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Symptom Clusters among Women with Breast Cancer Undergoing Chemotherapy

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ABSTRACT

Symptom Clusters among Women with Breast Cancer Undergoing Chemotherapy

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Symptom clusters research is an emerging field in oncology nursing, and little is known about symptom clusters among women with breast cancer undergoing treatment. The aims of the current study were to identify symptom clusters present in women with breast cancer undergoing chemotherapy using different symptom dimensions (i.e., frequency, severity, distress); identify which personal, health and illness, and treatment-related variables can predict severity of the symptom clusters; and evaluate how symptom clusters (clustered by severity dimension) change over time. A secondary analysis of a sample of 219 women with breast cancer undergoing chemotherapy was conducted. Ten symptoms were assessed using the symptom experience scale (SES) and the hospital anxiety and depression scale (HADS). Exploratory factor analysis and simple and multiple regressions were used to identify symptom clusters and predictors of severity of symptom clusters. Two symptom clusters were identified and stayed approximately constant across different symptom dimensions. The first cluster consisted of nausea, loss of appetite, ± sleep disturbance. The second cluster consisted of pain, fatigue, bowel pattern, concentration, appearance, ± sleep disturbance, anxiety, and depression. However, the symptom clusters seemed to be dynamic over time. Among 16 variables that were assessed, baseline age, hemoglobin level, symptoms severity, and the mental component summary score were significant predictors of the severity of first symptom cluster. Employment status and baseline Karnofsky performance status, mental component summary, physical component summary, and symptom severity scores were

significant predictors of the severity of the second symptom cluster. Symptom clusters may change over time even in a homogeneous sample. This may be related to the dynamic nature of symptoms and complex interactions among the symptoms within one cluster or across different clusters. Future research should further investigate symptom clusters trajectories over time.

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# CHAPTER I

## THE PROBLEM AND THEORETICAL CONTEXT

In the United States (US), breast cancer is the most common cancer to affect women (American Cancer Society [ACS], 2012). According to cancer statistics, breast cancer represents 29% of all cancers among women (Siegel, Naishadham, & Jemal, 2012). Approximately 232,340 new cases of invasive breast cancer are expected to occur among women in the US during 2013 (ACS, 2013). Most of these women will have active treatment such as chemotherapy (CTX), radiation therapy (RT), hormonal therapy (HT), and/or biological therapy (BT) during their illness. Biological therapy is a type of treatment that works with immune system to fight cancer (National Cancer Institute [NCI], 2004).

Breast cancer and its treatment lead to multiple symptoms. Knowledge of these symptoms is important. Breast cancer treatment-related symptoms vary according to the type of treatment (Honea, Brant, & Beck, 2007). The most common CTX side effects include fatigue, depression, sleep problems, pain, nausea, vomiting, mucositis, anxiety, loss of concentration, and problems with memory (Bender et al., 2005; Gift, Stommel, Jablonski, & Given, 2003; Rinder, 2005). The most common RT side effects include fatigue, sleep problems, pain, difficulty concentrating, skin problems, and itching (Kim, Barsevick, Tulman, & McDermott, 2008). The most obvious side effects of HT include sleep disturbance, mood changes, and fatigue. Finally, common BT side effects include fatigue, allergic reactions, fever, rash, headaches, and arthralgias (Polovich, White, & Kelleher, 2005).

In general, these symptoms are experienced simultaneously (National Institutes of Nursing Research [NINR], 2012) and are highly distressing (Cimprich, & Ronis, 2001). Patients with multiple symptoms are more likely to have multiplicative rather than additive experiences

(Lenz et al., 1997). Research that addresses multiple symptoms that relate to each other and are co-occurring is called symptom cluster research.

## Statement of the Problem

According to the Oncology Nursing Society (ONS), symptom cluster research is a priority in oncology nursing. Symptom cluster research with women who have breast cancer, however, is still insufficient and inconclusive (Albusoul, 2012). There is a variability in the symptom clusters described in the literature. Even the common clusters such as sickness behavior and gastrointestinal (GI) symptom clusters differ among the studies in number and type of symptoms. The variability in the symptom clusters may be related to many factors such as using different scales to assess symptoms, clustering symptoms in different dimensions, using different analytic approaches, using different symptom cluster approaches, measuring symptoms at different time points, including different treatment modalities, and including a study sample with other types of cancer in addition to breast cancer.

Several approaches can be applied to cluster symptoms. The two most common approaches are the all-possible symptom approach and the most-common symptom approach (Kim et al., 2005; Xiao, 2010). In general, the all-possible symptom approach is more accurate because the number of symptoms within a symptom cluster and the number of determined symptom clusters is larger in this approach. In the literature, only one study (Suwisith et al., 2010) used the all-possible symptom approach to cluster symptoms in women with breast cancer undergoing CTX. More studies need to be conducted before concluding what constitutes the most common and clinically significant symptom clusters for women with breast cancer during CTX.

Little is known about predictors of symptom clusters among women with breast cancer undergoing any treatment modality. Most predictors were assessed only once in a mixed cancer sample with different treatment modalities. In addition, there is some conflicting evidence in the literature. For example, Kim, Barsevick, and Tulman (2009a) found that age predicted the severity of symptoms in the psychoneurological and GI cluster; younger women had greater symptom severity. In contrast, Kim et al. (2008) reported that age did not significantly influence symptom clustering. Furthermore, some important predictors, such as activity level, body mass index (BMI), and hemoglobin (Hb) level were not studied in a sample specific to women with breast cancer undergoing CTX.

Evaluating symptom cluster stability is another issue that requires more research. Three studies assessed symptom cluster change over time (Kim et al., 2008; Kim et al., 2009b; Molassiotis, Farrell, Bourne, Brearley, & Pilling, 2012). Many differences between these studies exist, however, making it difficult to compare them. For example, only one study was specific to women with breast cancer (Kim et al., 2008). The researchers assessed the changes in symptom clusters before and after the initiation of CTX and clustered the symptoms based on the severity dimension. In another study, Kim et al. (2009b) assessed the changes in symptom clusters at the middle, end, and after finishing RT. The researchers included two types of cancer and clustered symptoms based on the severity dimension. Although these studies have increased knowledge about symptom clusters, more studies need to be conducted before we draw conclusions about how symptom clusters change over time.

## The Theory of Symptom Management

Various symptom theories are available in the literature (Armstrong, 2003; Humphreys et al., 2008; Lenz & Pugh, 2008). The theory of symptom management (TSM) is the most

comprehensive when dealing with symptoms and will be used to guide this study. The TSM is a middle range theory that illustrates the multidimensional aspects of the symptom management process.

From the TSM perspective, a symptom is a "subjective experience reflecting changes in the biopsychosocial function, sensation, or cognition of an individual" (Humphreys et al., 2008, p.145). In contrast, a sign is "any abnormality indicative of disease that is detectable by the individual or others" (Humphreys et al., 2008, p.145).

**Key Concepts of the TSM**

Within the context of person, health and illness, and environment, the TSM has three essential concepts for research and practice (Humphreys et al., 2008). These concepts are symptom experience, symptom management strategies, and symptom status outcomes (see Figure 1.1).

The first concept in the TSM is the symptom experience (Humphreys et al., 2008). The symptom experience includes three components: the person's perception of a symptom, evaluation of the meaning of a symptom, and response to a symptom. Perception refers to whether the person observes any difference in his or her behavior or feelings. If there is a difference, the person evaluates the importance and meaning of this change. Factors that can affect a person's evaluation of a symptom may include aspects such as frequency or severity of the symptom, or distress caused by the symptom. Responses to symptoms can be categorized as physiological, psychological, sociocultural, and behavioral. The three components interact together and affect one another. The TSM symptom experience is focused on the experience of one symptom, and does not explicitly address symptoms that "cluster" together. The concept of

symptom cluster is defined and discussed in more detail as part of the review of the literature in Chapter 2.

