a relationship was associated with greater symptom distress in one study, with marital status having no association to depression in two other studies. Being unemployed was linked to persistent symptoms in one study and had no association to depression in another study.

The symptom experience related to outcomes showed symptoms related to a variety of outcomes. Outcomes included optimism, well-being, quality of life, activity or functioning, and illness perception, but not specifically social role function.

The sample sizes in the research studies reviewed ranged from 23-418, with the majority of the sample sizes below 135. There were two outliers, a study of 2,645 participants who were part of a larger dietary study, and 3,754 participants who were

part of a nationwide study. Hierarchical, factor, regression, and cluster analysis were the most common methodologies used.

The significant findings that reveal the gaps in the literature requiring a production of new knowledge include a more inclusive view of the symptom experience looking at the physical health symptoms of pain, fatigue, sleep disturbance and the mental health symptoms of depression, anxiety, and anger in relationship to the outcomes of physical and social role functioning. There needs to be a consistent designation of symptom clusters for consistent reporting. There is a known higher incidence of older women surviving breast cancer, but little research linking age to the symptom experience. Many questions remain about the symptom experience of women survivors of breast cancer and the relationship of the symptom experience to background characteristics, especially age, and to functional physical and social outcomes. This study begins to address this gap in the empirical literature.

CHAPTER 3
METHODS

Introduction

The research aims are investigated using a descriptive, exploratory, cross-sectional, secondary analysis study design. This meets the "FINER" criteria for choosing a study design that is feasible, interesting, novel, ethical, and relevant (Hulley, Cummings, Browner, Grady, & Newman, 2007). The study is feasible with a secondary analysis dataset utilized. The study content is interesting and novel as indicated by the literature review of limited research on symptom clusters in oncology. Ethical considerations were met by obtaining University of Florida Health Science Center Institutional Review Board approval and maintaining data security. The study is definitely relevant with the increase of women breast cancer survivors and the need to identify and describe the symptom experience. By identifying symptom clusters in women survivors of breast cancer, this knowledge base can be expanded. The symptom clusters can be addressed and treatment strategies implemented by healthcare providers for the most positive physical and social functioning as women deal with breast cancer survivorship.

Design

This was a descriptive, exploratory, cross-sectional, secondary analysis of the dataset from the Patient Reported Outcomes Measurement Information System (PROMIS) Wave 1 from the National Institutes of Health (NIH) (PROMIS information retrieved from http://www.nihpromis.org/). The study describes and explores the symptom experience of women breast cancer survivors. The relationship between the symptom experience and the outcomes of physical and social role function were

investigated. Background characteristics were identified and associations with the symptom experience were examined.

NIH PROMIS Dataset

Overview

In 2004, a group of scientists from several United States academic institutions joined with the NIH to develop and evaluate measurements of patient-reported outcomes for a wide variety of chronic diseases to be made publicly available to the clinical research community (Cella et al., 2010). Based on the World Health Organization framework, domains were developed that resulted in three general components: physical, mental, and social health (Cella et al., 2007). Global items measuring one's location in each of these domains were calibrated using a sample of 21,133 participants who self-reported on these components within the domains (Cella et al., 2007; Cella et al., 2010). The five subdomains selected for initial item development were pain, fatigue, mental or emotional distress, physical functioning, and social role functioning (Cella et al., 2007). The physical health component included the domains of physical function, fatigue, pain, and sleep disturbance. The mental health component included the emotional distress domain including depression, anxiety, and anger. The social health component included the domains of social role performance and social role satisfaction. In addition to the domains, single item global indicators of pain, fatigue, mental or emotional distress, physical functioning, and social functioning were added. These are referred to in the PROMIS dataset as global health items (Cella et al., 2010).

PROMIS Sample

The PROMIS Wave 1 total sample dataset included 21,133 participants with data collected from July 2006 to March 2007. These participants were recruited from primary PROMIS research sites (n=1,532) or from YouGovPolimetrix (n=19,601). PROMIS network research sites included Duke University, University of Pittsburgh, Stanford University, and University of North Carolina. Recruitment from YouGovPolimetrix (Polimetrix) involved selection from a panel of over one million respondents who regularly participated in online surveys and had given pertinent personal information such as names and addresses. Polimetrix is a polling firm with a web portal allowing participants to express their views regarding public policy and current issues. These panelists were recruited via e-random digit dialing, web newsletter invitation, or through the internet where participants agree to participate in a survey for a compensation of less than $10. Polimetrix uses sample matching to obtain representative samples in a target population. The target selected for PROMIS was by gender (50% female), age (20% in each of five age groups: 18-29, 30-44, 45-59, 60-74, over 75), race/ethnicity (12.3% African American and 12.5% Latino/Hispanic to match the U. S. census), and education (10% less than high school graduate), with the added target of being representative of the U. S. general population (based on the 2000 U. S. census).

The overall sample (N=21,133) consisted of 52% female, median age of 50 years, with 12% age 18-29, 12% age 30-39, 16% age 40-49, 32% age 50-64, and 28% age 65 and older. Ethnicity included 82% White, 9% Black, 8% multi-racial, and 1% Asian/Pacific Islanders and Native Americans. Hispanic or Latino comprised 9% of the sample population. Education was 3% less than high school, 16% high school diploma, 39% some college, 24% college degree, and 19% advanced degree.

A non-clinical sample was designated as the general population. A clinical sample was designated if the participant reported receiving a specific diagnosis from a physician. The diagnosis or diagnoses related to the presence and degree of limitation of 25 chronic medical conditions such as coronary artery disease, stroke, diabetes, or cancer.

The clinical sample (n=7,883) was recruited from three universities who participated as PROMIS network research sites (University of Pittsburgh, Stanford University, and Duke University) and from Polimetrix. The mean age of this subsample was 57.4, with 4.1% age 18-29, 7.6% age 30-39, 13.9% age 40-49, 27.2% age 50-59, and 15.3% age 60-64, 31.2% 65-84, and 0.7% age 85 and older. In this clinical sample, 46.7% were female. Ethnicity was reported as 88.6% White, 5% Black, 5.2% multi-racial, 0.7% Asian/Pacific Islanders and Native Americans, and 0.5% Asian. In addition, 3.8% of the sample was Hispanic or Latino.

A subsample from the clinical sample (n=7,883) consisted of participants with breast cancer (n=106). The breast cancer participants consisted of 1.3% of the total clinical sample. Figure 3-1 gives the overview of the total PROMIS sampling design. When the dataset was obtained from PROMIS, the breast cancer participants were found to be from the clinical sample from Polimetrix only (n=7,080). Three of these participants were male, so the final number of women survivors of breast cancer used for the study was 103.