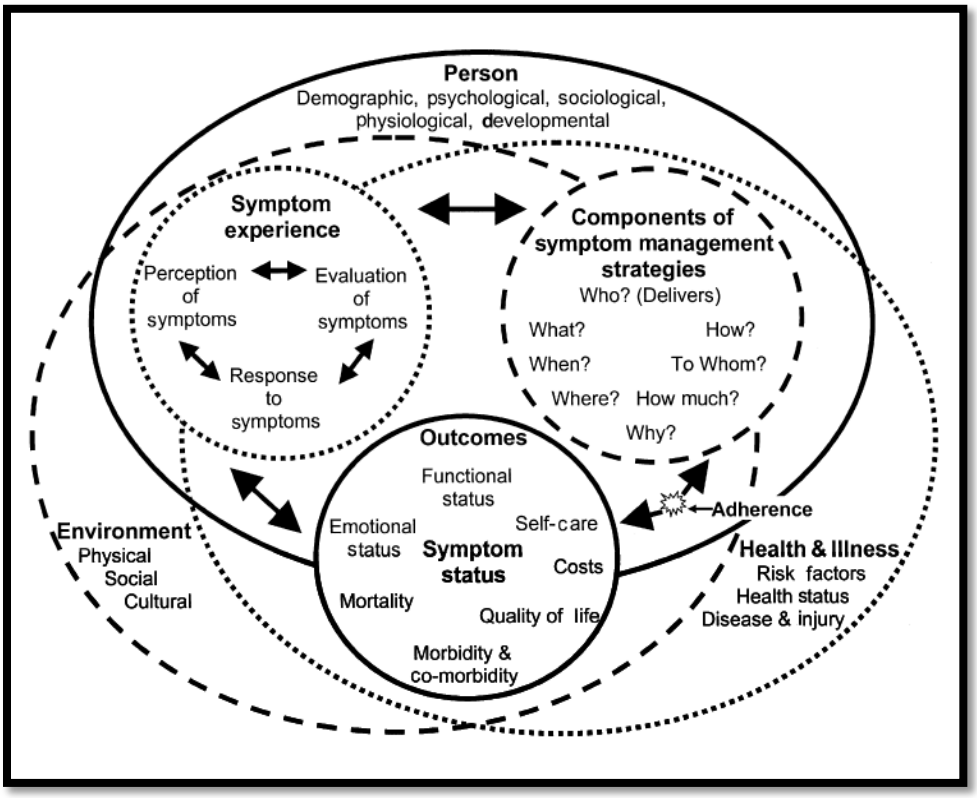


*Figure 1.1* Conceptual Model of Symptom Management (second version) from Dodd, M., Janson, S., Facione, N., Faucett, J., Froelicher, E., Humphreys, J., … Rankin, S. (2001). Advancing the science of symptom management. *Journal of Advanced Nursing, 33*, 670.

The second concept of the TSM is symptom management strategy. The main purpose of the strategy is to avert, delay, or minimize the symptom experience. The symptom experience can be minimized by reducing the frequency, minimizing the severity, or relieving the distress of the symptom. The symptom management strategy circle within the model includes a number of factors that can be used to assist clinicians in selecting appropriate interventions. Once the appropriate interventions are identified, they can be delivered to the patient, family members, or the community.

The third concept of the TSM is focused on outcomes. This concept includes eight quantitative outcomes that can be observed and measured. These outcomes are emotional status, functional status, self-care, cost, quality of life (QOL), morbidity, co-morbidity, and mortality. All outcomes are related to each other as well as to symptom status. Outcomes are satisfactory if the symptoms become less frequent, severe, or distressing.

The bidirectional arrows that connect the three concepts of the TSM indicate that there are interactions among the concepts (Humphreys et al., 2008). Any change in one concept can directly affect the others. The broken arrow between symptom management strategies and symptom status outcomes illustrates the importance of adherence in this relationship. Adherence is defined as "whether the intended recipient of the strategy actually receives or uses the strategy prescribed" (Dodd et al., 2001, p. 674). Adherence is essential for satisfactory outcomes.

**Domains of Nursing Science within the TSM**

The domains of nursing science (i.e., person, health and illness, and environment) depict the context in which the symptom management process occurs (Humphreys et al., 2008). The three domains are illustrated as overlapping ellipses that are connected to the concepts of the TSM. The theory explains how the domains of nursing science can affect the three concepts of the theory (i.e., symptom experience, management strategies, and outcomes).

The *person* domain contains five major categories: demographic (e.g., age, gender, ethnicity), psychological (e.g., cognitive capacity, motivation), sociological (e.g., family, culture, religion), physiological (e.g., rest and activity patterns, physical capacity; Larson et al., 1994), and developmental (e.g., maturation) variables (Dodd et al., 2001). These variables affect the person's symptom experience as well as management strategies and symptom status outcomes. The content of the domain is flexible and can be changed according to the symptom of interest.

The *health and illness* domain is defined as "variables unique to the health or illness state of an individual" (Dodd et al., 2001, p.670). It includes three categories. First, risks that involve hereditary or/and behavioral factors such as breast cancer mutations or cigarette smoking. Second, health status, which includes physiological rhythms, bodily structure, and function. Finally, disease and injury, which contains any deviations due to pathology of disease (Larson et al., 1994). The health and illness domain has direct and indirect effects on all three concepts of the theory (Dodd et al., 2001).

The *environment* domain is defined as "conditions or the content within which a symptom occurs" (Dodd et al., 2001, p. 671). It contains three categories: physical (e.g., home, work, hospital), social (e.g., family, interpersonal relationships, social support groups), and cultural (e.g., beliefs, values, religious practices). Similar to the other domains, the environment domain affects all three concepts of the TSM (Humphreys et al., 2008).

## Research Questions

This study focuses on symptom clusters, predictors of symptom clusters, and changes over time in symptom clusters. The research questions were developed from the TSM, specifically the symptom experience concept and the outcomes concept focused on symptom status and QOL. Aspects of person, health and illness (cancer) and treatment domains are included. The research questions are addressed in a sample of women with breast cancer undergoing intravenous CTX. With data obtained from a randomized controlled clinical trial entitled, *Fatigue in Breast Cancer: A Behavioral Sleep Intervention* (Berger, Kuhn, Farr, Lynch, Agrawal, Chamberlain, &Von Essen, 2009), the following three questions will be addressed:

(1) What symptom clusters are present in this population?

(2) What personal, health and illness, and treatment-related characteristics best predict severity of symptom clusters?

(3) How do symptom clusters (clustered by severity dimension) change over time?

## Significance of the Study

The proposed study addresses existing gaps in published research literature on symptom clusters among women with breast cancer undergoing CTX. It helps to identify more precisely common symptom clusters and their components in this population. Chemotherapy is a common treatment for breast cancer and causes numerous symptoms that are related and have effects on each other. Because there are correlations among these symptoms, the treatment of one symptom may have a positive effect on the other symptoms in the cluster or may trigger other symptoms. A better understanding of this relationship may lead to the discovery of new innovations in symptom management, development of more targeted intervention strategies, a reduction in polypharmacy, and fewer treatment side effects. In addition, it may increase pharmacoeconomic benefits and improve health outcomes such as QOL and functional status (Lacasse & Beck, 2007; Miaskowski, Dodd, & Lee, 2004; Skerman, Yates, & Battistutta, 2009; Walsh & Rybicki, 2006).Once identified, the most common and severe symptom clusters can be included in assessment protocols in CTX clinics.

In addition, the study results may reveal personal, health and illness, and treatment-related variables that can predict severity of the symptom clusters. Studying variables that predict symptom clusters is important in order to determine which variables should be controlled or included in future studies. In clinical practice, determining the predictors of symptom clusters will help to identify women who should be further evaluated for the presence of the symptom clusters, to receive a more targeted and effective intervention for symptom management. This

study will assess important new variables for the first time in a population of women undergoing CTX for breast cancer, such as severity of symptoms and QOL before initiation of CTX, activity level, body mass index (BMI), Karnofsky score, menopausal status, and hemoglobin (Hb) level. Other predictors such as disease stage and age have been previously studied, but need further evaluation before concluding their effects on symptom clusters.

In addition, this is the first study to evaluate symptom cluster changes over time from baseline to after CTX. Finally, this is the first study to evaluate how symptom clusters (clustered by severity) change over time in a sample specific to women with breast cancer. Knowing a symptom cluster's change trajectory over time is important in it may help researchers to choose the best time and frequency of measuring symptoms that lead to more comprehensive and accurate results.

## Definition of the Terms

**Symptom.** In this study, a symptom is defined conceptually as a "subjective experience reflecting changes in the biopsychosocial function, sensation, or cognition of an individual" (Humphreys et al., 2008, p.145). According to the TSM as described by Humphreys and colleagues, symptoms can be evaluated operationally by many dimensions, including severity and frequency. The severity dimension refers to the intensity, strength, or amount of the symptom experienced. The frequency dimension refers to how often the symptom occurs. The distress dimension refers to "the degree or amount of physical or mental upset, anguish, or suffering experienced from a specific symptom" (Rhodes & Watson, 1987, p. 243).

**Symptom Clusters.** Symptom clusters are defined conceptually as "two or more symptoms that are related to each other and that occur together" (Kim et al., 2005, p. 278). This relationship is associative, rather than causal, and there is no clear-cut agreement about the

minimum strength of the relationships among the symptoms inside a cluster. According to Kim and colleagues, relationships among symptoms within a cluster should be stronger than relationships among symptoms across different clusters, and symptoms cannot be present in more than one cluster simultaneously. In this study, symptom clusters are defined operationally with the all-possible symptom approach by including 10 symptoms in the factor analysis: nausea, pain, anxiety, depression, appetite, sleep disturbance, fatigue, bowel pattern, concentration, and appearance.

**Predictors.** Predictors in this study refer to personal, health and illness, and treatment-related characteristics. Conceptually, within the TSM (Humphreys, et al., 2008), the personal domain contains five major variables: demographic, psychological, sociological, physiological, and developmental. For the purpose of this study, three variables, namely demographic (age, race, ethnicity, marital status, employment, and education), developmental (menstrual status), and physiological (activity level) are the operational definitions of personal characteristics. The health and illness predictors are defined operationally as health status (Hb level, BMI, Karnofsky score, and QOL) and disease and injury (cancer stage and severity of pre-treatment symptoms). Finally, surgical procedure is the operational definition for treatment-related predictor.

## Assumptions of the Study

The following assumptions underlie the purpose, significance, and design of this study.

(1) There is a relationship between different symptoms.

(2) Each symptom is more related to some symptoms than to other symptoms.

(3) The related symptoms have effects on each other.

(4) Personal, health and illness, and treatment-related characteristics predict the severity of symptom clusters in women with breast cancer undergoing active intravenous CTX treatment.

(5) Women's individual responses to the questionnaires are unique, and their responses reflect their actual symptom experience.

# CHAPTER II

# LITERATURE REVIEW AND GAPS IN KNOWLEDGE

The purpose of this chapter is to summarize and evaluate the scientific literature that addresses the identification of symptom clusters among women with breast cancer undergoing active treatment, whether these symptom clusters change when analyzed using different dimensions (i.e., occurrence, frequency, severity, and distress), and how these symptom clusters change over time. This chapter will also describe the predictors and outcomes of these symptom clusters, identify the analytic approaches used to determine these symptom clusters, and identify limitations, gaps, and contraindications in the literature. First, the concept of symptom clusters will be presented, followed by a discussion of the literature related to symptom clusters among women with breast cancer undergoing active treatment.

## Defining the "Symptom Clusters" Concept

The concept of symptom clusters was first used in psychology and psychiatry as a basis for disease classification and diagnosis of psychiatric disorders, and then, in general medicine to investigate symptom associations and the underlying pathophysiology of diseases (Kim, McGuire, Tulman & Barsevick, 2005). In oncology nursing research, the idea of clustering symptoms was first mentioned by Sarna and Brecht (1997), who clustered symptoms using factor analysis to examine symptom distress among lung cancer patients.

### Definition of Symptom Clusters

The concept of symptom clusters was first defined by Dodd and colleagues (2001) as "three or more concurrent symptoms that are related to each other" (p. 465). This definition was then revised by Kim and colleagues (2005) as

> "Two or more symptoms that are related to each other and that occur together. Symptom clusters are composed of stable groups of symptoms, are relatively

> independent of other clusters, and may reveal specific underlying dimensions of symptoms. Relationships among symptoms within a cluster should be stronger than relationships among symptoms across different clusters. Symptoms in a cluster may or may not share the same etiology" (p. 278).

Moreover, Kim suggested that symptom clusters should include both symptoms and signs.

The revised definition specifies important attributes of symptom clusters. First, there is a relationship among the symptoms inside a cluster. This relationship is associative rather than causal (Kim et al., 2005). There is no clear-cut agreement about the minimum strength of the relationships among the symptoms inside a cluster. According to Aktas, Walsh, and Rybicki (2010), a minimum value of $r = .5$ is needed to derive prudent conclusions.

Second, a cluster should consist of two or more concurrent symptoms (Kim et al., 2005). When determining the presence of a cluster, at least 75% of the identified symptoms in that cluster should be present, including the most prevalent symptom (Kirkova & Walsh, 2007). Most researchers agree that a symptom cannot be present in more than one cluster at a time (Westbrook, Talley, & Westbrook, 2002).

Third, a cluster should be relatively stable (replicable across patients and time) (Kim et al., 2005). However, it is important to remember that stability across patients sometimes can be affected by patient characteristics such as age and comorbid diseases. In addition, symptoms have a dynamic nature and can change with disease course and treatment. It is not clear how long a symptom cluster should be present to define it as stable.

Fourth, a cluster is relatively independent of other clusters because the relationships among symptoms within a cluster are stronger than relationships among symptoms across different clusters (Kim et al., 2005). Finally, the symptoms within a cluster may result from more than one cause (Dodd et al., 2001; Kim et al., 2005).

## Distinguishing between Symptom Clusters and Related Concepts

In order to advance research it is important that researchers choose their terminology very carefully. There are many related concepts and surrogate terms that can be used when describing symptom clusters. These terms should be defined and distinguished from one another. Kim and colleagues (2005) described the most common concepts used to refer to symptom clusters. For example, *multiple symptoms* is a related concept that shares some of the meaning of symptom clusters. However, it does not require a relationship among symptoms within a cluster or co-occurrence of symptoms. Another related concept is *symptom experience.* Symptom experience is "the perception of the frequency, intensity, distress, and meaning occurring as symptoms are produced and expressed" (Armstrong 2003, p. 603). The symptom experience focuses on perceptions and the meaning of the symptoms to the patient and thus has a broader scope than symptom clusters. Most common surrogate concepts that can be used interchangeably with the concept of symptom cluster are grouped symptoms, symptom groups, groups of symptoms (Kim et al., 2005), symptom constellations (Miaskowski, Dodd, & Lee, 2004), co-occurrence of symptoms (Miaskowski et al., 2004), and symptom pairs (Parker, Kimble, Dunbar, & Clark, 2005).

## Mechanisms Related to Symptom Clustering

The possible mechanisms underlying the clustering of symptoms are: shared etiology (Cleeland et al., 2003; Miaskowski & Aouizerat, 2007), symptom interaction (Parker et al., 2005), and symptom stimulation of other symptoms (Armstrong, Cohen, Eriksen, & Hickey, 2004; Suwisith, Hanucharurnkul, Dodd, Vorapongsathorn, Pongthavorakamol, & Asavametha, 2010). As an example of shared etiology, a common biological mechanism may underlie the development of symptom clusters associated with cancer or its treatment (Cleeland et al., 2003;

Miaskowski & Aouizerat, 2007). For example, the sickness behavior cluster, which is a common cluster among women with breast cancer, may be caused by cytokine release during treatment (Kirkova, Walsh, Aktas, & Davis, 2010). This cluster contains four symptoms: fatigue, depression, pain, and insomnia. The sickness behavior cluster occurs most commonly during CTX and RT (Kirkova et al., 2010).

According to different symptom theories and models, such as the Theory of Unpleasant Symptoms (TOUS) (Lenz & Pugh, 2008), the Symptom Experience Model (SEM) (Armstrong, 2003), and the Symptom Interactional Framework (SIF) (Parker et al., 2005), there are interactions among multiple symptoms. Parker and colleagues define symptom interactions as "occurring when two or more symptoms coexist, precipitate, or synergize each other, or trigger the development of other symptoms" (p. 213). According to symptom theories/models such as the TOUS, the SEM, the SIF, and the TSM, there are different domains that may affect symptoms. These include the demographic, physiological, psychological, developmental, behavioral, health-illness, and socio-cultural domains. Shared or interactive mechanisms from these domains can result in the formation of symptom clusters (Parker et al., 2005).

**Approaches to Symptom Clustering**

There are two main approaches to symptom clustering: the all-possible symptom approach and the most-common symptom approach (Kim et al., 2005; Xiao, 2010). In the all-possible symptom approach, there is no previous assumption about the symptom clusters that can be present. All potential symptoms that patients can experience are included in the statistical analysis. The most common statistical methods used to cluster the symptoms in the all-possible symptom approach are factor analysis (FA), principle component analysis (PCA), and cluster analysis (CA) (Xiao, 2010). This approach is mainly used to identify comprehensively the

symptom clusters that a patient may experience. It is used to find the central symptom (the main symptom in the cluster that is responsible for connecting the other symptoms together) within symptom clusters. It can be used to investigate connections among symptoms within the symptom cluster and to understand changes in the symptom cluster trajectory over time.

In general, the number of symptoms within a symptom cluster and the number of determined symptom clusters is larger in the all-possible symptom approach. The main disadvantage of the all-possible symptom approach is that the statistically significant symptom clusters that have been determined by this approach need further evaluation to determine if they are also clinically significant (Xiao, 2010). Skerman and colleagues (2009) suggested criteria that should be used to identify clinically significant symptom clusters. The identified symptoms should be important to the patient's experience and the cluster should occur commonly and have practical consequences for both symptom management and patient outcomes.

With the most-common symptom approach, the researcher identifies symptoms that should be grouped together according to clinical observation and then determines statistically whether there are significant relationships among these symptoms (Matthews, Schmiege, Cook, & Sousa, 2011). This approach is a good method for understanding specific symptom clusters in depth, and can be used to explain the nature of symptom clusters. For example, it can explain how symptoms are related to each other, and whether there are any mediation or interaction effects. In addition, it assesses the influence of the selected symptom cluster on patient outcomes (Xiao, 2010).