Study Sample

The sample of 103 women survivors of breast cancer ranged in age from 30 to 85, with a mean age of 60.4 years (SD=10.1). The vast majority of the sample (n=92, 89%) were between the ages of 50 and 85. The majority were ethnically White (n=98,

95%), highly educated with a college or advanced college degree (n=77, 75%), partnered (n=62, 60%), and employed (n=55, 53%). One third of the sample had no comorbid conditions, another third had only one comorbid condition, with the final third having two to five comorbid conditions. Table 3-1 provides a detailed description of the sample of 103 women survivors of breast cancer.

Measures

Original PROMIS Measurement Bank

All PROMIS instrument items were identified from a systematic search of measures with established psychometrics, as well as new item development by experts working in each domain area. The items were selected, classified, reviewed, and revised by domain experts. Focus groups confirmed definitions and assisted in identifying any new areas for item development in the future. Items were then sent for field testing. Final revisions were made after field testing.

Each of the domains had an investigative research team of experts in measuring and assessing each specific domain area. Each team completed an extensive literature review. Item response theory was utilized. Item development was accomplished using existing questionnaires as well as new item generation. Psychometric results were analyzed and presented to each domain working group. Response options use a five-option scale: 1=poor or not at all or never or none, 2=fair or a little, or rarely or mild, 3=good or moderately or sometimes or moderate, 4=very good or mostly or often or severe, 5=excellent or completely or always or very severe. It was determined that there was good discrimination of item fit with these five options. Respondent burden was considered in keeping responses available consistent. The pain intensity scale had an 11-point intensity scale, ranging from 0=no pain to 10=worst imaginable pain. The

response categories were pre-tested to confirm patient understanding followed by field testing for item calibration (Cella et al., 2010).

Measurement of Key Study Variables

For the purpose of this study, a subset of variables was selected representing the study concepts. These variables and their measurement are described below.

Five global variables from the PROMIS Wave 1 testing were analyzed. The three independent variables included the physical health symptoms of pain and fatigue and the mental health symptom of emotional distress (depression/anxiety/anger). The two dependent variables were physical functioning and social role functioning. The physical health symptom of sleep disturbance was not available for analysis since this variable was not included in the Polimetrix clinical sample which included the breast cancer participants. Background characteristics included age, ethnicity, education, relationship status, and employment status. Covariates included the number of comorbid disease conditions.

Independent variables

Pain: Pain was measured by a single item indicating the self-reported average pain intensity rating in the past seven days. Pain intensity was rated on an ordinal 11-point scale, ranging from 0=no pain to 10=worst imaginable pain. This variable was recoded to evaluate the prevalence of pain (0=no pain, 1=pain).

Fatigue: Fatigue was measured by a single item on which participants rated their average level of fatigue over the past seven days. The response choices ranged ordinally from one to five: 1=none, 2=mild, 3=moderate, 4=severe, and 5=very severe. This variable was recoded to evaluate the prevalence of fatigue (0=no fatigue, 1= fatigue).

Depression/Anxiety/Anger: Depression, anxiety, and anger were measured using a single item. Participants were asked, "In the past 7 days, how often have you been bothered by emotional problems, such as feeling anxious, depressed or irritable?" The response choices ranged ordinally from one to five: 1=never, 2=rarely, 3=sometimes, 4=often, and 5=always. This variable was recoded to evaluate the prevalence of depression/anxiety/anger (0=no depression/anxiety/anger, 1=depression/anxiety/anger).

Dependent variables

Physical Functioning: Physical function was measured by self-report of the extent that participants were able to carry out everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair. This was a single item, with possible responses ranging ordinally from one to five: 1=not at all, 2=a little, 3=moderately, 4=mostly, and 5=completely. Since only three participants rated their functioning in the 1-3 categories, this variable was recoded. No participant responded with a "not at all". The two participants who answered "a little" were recoded as missing data. The one participant who answered "moderately" was recoded into the "mostly" group. This left 101 participants who could either "mostly" or "completely" carry out their everyday physical activities resulting in a binary variable.

Social Role Functioning: Social role functioning was measured by a single item ascertaining self-report of satisfaction with social activities and relationships. The responses ranged ordinally from one to five: 1=poor, 2=fair, 3=good, 4=very good, and 5=excellent. The variable was left in its original ordinal form.

Background characteristics

Demographic variables were assessed via a standardized clinical form. Participants' age, ethnicity, level of education, relationship status, and employment status were collected. This same clinical form asked participants to report a diagnosis confirmed by a physician of any of 25 chronic medical comorbidities or conditions such as hypertension or heart attack. Age was coded as a continuous variable by actual chronological age as well as by a binary ordinal variable of <50 or ≥ 50 years. Ethnicity was recoded as a categorical, nominal variable of White, Black, or other. Level of education was recoded into a binary variable of high school graduate/AA/technical degree or college/advanced degree. Relationship status was recoded into a dichotomous variable of partnered (married or living with partner in committed relationship) or not partnered (never married, separated, divorced, or widowed). Employment status was recoded as a dichotomous variable of employed (full-time or part-time) or not employed (unemployed, homemaker, retired, or on disability). This was the only variable that had missing data, with four participants not having employment status determined. Comorbidy was recoded from zero to five indicating the number of comorbid conditions as a categorical variable.

Procedures

Protection of Human Subjects

Institutional Review Board approval from the University of Florida Health Science Center was obtained for this study via electronic submission. The protocol number is IRB201200247 and exempt status was received for data collection determined to be non-human/exempt, completely anonymous information, with de-identified subjects.

The study qualified as "Nonhuman Subjects Research" according to University of Florida myIRB.

Data Acquisition

A research proposal was submitted to the National Institutes of Health (NIH) requesting the PROMIS Wave 1 database. This proposal was approved in November 2012. The NIH PROMIS data were transmitted to the investigator in an encrypted, password-protected file. The data were de-identified by the NIH staff prior to transmission. The data are stored and secured on an encrypted share drive in the University of Florida College of Nursing with access only by the researcher and the researcher's committee chair. The researcher's laptop was also encrypted by the University of Florida College of Nursing Information Technology Department to comply with all university and college security policies. The data are accessible only by passcode.

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Statistics

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The statistical software, PAWS Statistics, version 18 (formerly SPSS), was used for the univariate, bivariate, and multivariate analyses. Data were transmitted in SAS format and imported into the PAWS database. Results were considered statistically significant based on a p-value of less than .05. The analysis plan and procedures are presented below.

Aim 1

The prevalence and number of self-reported physical health symptoms (pain, fatigue) and mental health symptom (depression/anxiety/anger) among women survivors of breast cancer were determined using univariate, descriptive statistics including frequency data of numbers and percentages, means, and standard deviations.

The three independent variables were each recoded into dichotomous, categorical variables to determine prevalence. These same variables were used with their ordinal values to determine symptom intensity.