One of the familiar foci of the most-common symptom approach research is the identification of subgroups of patients according to their experience of specific symptom clusters. This method can help identify the predictors that have effects on a selected symptom

cluster by determining the differences in the characteristics of patients in different subgroups. The main disadvantage of the most-common symptom approach is that it lacks a theoretical foundation. Adding or deleting any symptoms may change the interactions among the symptoms within the cluster and then change the cluster results (Xiao, 2010).

## Symptom Clusters among Women with Breast Cancer Undergoing Active Treatment

### Search Methods

The literature search was primarily conducted using the PubMed database and Google Scholar using search terms such as: symptom clusters, concurrent symptoms, or constellation of symptoms combined with breast cancer, breast tumor, or breast neoplasm and active treatment, cancer treatment, or breast cancer treatment. In addition, reference lists from the articles were reviewed to find additional studies. The search was limited to English language and adults. The search was not limited to a specific timeframe; however, all included articles were published before December 2012.

Many studies were found and all abstracts were reviewed to determine if the studies met the inclusion criteria. The studies were included if they identified symptom clusters, symptom cluster changes over time, and/or predictors or outcomes associated with symptom clusters and (a) all participants were adult women with breast cancer undergoing CTX, RT, HT, or BT for treatment purposes or (b) breast cancer was the most common or second-most common cancer included in the study and represented at least 25% of the sample.

Many studies were excluded. The most frequent cause for exclusion was that patients were not receiving active treatment, followed by patients receiving palliative treatment, or the study was theoretical. The most frequent cause of exclusion in the studies that included mixed cancer diagnoses was that the number of breast cancer patients in these studies represented less

than 25% of the sample. In addition, studies that did not state clearly that symptom clusters were assessed were excluded.

Based on the search parameters, 18 studies were included in the literature review. In ten studies breast cancer was the only cancer diagnosis (Dodd, Cho, Cooper, & Miaskowski, 2010; Glaus et al., 2006; Golan-Vered & Pud, 2012; Kim, Barsevick, Beck, & Dudley, 2012; Kim et al., 2009a; Kim et al., 2008; Matthews, Schmiege, Cook, & Sousa, 2011; So et al., 2009; Suwisith et al., 2010; Thornton, Andersen, & Blakely, 2010). The other eight studies had mixed cancer diagnoses (Chen & Lin, 2007; Dodd, Miaskowski, & Paul, 2001; Given, Given, Azzouz, & Stommel, 2001; Kim et al., 2009b; Kim et al., 2009c; Miaskowski et al., 2006; Molassiotis et al., 2012; Pud et al., 2008). The 18 studies included in this review are comprehensively summarized in Appendix A.

**Design Characteristics of the Studies**

Most of the studies included in the literature review were published within the last 10 years. The publication dates ranged from 2001 (Dodd et al., 2001; Given et al., 2001) to 2012 (Golan-Vered & Pud, 2012; Kim et al., 2012; Molassiotis et al., 2012) with 13 (72.2%) of the studies being published after 2007. Eleven studies were conducted in the United States, two in the Middle East, one in the United Kingdom, one in China, one in Thailand, one in Taiwan, and one in Switzerland. Table 2.1 summarizes characteristics of the 18 studies included in the literature review.

Nine studies (50%) used cross-sectional designs (Chen & Lin, 2007; Glaus et al., 2006; Kim et al., 2009c; Matthews et al., 2011; Miaskowski et al., 2006; Pud et al., 2008; So et al., 2009; Suwisith et al., 2010; Thornton et al., 2010) and nine studies (50%) used longitudinal designs (Dodd et al., 2010; Dodd et al., 2001; Given et al., 2001;

Table 2.1 *Summary of the Design Characteristics of Studies of Symptom Clusters in Women with Breast Cancer Undergoing Active Treatment*

Design (*n* = 18)
- Cross-sectional (50%)
- Longitudinal (50%)

Symptom approaches used in the studies (*n* = 18):
- All-possible (55.6%)
- Most-common (44.4%)

Multiple symptom scales used to form symptom clusters in all-possible approach (*n* = 8):
- Memorial Symptom Assessment Scale (MSAS) (50%)
- Symptom Distress Scale (SDS) (12.5%)
- The MD Anderson Symptom Inventory (MDASI) (12.5%)
- Checklist for Patients with Endocrine Therapy (C-PET) (12.5%)
- Author developed (12.5%)

Symptom dimensions used to form symptom clusters based on all-possible approach (*n* = 10)*:
- Severity (80%)
- Occurrence (30%)
- Distress (20%)

Symptom dimensions used to form symptom clusters based on most-common approach (*n* = 8):
- Severity (75%)
- Occurrence (25%)

Analytic approaches used to form symptom clusters based on all-possible approach (*n* = 10) :
- Factor analysis (FA) (70%)
- Cluster analysis (CA) (20%)
- Random forest analysis (RFA) (10%)

Analytic approaches used to form symptom clusters based on most-common approach (*n* = 8) :
- Cluster analysis (CA) (50%)
- Correlation (37.5%)
-

Symptom cluster relationships (*n* = 18):
- Symptom cluster - Predictor (44.4%)
- Symptom cluster - Outcome (50%)

*Some studies used more than one symptom dimension.

Golan-Vered & Pud, 2012; Kim et al., 2009a; Kim et al., 2008; Kim et al., 2009b; Kim et al., 2012; Molassiotis et al., 2012). In most of the longitudinal studies (66.7%), the patients were followed at three time points. All longitudinal studies, except two (Dodd et al., 2010; Kim et al., 2009b), included a baseline assessment of symptoms that were measured before beginning treatment. The studies were heterogeneous in terms of when symptoms were evaluated. For example, in some studies (Dodd et al., 2010; Kim et al., 2009b; Molassiotis et al., 2012) symptoms were assessed at the end of the CTX cycle or at the end of the treatment, while in other studies (Kim et al., 2008; Kim et al., 2009a; Kim et al., 2012) symptoms were assessed 48 hours after initiation of the CTX cycle.

Various symptom scales were used to identify and form symptom clusters. Some authors used symptom-specific scales, while others used multiple symptom scales. The Memorial Symptom Assessment Scale (MSAS) was the most frequently used multiple symptom measure ($n$ = 4), followed by the Symptom Distress Scale (SDS) ($n$ = 1), the MD Anderson Symptom Inventory (MDASI) ($n$ = 1), the Checklist for Patients with Endocrine Therapy (C-PET) ($n$ = 1), and author-developed checklist ($n$ = 1). Most of the multiple symptom scales measured symptoms within the timeframe of 1 week. The number of symptoms on the multiple symptom scales ranged from 13 to 32. Finally, the time frame for the multiple symptom scales ranged from 2 days to 1 month, and most of the symptoms were measured within the timeframe of 1 week.

The symptom clusters were created based on three dimensions: occurrence ($n$ = 5; 27.7%), severity ($n$ = 14; 77.7%), and distress ($n$ = 2; 11.1%). Four of the studies used more than one dimension to create the symptom clusters (Kim et al., 2008; Kim et al., 2009c; Molassiotis et al., 2012; So et al., 2009; Suwisith et al., 2010). Both the all-possible and the most-common symptom approaches were widely used in the studies. Ten studies (55.6%) used

the all-possible symptoms approach (Chen & Lin, 2007; Glaus et al., 2006; Kim et al., 2009a; Kim et al., 2008; Kim et al., 2009b; Kim et al., 2009c; Kim et al., 2012; Matthews et al., 2011; Molassiotis et al., 2012; Suwisith et al., 2010) and eight studies (44.4%) used the most-common symptom approach (Dodd et al., 2010; Dodd et al., 2001; Given et al., 2001; Golan-Vered & Pud, 2012; Miaskowski et al., 2006; So et al., 2009; Pud et al., 2008; Thornton et al., 2010).

Three statistical approaches were used to form symptom clusters in the all-possible symptoms approach. Cluster analysis (CA) was used twice (Glaus et al., 2006; Kim et al., 2012) and random forest analysis was used once (Molassiotis et al., 2012) in the studies. Factor analysis (FA) was used in the other studies to form symptom clusters. Both confirmatory factor analysis (CFA) and exploratory factor analysis (EFA) were used. The CFA approach was used when the researchers had specific hypotheses about how symptoms would cluster based on symptom cluster literature reviews (Matthews et al., 2011) or to confirm symptom clusters found in previous research (Chen & Lin, 2007). In two studies, the authors did not mention what type of FA they used (Kim et al., 2008; Suwisith et al., 2010). In the most-common symptom approach, the authors used correlation (Dodd et al., 2001; So et al., 2009; Thornton et al., 2010) and CA (Dodd et al., 2010; Golan-Vered & Pud, 2012; Miaskowski et al., 2006; Pud et al., 2008) as analytic approaches to demonstrate relationships among symptoms in the cluster.