Aim 2

Bivariate correlational analysis examined relationships between symptoms. Since the independent variables of physical and mental health symptoms were not normally distributed, the non-parametric Spearman's correlation was used for the analysis. Associations were confirmed and multivariate analysis was conducted to determine how symptoms combined. Hierarchical cluster analysis revealed preliminary information leading to nonhierarchical *k*-means cluster analysis to determine the identifiable symptom clusters in women survivors of breast cancer.

Aim 3

Univariate analysis determined that none of the background characteristics (age, ethnicity, education, relationship status, employment status, comorbid conditions) were normally distributed. The data were categorical, ordinal, or nominal, with the exception of age, which was a continuous variable. Non-parametric bivariate analysis, which is distribution-free, indicated for categorical data, with the assumption of independence of data, was therefore employed to investigate the relationships between the background characteristics and the symptom clusters. The Kruskal-Wallis test (non-parametric equivalency of the one-way independent ANOVA), contingency tables, chi-square, and Fisher's exact test were the statistics utilized to determine any relationships between the background characteristics and the symptom clusters. Due to being unable to run more than a 2x2 contingency table in PAWS (version 18), SAS (version 9.3) was used

for tables over 2x2, so that a Fisher's exact test could be utilized if the cell assumption of no more than 10% of the cells having expected frequencies below 5 was violated.

Aim 4

Univariate analysis with frequencies and percentages was accomplished for description of the physical and social role function dependent outcomes. The physical function variable was not normally distributed and was recoded to a categorical, ordinal variable. Bivariate analysis with a contingency table, chi-square, and Fisher's exact test was used to investigate the relationship between symptom clusters and the physical function outcome. The social function variable was also not normally distributed. The categorical, ordinal variable was retained in its original form. Univariate analysis compared means and standard deviations of level of social function in the clusters. Bivariate analysis with the Kruskal-Wallis test (non-parametric equivalency of the one-way independent ANOVA), followed by the Wilcoxon rank-sum test (non-parametric equivalent of the independent *t*-test) was utilized to investigate the relationships between the symptom clusters and the social role function outcome.
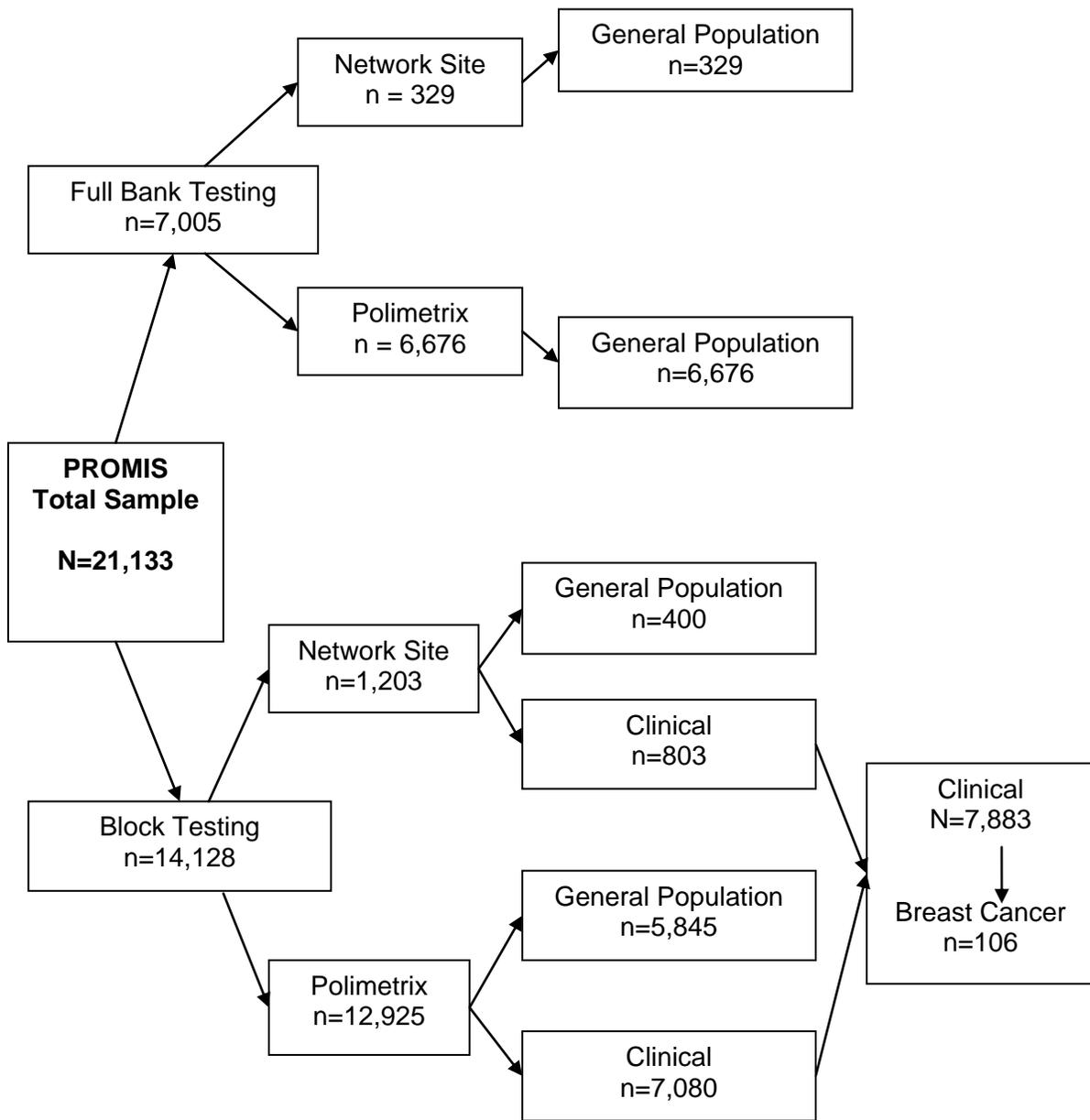
Figure 3-1. PROMIS sample design

Table 3-1. Description of sample (N=103)

Variables	N (%)	Mean (SD)
Age, age ranges: 30-85	103 (100%)	60.4 (10.1)
Age Group		
<50	11 (11%)	
≥50	92 (89%)	
Ethnicity		
White	98 (95%)	
Black	2 (2%)	
Other	3 (3%)	
Hispanic		
Yes	4 (4%)	
No	99 (96%)	
Education		
High school grad/AA or technical degree	26 (25%)	
College/advanced degree	77 (75%)	
Relationship status*		
Partnered	62 (60%)	
Not partnered	41 (40%)	
Employment status		
Employed	55 (53%)	
Not employed	44 (43%)	
Not determined	4 (4%)	
Number of comorbid conditions		
0	35 (34%)	
1	33 (32%)	
2	21 (20%)	
3	12 (12%)	
4	1 (1%)	
5	1 (1%)	

*Relationship status is coded as partnered or not partnered. Partnered included being married or living with a partner in a committed relationship. Not partnered indicated being never married, separated, divorced, or widowed.