**Characteristics of the Samples**

The sample size for the breast cancer studies ranged from 40 to 373. In nine studies (50%), the sample size was less than 100 (Dodd et al., 2001; Chen & Lin, 2007; Kim et al., 2009b; Kim et al., 2009c; Golan-Vered & Pud, 2012; Matthews et al., 2011; Miaskowski et al., 2006; Molassiotis et al., 2012; Pud et al., 2008). In seven studies (38.9%), the sample size ranged from 100 to 300 (Dodd et al., 2010; Given et al., 2001; Kim et al., 2009a; Kim et al., 2008; Kim

et al., 2012; So et al., 2009; Thornton et al., 2010), and in two studies (11.1%), the sample size was more than 300 (Glaus et al., 2006; Suwisith et al., 2010).

The mean age of study patients ranged from 45 to 61.1 years. Golan-Vered and Pud (2012) reported the youngest mean age with a standard deviation (*SD*) of 9.3 years and age range of 21 to 65 years, while Kim et al. (2009) reported the oldest mean age with a *SD* of 11.5 years. For the 17 studies that reported age, the mean age in 55.6% of the studies was older than 55 years. For the 10 studies that reported race and were done in the United States, the most common race was White and ranged from 72.8% to 93.5% of the sample.

Cancer stages and treatments differed across studies. In most of the breast cancer studies, the majority of patients had early breast cancer (i.e., stages 0, 1, or 2) that was diagnosed for the first time. Two studies included patients with recurrent breast cancer along with newly diagnosed breast cancer (Suwisith et al., 2010; Thornton et al., 2010). Eight studies (44.4%) were specific for one kind of treatment: CTX ($n$ = 4), RT ($n$ = 3), or HT ($n$ = 1). Ten studies (55.6%) included combinations of CTX and RT ($n$ = 6) or CTX, RT, and HT ($n$ = 4). In addition, two studies included BT with other treatments (Dodd et al., 2010; Miaskowski et al., 2006).

In studies with mixed cancer diagnoses, a wide variety of cancer diagnoses were included and ranged from two to more than nine diagnoses. Breast, prostate, colon, and lung cancers were the most common cancer diagnoses included in the studies. The proportion of patients with a breast cancer diagnosis ranged from 27% to 80.6% and was the most common diagnosis in 50% of mixed cancer studies. Female gender was more common in most studies that included mixed cancer diagnoses.

Finally, comorbid diseases were mentioned in seven studies. Kim and colleagues (2008, 2009a, 2012) stated that 55.7% of the patients had one or more comorbid diseases. In one of the

studies (Kim et al., 2009b), the mean number of comorbid diseases was five with a *SD* of 2.5. In another study, So and colleagues (2009) stated that the number of comorbid diseases ranged from two to six.

**Major Study Findings**

There were five main areas of focus synthesized in the studies: (1) identification of symptom clusters among women with breast cancer undergoing active treatment; (2) description of the symptom cluster change trajectory over time; (3) description of the predictors of symptom clusters; (4) description of health outcomes affected by symptom clusters; and (5) identification of subgroups of patients based on their experiences with a selected symptom cluster, subgroup membership change over time, predictors of subgroup membership, and effect of subgroup membership on outcomes. Major findings from the studies and limitations of each focus are highlighted below.

**1. Identification of symptom clusters.** One study identified symptom clusters among women with breast cancer undergoing HT (Glaus et al., 2006). The researchers explored how frequently menopausal symptoms occurred and how symptoms clustered in 375 women. Most of the women were post-menopausal, had early breast cancer (81%), and were taking tamoxifen (72%). A specific scale to assess side effects of HT in women with breast cancer was used. Symptoms were clustered by occurrence using cluster analysis. One symptom cluster was found and included five symptoms: hot flashes, tiredness, vaginal dryness, weight gain, and decreased sexual interest.

Nine studies identified symptom clusters among cancer patients undergoing RT and/or CTX. Three of the studies used the all-possible symptoms approach and were specific to women with breast cancer (Kim et al., 2008; Matthews et al., 2011; Suwisith et al., 2010). Matthews and

colleagues used 11 items from the SDS to identify symptom clusters in 93 women from the mid-Atlantic region of the US undergoing RT for breast cancer. Most women were White (93.5%) and had an early stage of breast cancer (89.2%). Symptoms were clustered in terms of distress. Using CFA, three symptom clusters were confirmed: pain-insomnia-fatigue; cognitive disturbance (concentration, appearance, and outlook); and GI (nausea and bowel patterns).

Suwisith and fellows (2010) identified symptom clusters in 320 Thai women undergoing CTX for breast cancer in four outpatient cancer clinics. Most of the women had second (51.6%) or third (27.5%) stage breast cancer and were newly diagnosed (73.4%). They were young with a mean age of 47.3 years (*SD* = 8.8 years). Twenty-five symptoms from the MSAS were included in the analysis. Using the severity and distress dimensions, symptoms were clustered using the FA approach. In the symptom severity dimension, four symptom clusters were found: emotional, GI and fatigue, image-related cutaneous symptoms, and pain and discomfort. In the symptom distress dimension, three symptom clusters were found: emotional and pain, GI and fatigue, and image-related cutaneous symptoms. There were many similarities in the two groups of symptom clusters. The symptoms that were clustered by severity explained more of the variance in the functional status (19.8%) than symptoms clustered by distress (17.4%).

Kim and colleagues (2008) identified symptom clusters in 282 women undergoing CTX, RT, or both in the US. Most women were White (91.5%), had early stage breast cancer (86.9%), and were undergoing RT (55.7%). A side effect checklist and three validated scales were used to measure symptoms. Symptoms were clustered on symptom severity using the FA approach. The outcomes were measured at baseline (T1) and at two follow-ups after treatment initiation (T2 and T3). At T2, two symptom clusters were identified: upper GI (nausea, vomiting, and decreased appetite), and cluster two which included pain, fatigue, insomnia, depressed mood, cognitive

disturbance, and hot flashes. At T3, two symptom clusters were identified: upper GI (nausea, vomiting, and decrease appetite), and cluster two which included pain, fatigue, insomnia, depressed mood, and cognitive disturbance.

Four studies identified symptom clusters among cancer patients undergoing RT and/or CTX using the all-possible symptoms approach, but were not specific to women with breast cancer (Chen & Lin, 2007; Kim et al., 2009b; Kim et al., 2009c; Molassiotis et al., 2012). In the Chen and Lin study, the aim was to validate the three symptom clusters that they found previously in a large cancer population; 321 patients from two university hospitals in Taipei comprised the sample. Of the seven cancer types diagnosed, breast cancer represented 29% of the diagnoses. Most of the sample was female (54.5%) with non-metastatic cancer (76%). The patients were treated with surgery (61.4%), CTX (53%), and/or RT (72.6%). Thirteen symptoms were assessed using the MDASI scale. The symptoms were clustered based on symptom severity using the CFA approach. Three symptom clusters were confirmed: sickness (pain, fatigue, disturbed sleep, lack of appetite, and drowsiness), GI (nausea and vomiting), and emotional (stress and sadness).

Kim and colleagues (2009b) investigated the number and types of symptom clusters in breast and prostate cancer patients undergoing RT. The sample included 160 cancer patients of which 48.7% had breast cancer. The MSAS was used to assess symptoms, and the EFA approach was used to cluster symptoms. In their longitudinal study, the authors clustered symptoms based on symptom severity after they excluded symptoms that were present in less than 20% of the patients. The symptoms were assessed at three time points: middle (T1), end (T2), and one month after RT (T3). Three symptom clusters were identified. The first two symptom clusters were mood-cognitive (difficulty concentrating, feeling sad, worrying, feeling irritable, and

feeling nervous) at T1 and the same cluster without "feeling nervous" at T2, and sickness-behavior (pain, lack of energy, feeling drowsy, difficulty sleeping, and sweats) at both T1 and T2. The third symptom cluster was not included in this literature review because, according to the authors, it was related to prostate cancer.

In another study, Kim and colleagues (2009c) investigated the differentiation between identified symptom clusters using the occurrence rate versus the severity rate. The authors used the second time point (T2; end of RT) for this study. The two symptom clusters based on symptom occurrence were mood-cognitive (difficulty concentrating, difficulty sleeping, feeling sad, worrying, feeling irritable, sweats, and itching), and sickness-behavior (pain, lack of energy, and feeling drowsy). The symptom clusters based on symptom severity showed the same results except that "difficulty sleeping" and "sweats" now became the part of the sickness-behavior symptom cluster. The authors reported that the symptom clusters derived from the severity rating fit the data better. It is important to note that there was a small difference between the two studies in symptom clusters that were formed based on symptom severity. The reason may be that in the second study the authors included symptoms that were presented in at least 20% of the patients and not more than 80%; however, in the first study only symptoms that were less frequent than 20% were excluded from the MSAS.