CHAPTER 4
RESULTS

The following sections present the results of the statistical analyses of the symptom experience among women breast cancer survivors. Results are organized according to the study research aims.

Aim 1: To Describe the Prevalence and Number of Self-Reported Physical Health Symptoms (Pain, Fatigue) and Mental Health Symptom (Depression/Anxiety/Anger) Among Women Survivors of Breast Cancer.

Symptoms for women survivors of breast cancer included both physical and mental health symptoms. Pain was the most common symptom reported with 67% of the sample experiencing this symptom. Fatigue was reported by 62% of the sample. Similarly, 63% of the women in this sample reported experiencing the mental health symptom (depression/anxiety/anger). The mean intensity of these symptoms was 1.6 (SD=1.8) for pain (0-10 scale), 1.8 (SD=0.7) for fatigue (1-5 scale), and 1.9 (SD=0.8) for mental health (1-5 scale). These intensity scores indicate low symptom severity (see Table 4-1).

The majority of women survivors of breast cancer in this sample reported experiencing two or three symptoms (n=68, 66%). Eleven women (11%) reported no symptoms and 24 (23%) reported experiencing only one symptom (see Table 4-2).

Aim 2: To Determine Whether and How Symptoms Combine to Create Identifiable Clusters In A Sample Of Women Survivors Of Breast Cancer.

Bivariate Analysis

The results of correlation analysis revealed statistically significant associations between symptoms. Since the independent variables were not normally distributed, the non-parametric Spearman's correlation was used to examine relationships. Correlations were as follows: pain-mental health (r_s=.26, $p<.01$), pain-fatigue (r_s=.42,

59

p<.001), and fatigue-mental health (r_s=.34, p=.001) indicating small to moderate relationships between these symptom variables, and leant support for the identification of symptom clusters.

Multivariate Cluster Analysis

Hierarchical cluster analysis was selected to analyze the data using the independent symptom variables to reveal any natural groupings or clusters. This type of cluster analysis lends itself to smaller samples of less than a few hundred (PAWS, version 18). The agglomerative method was selected with each participant with their specific symptom(s) forming the initial individual clusters, progressing to similar clusters merging to form new clusters based on similarity or proximity based on distance (Hair & Black, 2000; Meyers, Gamst, & Guarino, 2013).

One goal of cluster analysis is to maximize the distance between clusters. This facilitates detection of true, independent clusters. In this study, the squared Euclidean distance, which is the distance between any two clusters determined by the sum of the score differences across all participants, was used (Hair & Black, 2000; Meyers et al., 2013). The clustering algorithm used in the majority of the cluster research reviewed was used for this study: average linkage or between-group linkage. This average linkage measures the average distance between all pairs of two clusters' members. Since the pain measurement (0-10 scale) varied from the fatigue (1-5 scale) and the mental health (1-5 scale) measurement, standardization procedures were used to create z-scores. These *z* scores are standardized to a mean of 0 and a SD of 1.

The analysis revealed from two to eight clusters with no convergence into a parsimonious solution. Analysis of the cluster dendrograms revealed that a three-

cluster solution showed the most discrimination and reduced the outliers. Thus, the

decision was made to proceed to the nonhierarchical *k*-means cluster analysis which

has been noted to complement hierarchical clustering (Hair & Black, 2000).

A second type of cluster analysis, *k*-means clustering, is indicated with a larger

number of cases or participants with fewer variables (Meyers et al., 2013). Given that

only three symptoms were being analyzed, this method was thought to be appropriate.

This clustering method uses the agglomerative procedure with clusters joined at each

stage. The process is also considered iterative as each stage begins over again based

on the results of the prior stage. The Euclidian distance between the center of each

cluster, or an average of the clustering variables and the non-clustered variables

occurs, with the cluster with the smallest distance absorbed within the next closest

cluster (Meyers et al., 2013). The major difference between hierarchical and *k*-means

clustering is that the number of clusters is specified a priori. Three clusters were

stipulated by the researcher based on the preliminary hierarchical clustering results and

the sample's low symptom intensity scores. Two and four clusters were also examined

and rejected, with two clusters exhibiting less discrimination and little variability and four

clusters adding a one-participant outlier.

Using *k*-means cluster analysis, results are presented based on the final cluster

centers and cluster membership as the significant components (Meyers et al., 2013).

The final cluster centers are the *z*-score means of the cluster variables (Meyers et al.,

2013). The symptom variables were standardized and transformed into *z*-scores.

Iteration is recommended to be set at 50 to assure a criterion threshold is reached.

Iteration continues until 50 is reached or until the threshold is revealed. In effect, a

reassignment of membership occurs at each iteration with the cluster centers based on each new cluster reconfiguration until convergence is achieved due to no change or a very small change in the final cluster centers.

Based on the *k*-means approach, a 3-cluster solution emerged from the data. Convergence was reached in six iterations. Univariate ANOVAs indicated that the clustered groups differed significantly on all three symptom variables (all p values <.001). The final cluster centers, together with the number of cases in each cluster, are shown in Table 4-3. The range of *n* for each cluster was 8 to 53, with two clusters relatively equivalent in size (42 and 53 cases). Cluster 1 (n=53) can be characterized as all minimal symptoms for pain, fatigue and mental health. Cluster 2 (n=42) had all mild symptoms. Cluster 3 (n=8) had all moderate symptoms.

Aim 3: To Investigate the Relationships Between Background Characteristics (Age, Ethnicity, Education, Relationship Status, Employment Status, Comorbid Conditions) and Symptom Clusters.

The investigation of the relationships between background characteristics (age, ethnicity, education, relationship status, employment status, comorbid conditions) and the three identified clusters was completed using bivariate analysis. Non-parametric statistics were used since the variables were not normally distributed, were categorical, and met the assumption of independence of data. These measures included the independent-samples Kruskal-Wallis test, contingency tables, chi-square, and Fisher's exact test. Fisher's exact test was used for the p-value when the frequency assumption was violated with sparseness of the cells not meeting the assumption of no more than 10% of the cells having the expected frequency below 5 (Portney & Watkins, 2009). No significant relationships between any of the background characteristics and the three symptom clusters were found (see Table 4-4).

Age was left as a continuous variable when looking at the cluster groupings, as well as comparing younger (<50 years) versus older (≥50 years). The independent-samples Kruskal-Wallis test indicated that age was not significantly different across the three clusters (χ^2=4.7, p=.097). The data showed that women's ages in Cluster 3 (All Moderate Symptoms) were 10 years younger than the women in Cluster 1 (All Minimal Symptoms). Due to the small sample size, there was limited power to detect an age difference. When comparing younger (<50 years) to older (≥50 years) women survivors of breast cancer via contingency tables, chi-square, and Fisher's exact test, there was a trend of women being younger as symptom severity increased from Cluster 1 to Cluster 2 to Cluster 3 (χ^2=6.6, p=.06).

Ethnicity and cluster membership was evaluated with Fisher's exact test, and no significant relationship was found (χ^2=1.4, p=.89). Education was examined with contingency tables and chi-square and revealed no significance between education and cluster groupings (χ^2=.03, p=.98). The assumption of frequency of no more than 10% cells below 5 was met, so no further testing was required. Relationship status revealed through contingency tables and chi-square analysis a need to run the Fisher's exact test due to low cell frequencies. No significant relationship between being partnered or not partnered and the cluster groups was found (χ^2=.40, p=.86). Contingency tables and chi-square analysis advising a Fisher's exact test demonstrated no significant relationship between employment and cluster groupings (χ^2=.17, p=1.00). Employment status was the only background characteristic for which the entire sample did not give complete information. The statistics were evaluated based on 99 rather than 103 women survivors of breast cancer. Contingency tables and chi-square analysis

required running the Fisher's exact test which confirmed no significant relationship between the number of comorbid conditions and the cluster groups (χ^2=17.36, p=.29).

Aim 4: To Investigate the Relationships Between Symptom Clusters and the Functional Outcomes (Physical Function, Social Role Function).

The relationships between the identified symptom clusters and the functional outcomes of physical function and social role function showed significant relationships. Univariate analysis showed the frequencies and percentages of the sample responses for physical function in Table 4-5 for the extent the women were able to carry out physical activities such as walking, climbing stairs, or carrying groceries. The majority of women survivors of breast cancer (n=100, 97%) were "mostly" or "completely" able to carry out physical activities. Social role function of satisfaction with social activities and relationships scoring with frequencies and percentages is exhibited in Table 4-6 for this study sample. The majority of women (n=92, 89%) were satisfied with their social role activities and relationships by rating social role function as "good", "very good", or "excellent".

Bivariate analysis was conducted with contingency tables and chi-square tests and the expected cell count frequencies less than 10% required a Fisher's exact test. A significant relationship between the three identified cluster groups and the physical function outcome (χ^2=6.9, p=.03) was revealed. As the symptom severity increased from Cluster 1 (All Minimal Symptoms) to Cluster 2 (All Mild Symptoms) to Cluster 3 (All Moderate Symptoms), the level of physical functioning was lower. See the final cluster analysis of physical function in Table 4-7.

Social role function was examined with univariate analysis of means and standard deviations. The independent-samples Kruskal-Wallis test revealed a

significant difference (χ^2=11.9, p=.00) between the cluster groups. The mean social role

function values were lower in clusters with higher symptom severity (see Table 4-8).

With this significant result, a multiple comparison of cluster groups was conducted using

the bivariate analysis of Wilcoxon rank-sum test (non-parametric equivalent of the

independent t-test) to identify which clusters were different. Clusters 1 and 2 were not

significantly different related to social role function (W_s=1783.5, p=.07). Clusters 1 and

3 were significantly different related to social role function (W_s=103.5, p=.00). Clusters

2 and 3 were also significantly different related to social role function (W_s=120.0, p=.03).

When comparing the means and standard deviation in the three cluster groups

regarding social role function the means were significantly lower from Cluster 1 to

Cluster 3 and from Cluster 2 to Cluster 3, indicating that higher symptom severity was

associated with lower social role functioning (see Table 4-9).

Table 4-1. Prevalence and intensity (0-1=none) of symptoms (N=103)

Symptom	N (%)	Mean (SD)
Pain		
Prevalence	69 (67%)	
Intensity (0-10)		1.6 (1.8)
Fatigue		
Prevalence	64 (62%)	
Intensity (1-5)		1.8 (0.7)
Mental health symptom (depression/anxiety/anger)		
Prevalence	65 (63%)	
Intensity (1-5)		1.9 (0.8)

Table 4-2. Frequency distribution of number of symptoms reported (N=103)

Number of symptoms	Frequency	%
0	11	11
1	24	23
2	30	29
3	38	37
Total	103	100

Table 4-3. Final cluster analysis *z* score means on pain, fatigue, and mental health variables

Variable	Cluster 1 All Minimal Symptoms n=53	Cluster 2 All Mild Symptoms n=42	Cluster 3 All Moderate Symptoms n=8
Pain Intensity (0-10 with 0: no pain and 10: worst pain imaginable)	-.60	.36	2.11
Fatigue Intensity (1-5 with 1: none and 5: very severe)	-.65	.47	1.86
Mental health (depression/anxiety/ anger) Intensity (1-5 with 1: never and 5: always)	-.43	.25	1.52

Table 4-4. Final cluster analysis relationship to background characteristics

Background Characteristic	Cluster 1 All Minimal Symptoms n=53	Cluster 2 All Mild Symptoms n=42	Cluster 3 All Moderate Symptoms n=8	Chi-square/ p-value
Age, ranges: 30-85	M (SD) 62.0 (10.5)	M (SD) 60.1(8.5)	M (SD) 51.9 (11.5)	χ^2=4.7 p=.10
Age Group:				
<50	n= 4, 7.5%	n= 4, 9.5%	n= 3, 37.5%	χ^2=6.6
≥50	n=49, 92.5%	n=38, 90.5%	n= 5, 62.5%	p=.06
Ethnicity:				
White	n=50, 94.3%	n=39, 92.8%	n= 8, 100%	χ^2=1.4
Black	n= 2, 3.7%	n= 1, 2.4%	n= 0, 0%	p=.89
Other	n= 1, 2.0%	n= 2, 4.8%	n= 0, 0%	
Education:				
High school grad/AA/ technical degree	n=13, 24.5%	n=11, 26.2%	n= 2, 25%	χ^2=.03 p=.98
College/advanced degree	n=40, 75.5%	n=31, 73.8%	n= 6, 75%	
Relationship Status:				
Partnered	n=32, 60.4%	n=26, 61.9%	n= 4, 50%	χ^2=.40
Not partnered	n=21, 39.6%	n=16, 38.1%	n= 4, 50%	p=.86
Employment Status: (N=99)	N=51	N=40	N=8	
Employed	n=28, 54.9%	n=22, 55%	n= 5, 62.5%	χ^2=.17
Not employed	n=23, 45.1%	n=18, 45%	n= 3, 37.5%	p=1.00
Number of comorbid conditions				
0	n=21, 39.6%	n=12, 28.6%	n= 2, 25.0%	
1	n=18, 33.9%	n=13, 30.9%	n= 2, 25.0%	
2	n=10, 18.9%	n=10, 23.8%	n= 1, 12.5%	χ^2=17.36 p=.29
3	n= 4, 7.6%	n= 6, 14.3%	n= 2, 25.0%	
4	n= 0, 0.0%	n= 0, 0.0%	n= 1, 12.5%	
5	n= 0, 0.0%	n= 1, 2.4%	n= 0, 0.0%	

Kruskal-Wallis test was used for chi-square and p-value for the age continuous variable. Contingency tables were used with chi-square for the age categorical variable, ethnicity, education, relationship status, employment status, and number of comorbid conditions. The p-value for education only was associated with the chi-square, with the remaining variables using the p-value of Fisher's exact test (due to cell sparseness).