In the last study (Molassiotis et al., 2012), the researchers wanted to determine if nausea exists as a part of a symptom cluster. In a sample of 104 patients, breast cancer was the most common type of cancer and represented 80.6% of the sample. Three types of CTX were included: anthracyclines (78.7%), taxanes (2.9%), and platinum-based (18.5%). Symptoms were assessed using the MSAS at three time points: the day of the first cycle of CTX (T1), end of cycle 1 (T2), and the end of cycle 2 (T3). The RFA was used to determine available symptom

clusters based on severity and occurrence approaches. In the severity approach, nausea clustered with pain and lack of energy at T2 and lack of energy and feeling bloated at T3. In the occurrence approach, nausea clustered with pain, taste change, lack of energy, dizziness, appetite loss, and vomiting at T2 and with pain and feeling bloated at T3.

There were many differences in symptom clusters across the studies that used the all-possible symptoms approach. For example, the GI symptom cluster appeared in five studies (Chen & Lin, 2007; Kim et al., 2008; Matthews et al., 2011; Molassiotis et al., 2012; Suwisith et al., 2010); however, in each study it consisted of different symptoms. In the Matthews et al. study, it included nausea and bowel patterns. In Suwisith et al. study, the GI symptoms clustered with fatigue. In the Kim et al. study, the GI cluster included nausea, vomiting, and decreased appetite. In Molassiotis et al. study, the GI cluster differed according to time of assessment and assessing approach. At T1, the GI cluster consisted of nausea, pain, and lack of energy when clustered by a severity approach, and nausea, pain, taste change, lack of energy, dizziness, appetite loss, and vomiting when clustering by a occurrence approach. At T2, the GI cluster consisted of nausea, lack of energy, and feeling bloated when clustered by a severity approach and nausea, pain, and feeling bloated when clustered by a occurrence approach. In the Chen and Lin study, the GI cluster consisted of nausea and vomiting while decreased appetite was part of the sickness cluster.

The pain-insomnia-fatigue cluster is another common cluster that appeared across studies. This symptom cluster was identified in five studies (Chen & Lin, 2007; Kim et al., 2008; Kim et al., 2009c; Matthews et al., 2011; Suwisith et al., 2010). In the Kim et al. (2008) study, the cluster had additional symptoms, namely depressed mood, cognitive disturbance, and hot flashes. In the Chen and Lin study, the cluster was named the sickness cluster and included lack

of appetite and drowsiness, in addition to the previously described symptoms. In the Kim et al. (2009) study, the sickness-behavior cluster included pain, lack of energy, and feeling drowsy, while difficulty sleeping was a part of another cluster. Finally, in the Suwisith et al. study, fatigue and pain were in two separate clusters. In addition, some clusters appeared only once in the studies, such as the cognitive disturbance-outlook cluster identified by Matthews and colleagues.

The last two studies that identified symptom clusters among cancer patients undergoing RT and/or CTX used the most-common symptom approach (Dodd et al., 2001; So et al., 2009). In the study by Dodd and colleagues, the researchers examined three symptoms (fatigue, pain, and sleep insufficiency) and their occurrence in the cluster in a sample of 93 patients. Of four cancer diagnoses, breast cancer represented 45% of the sample. To assess symptoms, three items from the Quality of Life-Cancer (QOL-CA) scale were used. The symptom cluster was created based on symptom severity at the end of the third cycle of CTX. The results showed there were small inter-correlations among the three symptoms (pain-fatigue, $r = .22$, $p < .05$; pain-sleep insufficiency, $r = -.06$, $p$ = n.s.; and fatigue-sleep insufficiency, $r = -.13$, $p$ = n.s.).

Low strength among the fatigue-pain-insomnia correlations in the Dodd et al. (2001) study may be related to the fact that the symptoms were not assessed by symptom specific scales. As mentioned in the all-possible symptoms approach studies, the cluster of fatigue, pain, and insomnia is a common cluster supported by many studies in the literature (Chen & Lin, 2007; Kim et al., 2008; Kim et al., 2009c; Matthews et al., 2011; Suwisith et al., 2010). In addition, the correlation between fatigue and sleep in women with breast cancer was supported by Liu et al. (2012). Liu and colleagues assessed symptoms in 97 women during each week of CTX cycles one and four. The results showed that the Multidimensional Fatigue Symptom Inventory-Short

Form (MFSI-SF) total score and its subscales were correlated with the total Pittsburgh Sleep Quality Index (PSQI) scores at all time points. Fatigue was positively associated with objective measures of total nap time and negatively associated with total wake time during the day.

In the study by So and colleagues (2009), 215 Chinese women with breast cancer were examined for the symptom cluster of fatigue, pain, anxiety, and depression. Most of the patients had second (52%) or third (32%) degree breast cancer and were receiving CTX (60%) or RT (40%). The symptoms were measured by severity dimension by three symptom specific scales (Brief Fatigue Inventory [BFI], Brief Pain Inventory [BPI], Hospital Anxiety and Depression Scale [HADS]). The results showed significant correlations among the symptoms ranging from .25 (pain-depression) to .63 (anxiety-depression). These correlations supported the existence of the symptom cluster.

In summary, studying common symptom clusters in women with breast cancer is important in oncology nursing research. The correlations among symptoms within a symptom cluster may help in developing more targeted intervention strategies to decrease treatment side effects and improve patients' health-related quality of life (HRQOL) (Lacasse & Beck, 2007; Miaskowski et al., 2004; Skerman et al., 2009; Walsh & Rybicki, 2006). However, the literature that focuses on the identification of symptom clusters among women with breast cancer undergoing active treatment is complex and inconclusive. Appendix B summarizes the symptom clusters in women with breast cancer undergoing active treatment.

The two most common symptom clusters that were found were the GI and sickness behavior symptom clusters. The symptoms within the clusters differed from study to study. The differences in symptom clusters may be related to many factors such as using different scales with different dimensions and timeframes among the studies, clustering symptoms in different

dimensions, using different analytic approaches, using different symptom cluster approaches, and measuring symptoms at different time points. In addition, using samples that included patients with many different types of cancer or active treatments and the differences in patient characteristics among the studies may have affected the results. For example, if more than one type of cancer was included in a study, it is difficult to conclude that the final symptom clusters would be present in all patients with different cancer types. In the Kim et al. (2009b) study, the authors included a mixed sample that consisted of both breast and prostate cancer patients. The findings showed that the treatment-related symptom cluster at T1 included two symptoms (diarrhea and problems with urination). However, this cluster was not related to women with breast cancer.

Many multiple symptom and multidimensional single symptom scales were used to identify symptom clusters. Use of multiple scales resulted in the clustering of different symptoms among the studies. Some studies focused on physical symptoms only, others focused on treatment-related symptoms, and others used comprehensive symptom scales. In addition, some studies used a specific scale for each symptom without considering time frame differences between the measures. For example, in the Kim et al. (2008) study, depressive mood and cognitive disturbance were measured over the previous two to three days, fatigue was measured over the past week, and insomnia over the past month. The differences in time frames might affect the accuracy of the results.

The MSAS was the most comprehensive and commonly used multiple symptom scale in the reviewed studies that focused on the identification of symptom clusters. The MSAS contains many of the physical and psychological symptoms that are common among women with breast

cancer undergoing acute treatment, which makes using the MSAS in breast cancer symptom cluster research an optimal choice.

It is unclear how clustering by a particular dimension would alter findings. Some studies compared symptom clusters in different dimensions and found minimal-to-moderate differences (Kim et al., 2009c; Molassiotis et al., 2012; Suwisith et al., 2010). More studies are needed before drawing conclusions about difference in clustering based on different dimensions; it is not clear which dimension is the most comprehensive.

**2. Symptom cluster change over time.** Three studies assessed symptom cluster change over time in patients with breast cancer (Kim et al., 2008; Kim et al., 2009b; Molassiotis et al., 2012). Two of the studies described the change between baseline and treatment. Kim and colleagues (2008) used the all-possible symptoms approach and clustered the symptoms based on severity using the FA approach. Approximately 44% of the women received CTX and 56% received RT. The outcomes were measured at baseline (T1) and at two follow-ups after treatment initiation (T2 and T3). For CTX patients, T2 was 48 hours after the second dose of CTX, and T3 was 48 hours after the third dose. For RT patients, T2 was after six weeks of RT and T3 was 1 month after completion of RT. The results showed differences in the number of symptoms and symptom clusters among the three time points. At T1, one symptom cluster was identified and was composed of pain, fatigue, insomnia, depressed mood, and cognitive disturbances. At T2, one symptom (hot flashes) was added to the symptom cluster. At T3, hot flashes was removed from the symptom cluster and other symptoms remained stable. In addition, a new cluster (upper GI) appeared after the beginning of the treatment and remained unchanged between T2 and T3. The GI cluster was composed of nausea, vomiting, and decreased appetite.