Table 4-5. Physical function responses: able to carry out physical activities (N=103)

Response	Frequency	%.
5: completely	81	79
4: mostly	19	18
3: moderately	1	1
2: a little	2	2
1: not at all	0	0
Total	103	100

Table 4-6. Social role function responses: satisfaction with activities and relationships (N=103)

Response	Frequency	%.
5: excellent	35	34
4: very good	34	33
3: good	23	22
2: fair	9	9
1: poor	2	2
Total	103	100

Table 4-7. Final cluster analysis of physical function

Dependent Variable	Cluster 1 All Minimal Symptoms n=53 % (n)	Cluster 2 All Mild Symptoms n=42 % (n)	Cluster 3 All Moderate Symptoms n=6 % (n)	Chi-square/ p-value
Physical function				
4 (Mostly)	11.3% (6)	26.2% (11)	50% (3)	χ^2=6.9
5 (Completely)	88.7% (47)	73.8% (31)	50% (3)	p=.03

Table 4-8. Final cluster analysis of social role function

Dependent Variable	Cluster 1 All Minimal Symptoms n=53 Mean (SD)	Cluster 2 All Mild Symptoms n=42 Mean (SD)	Cluster 3 All Moderate Symptoms n=8 Mean (SD)	Chi-square/ p-value
Social role function (1=poor to 5=excellent)	4.15 (.91)	3.76 (1.06)	2.75 (1.04)	χ^2=11.9 p=.00

Table 4-9. Multiple comparisons of social role function in clusters

	First Cluster for Comparison	Second Cluster for Comparison	Wilcoxon (W_s)/ p-value
	Cluster 1 All Minimal Symptoms n=53	Cluster 2 All Mild Symptoms n=42	
Mean (SD)	4.15 (.91)	3.76 (1.06)	W_s=1783.5 p=.07
	Cluster 1 All Minimal Symptoms n=53	Cluster 3 All Moderate Symptoms n=8	
Mean (SD)	4.15 (.91)	2.75 (1.04)	W_s=103.5 p=.00
	Cluster 2 All Mild Symptoms n=42	Cluster 3 All Moderate Symptoms n=8	
Mean (SD)	3.76 (1.06)	2.75 (1.04)	W_s=120.0 p=.03

CHAPTER 5
DISCUSSION

Summary of Results

This study explored the prevalence, predictors, and consequences of symptom clusters in a secondary analysis of 103 women survivors of breast cancer using NIH PROMIS data. An adapted version of the New Symptom Management Model was used as the theoretical framework and organization for this exploration. The results indicated that the majority of women survivors of breast cancer experienced symptoms: 67% reported experiencing pain, 62% reported fatigue, and 63% reported mental health symptoms (depression/anxiety/anger). In addition, the majority of women (n=68, 66%) in this sample experienced two or three symptoms concurrently. The symptom intensity scores indicated overall low symptom severity. Three symptom clusters were identified that give insight into the symptom experience of women survivors of breast cancer based on the severity of the symptoms in the clusters: Cluster 1 (All Minimal Symptoms) (n=53), Cluster 2 (All Mild Symptoms) (n=42), and Cluster 3 (All Moderate Symptoms) (n=8). The background characteristic predictors (age, ethnicity, education, relationship status, employment status, comorbid conditions) revealed no significant relationships with the three identified symptom clusters. There was a trend that women in the more symptomatic cluster were younger. Symptom clusters did significantly relate to the physical and social role functional consequences or outcomes. Women in the more symptomatic clusters had lower physical and social role function.

Symptom Experience of Women Survivors of Breast Cancer

The symptom experience of women survivors of breast cancer is multifaceted and includes the conceptual issue of operationally defining a breast cancer survivor, the

prevalence of symptoms, the severity or intensity of the symptoms, and the number of self-reported symptoms. For this study, women survivors of breast cancer were operationally defined as women from the time of diagnosis and continuing throughout their lives, consistent with the current literature review. The women in this sample were part of a clinical sample recruited for a large NIH study. Breast cancer diagnosis was self-reported by the sample participants as being confirmed by a physician. Approximately two thirds of the women in this sample reported experiencing the three symptoms that were the focus of this study: pain, fatigue, and mental health symptoms (depression/anxiety/anger). The results of this study are consistent with the existing literature on fatigue (range in literature=60-80%) and higher than the published prevalence ranges for pain (40-50%) and depression and anxiety (20-30%). Anger has not been extensively studied in relation to breast cancer, thus there is no information about the prevalence of anger in this population in the literature.

The higher prevalence rate for pain may be indicative of using only one question in this study for that score, whereas other studies in the literature used multiple questions (intensity, location, severity). The literature did have one comparable study of 85 women with breast cancer in which pain was scored by one measure using a visual analog scale resulting in a higher pain prevalence of 75% (Khan et al., 2012). The high prevalence for the mental health symptom may reflect that the depression, anxiety, and anger symptoms were combined into one question for the current study, so the percentage may be cumulative based on this combination. This finding, however, is relatively consistent with one study that reported 79% prevalence of anxiety in a sample

of 154 women with breast cancer (Bender et al., 2005), with an expert panel selecting the items for representation of the symptom.

In this study, the range of symptom intensity scores indicated overall low symptom severity. For each symptom investigated, the means were below 2, indicating mild symptoms. As such, the pain experienced by most study participants did not meet the threshold of clinically significant pain (e.g., 4 on a 0-10 scale). These findings indicate that the majority of women breast cancer survivors experience mild, persistent symptoms. Surprisingly, most articles in the empirical literature on breast cancer described the symptom or symptoms experienced without addressing the severity of the symptoms. Thus, it is difficult to put the findings of this study into the extant literature on this topic.

Symptom Clusters in Women Survivors of Breast Cancer

Until recently, study of the symptom experience of cancer survivors has focused on single symptoms (e.g., pain or fatigue or depression or sleep disturbance). Within the past decade, attention has shifted to the multidimensional symptom experience, referred to as symptom clusters. Several studies in this area have confirmed the presence of symptom clusters, although the composition of the clusters varies from study to study. In the present study, three symptom clusters were found that were characterized by the intensity of pain, fatigue, and mental health symptoms experienced. This finding was comparable with one other research study on breast cancer in the literature. That study was a secondary analysis of 112 women with breast cancer receiving chemotherapy, with or without radiation, that identified four clusters based on pain, fatigue, depression, and sleep disturbance clustered by all low, mild, moderate, or all high symptom severity (Dodd et al., 2010). Using hierarchical cluster

analysis, the all high symptom group experienced poorer physical functional status and quality of life.

There are several conceptual and methodological issues in the symptom cluster literature, and each of these was addressed in the current study. One issue is the definition of a symptom cluster, and how many symptoms must be present to constitute a cluster. A symptom cluster in the nursing oncology literature initially was conceptually defined as having three or more coexisting symptoms (Dodd, Miaskowski, et al., 2001). This initial conceptual definition did not reflect the nature, intensity, or temporal aspect of concurrent symptoms. This original definition was challenged several years later (Kim et al., 2005) with the alternate definition of a symptom cluster having two or more symptoms related to each other and occurring simultaneously. A symptom cluster was operationally defined as having two or more symptoms for this study. This definition is congruent with the prevailing literature on this topic, but warrants further development and clarification as a means to assist in assessment and management of symptoms among cancer survivors (Dodd et al., 2004; Fan et al., 2007; Xiao, 2010).

Symptom cluster research has also focused on the number of symptoms in a cluster and what specific symptoms interact to constitute a cluster. The number and type of symptoms has varied across studies, and there is no clear consensus on this question. In addition, the characteristics of symptom clusters varied across type of cancer. Further, few studies have examined the symptom experience based on the intensity or severity of symptoms in the cluster formation. Despite these conceptual questions, the results of this study are congruent with one other research study that found four clusters of symptoms based on intensity or severity of a group of symptoms

(Dodd et al., 2010). This latter view is consistent with the theoretical framework of this study that indicates the symptom experience relates to more than just the presence; it also relates to the intensity, distress, or quality of the experience. Three symptom clusters were identified in this study using three independent variables of pain, fatigue, and mental health (depression/anxiety/anger) symptoms: Cluster 1 (All Minimal Symptoms) (n=53), Cluster 2 (All Mild Symptoms) (n=42), and Cluster 3 (All Moderate Symptoms) (n=8). This study result is consistent with a research study that looked at symptom severity in their analysis (Dodd et al., 2010). This study revealed that the symptom experience varied based on the intensity of the symptoms in the clusters. One distinct difference between this published study and the present study is that the study sample involved women survivors of breast cancer undergoing active treatment. In the current study, it was not possible to ascertain where the women were in their treatment trajectory as that data was not collected in the PROMIS data. Proximity to treatment might impact the number and severity of symptoms experienced by women with breast cancer (Dodd et al., 2010). In the study by Dodd and colleagues, the symptoms were milder at the beginning of treatment trajectory, progressing to moderate to severe symptoms at the conclusion of treatment, with a return to milder level of symptoms six months later. This is a consistent finding related to active treatment in an oncology sample of patients, over half of whom had moderate to severe levels of two or more symptoms while undergoing treatment (Miaskowski et al., 2006). It is possible that the results of the current study might be different if it were known where in the treatment trajectory the women were.

A second issue is the method of establishing a cluster. In the empirical literature on this topic, two statistical methods have been used, factor analysis and cluster analysis. Factor analysis and cluster analysis have similarities in that both analyses seek to identify groups. Factor analysis is a data reduction statistical method to combine variables to a manageable size (Field, 2009), and it has been used in the oncology literature. This approach has been most commonly used in studies that had a large cadre of symptoms to analyze. For example, two oncology research studies used factor analysis with 22 to 26 symptoms (Breen et al., 2009; Cleeland et al., 2000). One combined sample of breast and prostate cancer patient data used factor analysis with 16 symptoms (Kim et al., 2009a), while a breast cancer only sample factor analyzed 16 symptoms (Fu et al., 2009).

In comparison, cluster analysis is used to sort groups or cases based on a small set of variables (Meyers et al., 2013). In the general oncology literature, hierarchical cluster analysis has been used with four symptoms (Miaskowski et al., 2006). In the breast cancer literature, four symptoms were also investigated using hierarchical cluster analysis (Dodd et al., 2010). Based on the two statistical options of factor or cluster analysis, and the oncology and breast cancer research literature, cluster analysis was selected for this study. Hierarchical followed by *k*-means cluster analysis was selected as the most appropriate way to look at relating symptom variables and combining these symptom variables into realistic, applicable numbers and types of clusters to contribute to the science and to find meaningful answers to help women survivors of breast cancer towards productive functioning.

Background Characteristics as Predictors of Symptom Clusters in Women Survivors of Breast Cancer

In this study, the background characteristics (age, ethnicity, education, relationship status, employment status, comorbid conditions) were not significantly associated with the symptom clusters. That is, these background variables were not significantly influencing whether women had all minimal, all mild, or all moderate symptoms. The fact that background characteristics did not influence the identified symptom clusters is consistent with the majority of the breast cancer research literature. Other studies found Hispanic women more likely to report multiple symptoms compared to Black or White women (Fu et al., 2009), while Mosher and Duhamel (2010) found ethnicity not associated with distress. Education level associated with symptoms was equivocal in the literature (Akin-Odanye et al., 2011; Bardwell et al., 2008; Kenefick, 2006), as was relationship status (Akin-Odanye et al., 2011; Brunault et al., 2012; Kenefick, 2006). Employment status was not related to symptomotology in some studies and related in others (Akin-Odanye et al., 2011; Fu et al., 2009; Villaverde et al., 2008). Thus, the role of these background variables remains equivocal.

No research articles were found that examined the relationship of comorbid conditions to symptoms. Descriptive statistics on the number of comorbid conditions was mentioned, but no studies examined this variable in relation to the symptom experience. Perhaps the prior research on this topic did not address comorbidity because the focus was primarily on identifying clusters and their outcomes since the sample participants were undergoing active cancer treatment (Dodd et al., 2010; Miaskowski et al., 2006).

It would be easy, however, to attribute differences in cluster group membership to the health status of the women. For instance, one could argue that women with more symptoms were simply more ill. The results of this study, however, revealed no significant differences across symptom clusters in the number of diagnosed comorbid conditions experienced by the women in this sample. This finding reflects the fact that overall, the women in this sample were relatively healthy and high functioning. It may also indicate that the 25 diagnoses examined in this study (e.g. high blood pressure, asthma) may have clinical relevance to overall health, but may not be associated with physical symptoms of pain or fatigue, or mental health symptoms.