In the second study, the researchers wanted to determine whether nausea exists as a part of a symptom cluster (Molassiotis et al., 2012). Three time points were evaluated: the day of the first cycle of CTX (T1), the end of cycle 1 (T2), and the end of cycle 2 (T3). The symptoms were clustered by occurrence and severity. At baseline (T1) nausea clustered with loss of appetite, dry mouth, feeling drowsy, feeling bloated, and vomiting when clustered by occurrence, and with loss of appetite, dry mouth, feeling drowsy, and lack of energy when clustered by severity. Both clusters changed after treatment initiation. In the occurrence approach, nausea clustered with pain, taste change, lack of energy, dizziness, appetite loss, and vomiting at T2, and pain and feeling bloated at T3. In the severity approach, nausea clustered with pain and lack of energy at T2, and lack of energy and feeling bloated at T3. There was a big change between symptoms that clustered with nausea at baseline and during treatment. In addition, there were some changes in nausea-related symptom clusters during treatment. Both studies demonstrated that symptom clusters may change during treatment.

The final study in this category was conducted by Kim et al. (2009b), who evaluated the occurrence and severity of symptom clusters at the middle, end, and 1-month after completion of RT to see if symptom clusters changed over time. The sample consisted of 160 patients, of whom 48.7% had breast cancer. Mood-cognitive and sickness-behavior symptom clusters were identified and remained approximately similar over time.

In summary, knowing a symptom cluster change trajectory over time is important in symptom cluster research. This knowledge helps researchers to choose the best time and frequency of measuring, leading to more comprehensive and accurate results. The previous three studies focused on change in symptom clusters over time. The findings indicate there was some change in the number of symptom clusters and symptoms (within a cluster) over time among

patients with breast cancer before, during, and after active treatment such as CTX or RT. It is unclear at what time during treatment symptom clusters should be evaluated. More studies are needed to confirm the results. Furthermore, no study assessed change in symptom clusters in women with breast cancer undergoing hormone and biological therapies.

**3.Predictors of symptom clusters.** According to symptom theories, symptoms and symptom clusters can be affected by many predictors. Four reviewed studies were related to predictors of symptom clusters, such as demographic variables (age, race, and employment status) (Kim et al., 2008; Kim et al., 2009a), personal characteristics (physical performance and biological factors) (Kim et al., 2009a; Thornton et al., 2010), disease characteristics (disease stage and comorbidities) (Chen & Lin, 2007; Kim et al., 2008), treatment modality (Chen & Lin, 2007; Kim et al., 2008; Kim et al., 2009a), and hospitalization (Chen & Lin, 2007).

Three demographic variables were tested across the studies. The first variable, age, was tested in two studies. In the Kim et al. (2009a) study, age predicted the severity of symptoms in the psychoneurological cluster before and after treatment initiation. In addition, age predicted the severity of symptoms in the upper GI cluster at two follow-up points after treatment initiation. Younger participants had greater symptom severity. In another study, Kim et al. (2008) found that age did not significantly influence symptom clustering.

Race and employment status were examined in one study (Kim et al., 2009a). Race predicted severity of symptoms in the upper GI cluster at T3 (48 hours after the third dose of CTX or one month after completion of RT). Caucasian ethnicity predicted increased severity of symptoms in the cluster. Employment status had no significant effect on symptom clustering.

Two studies tested the relationship between symptom clusters and two personal characteristics; physical performance and biological factors (Kim et al., 2009a; Thornton et al.,

2010). Kim et al assessed physical performance and its relationship to symptom clusters during CTX and RT. The authors noted that patients with poorer physical performance had more severe symptoms in the psychoneurological cluster over the entire treatment time. Furthermore, poorer physical performance increased severity of symptoms in the upper GI cluster, but only at the end of treatment.

In a study by Thornton et al (2010), researchers tested the effect of biological factors such as hormones of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis on the pain, depression, and fatigue (PDF) symptom cluster in 104 women from oncology clinics in Ohio. Most of the women were Caucasian (89%) and had recurrent breast cancer (77%). Patients were treated with CTX (61%), RT (15%), and/or hormone therapy (22%). The results showed that the shared variance among hormone levels predicted shared variance among PDF symptoms. Moreover, norepinephrine levels predicted the PDF symptom cluster when controlling for other variables, such as diseases and demographics.

Disease characteristics, such as disease stage and comorbidities, were examined in two studies (Chen & Lin, 2007; Kim et al., 2008). In one study, Chen and Lin examined the association between disease stage and symptom clusters. The sample population included patients with seven types of cancer; patients with breast cancer represented 29% of the sample. The authors divided the cancer stage into two groups: non-metastatic (76%) and metastatic. The results showed patients who had metastatic disease had higher scores on the sickness and GI symptom clusters. Because symptoms were clustered based on the symptom severity dimension, the results indicated patients with advanced cancer had more severe sickness and GI symptom clusters.

In the second study, Kim and colleagues (2008) examined the influence of disease stage and comorbid conditions on symptom clustering. Of the 282 patients, 55.7% had one or more comorbidities. Hypertension was the most frequently reported comorbid condition. The authors divided breast cancer into five stages: 0 (8.9%), 1 (40.4%), 2 (37.6%), 3 (9.6%), and 4 (1.4%). No disease stage or comorbid conditions were found to be significantly related to symptom clustering.

Treatment modality was the most common predictor evaluated in the studies. All studies evaluating treatment modality focused on RT and CTX. Kim et al (2009a) found that patients who were receiving CTX had more severe symptoms in the psychoneurological and upper GI clusters. In another study, Chen and Lin (2007) found that patients who received both CTX and RT had higher scores in the sickness and GI symptom clusters. Kim et al (2008) was the only study that found treatment modality to have no effect on symptom clustering. The effects of hormone and biological therapies on symptom clusters was not evaluated in any study.

Hospitalization may have an effect on symptom clusters. Chen and Lin (2007) found that hospitalized patients had higher scores in the sickness, GI, and emotional clusters.

In summary, studying predictors of symptom clusters is important in order to determine what variables should be controlled for or included in a study. The effects of many predictors on symptom clusters were examined across the studies. However, most predictors were examined only once, which leads to inconclusive results. More studies are needed before we can conclude which predictors may affect which types and dimensions of symptom clusters and how these symptom clusters are affected.

**4. Health outcomes affected by symptom clusters.** Six of the 18 studies examined the relationship between symptom clusters and patient outcomes (Chen & Lin, 2007; Dodd et al.,

2001; Given et al., 2001; Molassiotis et al., 2012; So et al., 2009; Suwisith et al., 2010). Functional status was the most common outcome across the reviewed studies. In four studies, symptom clusters had a negative effect on functional status (Chen & Lin, 2007; Dodd et al., 2001; Given et al., 2001; Suwisith et al., 2010). Suwisith and colleagues found that the GI and fatigue cluster was the strongest predictor of functional status in women with breast cancer undergoing CTX in both dimensions of symptom severity ($t$ = -5.674, $p$ < .0005) and distress ($t$ = -5.675, $p$ < .0005). However, all symptom clusters in the study had a significant negative effect on functional status.

In another study, functional status was negatively associated with symptom clusters (sickness, GI, and emotional) (Chen & Lin, 2007). The strongest association was with the sickness symptom cluster ($r$ = -.44). Given and colleagues (2001) divided 826 patients undergoing CTX and RT treatment into four groups according to the number of symptoms presented in the pain-insomnia-fatigue cluster; of the four cancer diagnoses represented, patients with breast cancer represented 27.6% of the sample. Eighteen percent of the patients experienced the symptom cluster and 33% experienced only two symptoms from the clusters. The authors found that the patients who did not experience any symptoms (no symptom cluster) (19%) had higher physical functioning compared to patients with one, two, or three symptoms six to eight weeks following diagnosis. In the study by Dodd et al (2001), the selected symptom cluster (pain-fatigue-sleep insufficiency) did not demonstrate a synergistic effect on functional status during three cycles of CTX.

The effect of symptom clusters on QOL was examined in two studies (Molassiotis et al., 2012; So et al., 2009). Molassiotis and colleagues (2012) examined nausea-related symptom clusters and found that a chemotherapy-induced nausea symptom cluster, with more than two

symptoms, has a greater negative impact on patients' physical and functional QOL during CTX than nausea alone. So and colleagues (2009) examined the effect of the "fatigue, pain, anxiety, and depression" symptom cluster on the QOL of women with breast cancer undergoing CTX or RT. The findings supported the hypothesis of a detrimental effect of this symptom cluster on QOL. In addition, the results showed that the cluster with the covariates of social support and type of treatment explained 66% of the variance in QOL.

Finally, Molassiotis et al. (2012) studied effects of nausea-related symptom clusters on outcomes such as physiological distress and nutritional status. Physiological distress was assessed by the HADS and nutritional status by the Patient-Generated Subjective Global Assessment (PG-SGA). The results showed that nausea-related symptom clusters have an impact on patients' nutritional status. However, there was no significant difference between nausea or nausea-related symptom clusters and physiological distress during CTX treatment.