The results of this study did not show a significant association between age and symptom clusters. However, the data showed that women's ages in Cluster 3 (All Moderate Symptoms) were 10 years younger than the women in Cluster 1 (All Minimal Symptoms). When comparing younger (<50 years) to older (≥50 years) women, there was a trend for younger women to be in more highly symptomatic clusters (χ^2=6.6, p=.06). Several research studies revealed that younger women tended to have more severe symptoms for pain, depression, anxiety, and distress. Younger women (<40) in a sample of 174 women post mastectomy were found to have a significantly increased risk of pain (Fabro et al., 2012). Three studies reported younger women had greater depression and anxiety than older women (Howard et al., 2012; Khan et al., 2012; Mosher & Danoff-Burg, 2005). Distress was noted to be lower in older women (Knopf, 2007; Knopf, 2011; Matthews et al., 2012). Fatigue was higher in older women (≥50 years) survivors of breast cancer in 80% of the study participants (N=373) undergoing hormonal treatment (Glaus et al., 2006). The mean age of the women in this current

study was 60.4 years (SD 10.1) which approximates the median age for a breast cancer diagnosis, which is 61 years (ACS, 2011). This is a somewhat encouraging finding for older women who are breast cancer survivors in that their symptom experience may be reduced relative to younger women. This may also reflect that younger women often have more invasive forms of breast cancer.

Outcomes or Consequences of Symptoms Clusters in Women Survivors of Breast Cancer

One of the fundamental questions addressed in this study was whether the experience of living with multiple symptoms mattered in terms of everyday functioning. The results of this study confirm these relationships: symptom clusters were significantly associated with lower physical functioning and lower satisfaction with social role functioning.

The majority of women survivors of breast cancer in this study (n=100, 97%) were "mostly" or "completely" able to carry out physical activities. However, women in symptom clusters identified as more intense reported significantly lower physical functioning. This result is consistent with the breast cancer research associating high symptom experiences with poorer physical functional status (Dodd et al., 2010) and greater physical functional impairment (Mosher & Duhamel, 2010).

In addition, the majority of women (n=92, 89%) were satisfied with their social role activities and relationships and rated their social role function as "good", "very good", or "excellent". However, there were significant associations between the symptom clusters and satisfaction with their social role functioning. Post-hoc analysis revealed that Cluster 3 (All Moderate Symptoms) was significantly different from the other two clusters and women in this group had lower satisfaction with social role

functioning. This is a new finding to add to the science of cluster analysis. Social role function was not examined in any of the empirical breast cancer literature related to symptom clusters and outcomes. Outcomes included in the literature typically included quality of life, well-being, optimism, activity or physical functioning, and illness perception, but no reference specifically to social role function. Not surprisingly, more frequent and intense symptoms are associated with lower quality of life (Dodd et al., 2010) and lower well-being (Khan et al., 2012). Thus, these findings on physical functioning and social role functioning are consistent with the broader study of quality of life and well-being outcomes, and highlight the fact that these constructs are multidimensional, incorporating both physical and social functioning.

Taken together, however, the results of this study highlight several important findings. First, symptom clusters are discernible and they differ according to the intensity of the symptom experience. Second, symptom clusters have an impact on the daily lives of women breast cancer survivors. Even in this relatively small sample with a restricted range of symptom intensity (mean intensity scores for pain, fatigue, and mental health concerns were all in the mild range), women in clusters identified as representing elevated symptoms reported worse functioning. Thus, the experience of having three symptoms as opposed to just one, even when they are mild in intensity, has an impact on daily life. This has implications for survivorship that healthcare practitioners need to be aware that even mild, concurrent pain, fatigue, and mental health symptoms may require treatment for optimal functioning.

Limitations

There are several limitations of this study that must be acknowledged. First, the study was a secondary analysis of collected data. Thus, there were limitations on the

number and type of data that was available for analysis. For instance, there was no data on sleep disturbances, which is often considered an important symptom among cancer survivors. In addition, the measurement of the study variables was predetermined and could not be influenced by the author of this study. Further, some variables were not included in the dataset, such as stage of breast cancer or time since diagnosis or treatment. Second, the study design was cross-sectional. Thus, it is not possible to establish causality. Third, the sample size was fairly small and may not be representative of the population of women survivors of breast cancer. Even though the initial dataset had 21,133 participants with representation similar to the U. S. census characteristics, the 103 women survivors of breast cancer in this study were fairly homogenous in terms of their personal characteristics. They were relatively healthy, predominantly White, highly educated, partnered, and employed. Any generalization to other women survivors of breast cancer must be made cautiously. Finally, the women in this sample had only mild symptoms that did not have much variability, which limited cluster discriminations. Thus, conclusions must be tempered and study results should be replicated in a larger sample with more symptom variability.

Implications for Clinical Practice

The implications for clinical practice of this study revolve around healthcare practitioners being aware of current research concerning symptom clusters in women survivors of breast cancer. With the knowledge that the majority of women survivors of breast cancer present with multiple symptoms and not single symptoms, practitioners may assess and treat the multiple symptoms concurrently to positively impact physical and social role functioning. Even with the low intensity symptoms in this study, physical and social role functioning outcomes were significantly affected. Decreasing symptoms

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in women survivors of breast cancer can lead to positively impacting physical and social function as women deal with breast cancer survivorship.

Implications for Future Research

Future research could yield prospective data through the use of the PROMIS surveys available from NIH. A larger sample could be selected to obtain a more diverse sample for comparison of background characteristics and the effect on symptom clusters and the effect of the symptom clusters on physical and social role outcomes. Separate questionnaires could be used for each of the variables with the addition of the sleep disturbance variable. Data regarding stage of disease and place in the treatment or post treatment survival trajectory could be collected. A longitudinal study examining change over time could be completed. Data could be collected from women survivors of breast cancer following concurrent treatment for their symptoms related to the physical and social role functional outcomes.

Conclusion

This study gives insight into the symptom experience of women survivors of breast cancer and the functional outcomes of the symptom clusters for these women. This study adds to the growing body of literature on the importance of symptom clusters by highlighting that even low intensity symptom clusters significantly influence physical and social role functional outcomes. Thus, healthcare practitioners should consistently assess and treat even mild symptoms to facilitate optimal health.

Cancer survivors are growing in numbers and surviving longer. One in eight women in the United States develops breast cancer in their lifetime. Symptoms do cluster in these women and affect their physical and social role functional outcomes. It

is imperative that research continue in this area to enhance the survivorship years for

women survivors of breast cancer to productively continue their daily lives.

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BIOGRAPHICAL SKETCH

Lois Meta Ritz Ellis is employed as the director of a nursing program educating nursing assistants, practical nurses, associate's degree nurses and registered nurses completing their bachelor's degree in nursing. She graduated from University of Florida with her Bachelor of Science in Nursing in 1972 and with her Master of Science in Nursing in 1984.   She worked in cardiology, dialysis, pediatrics, and women's health care prior to receiving her master's degree. Following this degree, she worked as a nurse practitioner in women's health care. She began teaching in a community college in 1987. During this tenure as a faculty member, she taught women's health care and medical-surgical nursing in the associate's degree nursing program. In 1996, she became the coordinator of a nursing simulated lab at the same community college and remained in that position until becoming the director of all of the nursing programs in 2007. While earning her Doctorate of Philosophy in Nursing Sciences, she focused on researching women survivors of breast cancer, with a minor in aging.