In summary, the effect of symptom clusters on functional status was well tested among the studies. The symptom clusters that occurred during active treatment in women with breast cancer had negative effects on functional status. The effect of symptom clusters on QOL was examined in two studies. The results showed that symptom clusters had negative effects on patients' QOL. The effect of symptom clusters on physiological distress and nutritional status cannot be determined because it was examined only once among the studies.

Overall, the results of this section should be interpreted with caution, as four of the studies included other types of cancer in addition to breast cancer (Chen & Lin, 2007; Dodd et al., 2001; Given et al., 2001; Molassiotis et al., 2012). In addition, according to the TSM and the Symptom Experience Model (SEM), symptom clusters can affect many outcomes such as survival, disease progress, mood, emotional status, self-care, mortality, cost, and morbidity.

More comprehensive evaluations of symptom clusters on different outcomes are needed in future studies.

**5. Subgroups of patients and symptom cluster experiences.** Six of the 18 studies focused on the identification of subgroups of patients according to selected symptom clusters (Dodd et al., 2010; Given et al., 2001; Golan-Vered & Pud, 2012; Kim et al., 2012; Miaskowski et al., 2006; Pud et al., 2008). All studies except one (Kim et al., 2012) used the most-common symptom approach. Three of the studies were specific to women with breast cancer (Dodd et al., 2010; Golan-Vered & Pud, 2012; Kim et al., 2012) and these three studies were longitudinal. All studies except one (Kim et al., 2012) focused on the sickness behavior symptom cluster. In one study, the cluster consisted of three symptoms (pain, fatigue, and insomnia) (Given et al., 2001). Other studies added depression to the cluster and used the concept *sleep disturbance* instead of *insomnia.*

In one longitudinal study, researchers investigated whether subgroups of oncology outpatients could be identified based on the sickness behavior symptom cluster (Dodd et al., 2010). The sample included 112 women receiving CTX with or without other active treatments. Most of the women were White (74.1%) and had early stage breast cancer (84.8%). Each symptom in the cluster was measured by a specific symptom scale. Symptoms were measured at three time points: baseline (one week before second cycle of CTX; T1), end of cancer treatment (T2), and 1 year after starting CTX (T3). Cluster analysis identified patient subgroups according to the response to the four symptoms. The results showed there were four subgroups at T1 and T2: (a) low (< 2 symptoms greater than the cut score), (b) mild (two symptoms greater than the cut score), (c) moderate (three symptoms greater than the cut score), and (d) high (four symptoms greater than the cut score).

In another study, researchers divided patients into four groups according to the number of symptoms they experienced (Given et al., 2001). Four cancer types were included in the study; breast cancer patients accounted for 27.6% of the sample ($n$ = 228). The patients were receiving CTX, RT, or both. The results showed 18% of the patients in the breast cancer sample had all of the symptoms, 33% had two symptoms, 30% had one symptom, and 19% had no symptoms.

Golan-Vered and Pud (2012) wanted to determine if subgroups of breast cancer patients could be identified based on the sickness behavior symptom cluster. Forty women who were receiving Paclitaxel were included in the study. The mean age of the women was 45 years (SD = 9.3). Most had second stage (45%) or third stage (52%) breast cancer. Data were collected at two time points: pre-treatment and after at least two courses of Paclitaxel. Two subgroups were found: low cluster group (62.5%) who reported low levels of four symptoms (pain, fatigue, depression, sleep disturbance) and high cluster group (37.5%).

In a study by Miaskowski et al (2006), 191 cancer patients were studied, and 27% had breast cancer. The patients were receiving various types of active treatments. The sample was divided into four groups based on their ratings of the severity of the cluster. The groups were low (low levels of all symptoms) (38%); high fatigue and low pain (33%); low fatigue and high pain (17%); and high (high levels of all symptoms) (12%).

Pud and colleagues (2008) included 228 patients with various cancer diagnoses; women with breast cancer constituted 37.6% of the sample. Most of the patients were on CTX (82.6%) and some were receiving RT (0.9%) and hormone therapy (2.2%). The authors divided the sample into subgroups based on patient experience of symptom severity using hierarchical cluster analysis (HCA). There were four subgroups: low (low levels of all symptoms) (32.9%);

high pain and moderate fatigue (42.5%); low pain and high fatigue (18%); and high (high levels of all symptoms) (6.6%).

Differences in subgroups of patients existed across the studies. The percentage of patients in the low symptom group ranged from 19% to 62.5%. The percentage of patients in the high group ranged from 6.6% to 37.5%. Most of the patients had some of the symptoms from the sickness behavior cluster. Some studies showed that high fatigue was associated with low pain (Kim et al., 2012; Miaskowski et al., 2006; Pud et al., 2008) and vice versa (Miaskowski et al., 2006).

Kim et al (2012) investigated clinical subgroups using a psychoneurologic symptom cluster (pain, fatigue, insomnia, depressive mood, and cognitive disturbance) that was found in their previous study (Kim et al., 2008). The authors included 282 women with breast cancer who were receiving CTX (44.3%) and/or RT (55.7%). The outcomes were measured at baseline (T1) and at two follow-up points after treatment initiation (T2 and T3). For CTX patients, T2 was 48 hours after the second dose of CTX and T3 was 48 hours after the third dose. For RT patients, T2 was after six weeks of RT and T3 one month after completion of RT. Subgroups were formed according to symptom severity. At T2, five subgroups were identified: low symptoms, high fatigue and low pain, high pain, high symptoms, and high depressed-mood and cognitive disturbance. At T3, six subgroups were identified: low symptoms, high fatigue and low pain, high pain, high symptoms, high depressed mood and cognitive disturbance, and high fatigue and insomnia.

***Subgroup membership change over time.*** Only one study investigated whether subgroup membership changed over time (Dodd et al., 2010). Researchers measured outcomes a week before the second cycle of CTX (T1), and at the end of cancer treatment (T2) and noted subgroup

membership changed during the study. Of the 47 women who were clustered in the a*ll low* subgroup at T1, 18 migrated to the *mild* (*n* = 10) and the *moderate* (*n* = 8) subgroups at T2. In addition, some women migrated from the more severe symptom subgroup to less severe symptom subgroup. For example, four women migrated from the *moderate* to the *all low* subgroup and eight migrated from the *moderate* to the *mild* subgroup. The results showed that over time the severity of the symptoms and the symptom cluster increased. However, more studies should be conducted to determine how subgroup membership changes over time with active treatment.

***Predictors of subgroup membership.*** Three studies investigated the demographic and disease characteristic differences between patients in different subgroups (Kim et al., 2012; Miaskowski et al., 2006; Pud et al., 2008). According to Kim and colleagues (2012), pain was the biggest contributor to subgroup separation at the beginning of treatment, and cognitive disturbance was the biggest contributor to subgroup separation at the end of the treatment. In addition, poor performance status at baseline and high symptom burden were predictors of belonging to the high symptom subgroup. Miaskowski and colleagues (2006) reported age and marital status to be the only predictors of subgroup membership. Patients in the high symptom subgroup were younger and less likely to be married. Finally, Pud et al (2008) did not find any differences in the four subgroups according to demographics or disease characteristics. More studies need to be conducted to determine the predictors of subgroup membership.

***Subgroup membership for health outcomes.*** Four studies examined the relationship between subgroup membership and outcomes (Dodd et al., 2010; Given et al., 2001; Miaskowski et al., 2006; Pud et al., 2008). Two health outcomes were measured in the studies: functional status and QOL. The results showed that severity of a symptom cluster correlates with patient

functional status and QOL. Patients who were in the high symptom group had lower QOL (Dodd et al., 2010; Miaskowski et al., 2006; Pud et al., 2008) and functional status (Dodd et al., 2010; Given et al., 2001; Pud et al., 2008). Conversely, patients who were in the low symptom group had significantly higher QOL and functional status (Miaskowski et al., 2006; Pud et al., 2008). Other outcomes such as self-care, costs, and co-morbidity need to be examined in future research.

In summary, the identification of subgroups of patients based on their experiences with a specific symptom cluster is as equally valuable as the identification of symptom clusters in cancer patients and can be used as a complementary approach to analyzing symptom experience (Miaskowski, Aouizerat, Dodd, & Cooper, 2007). This approach can help researchers understand differences among patients in the experience of selected symptom clusters. Comprehensive research has been done on the identification of subgroups and their predictors in a sickness behavior symptom cluster. Other common symptom clusters among women with breast cancer undergoing active treatment should be studied. In addition, more studies need to be done to determine the predictors of subgroup membership, as there are many conflicting findings between the studies.

**Conclusions**

Many outcomes can be summarized from this comprehensive literature review. Numerous symptom clusters were found among women with breast cancer undergoing active treatment. The results are not conclusive, and most of the symptom clusters need further research to be confirmed. The two most common symptom clusters were GI and sickness behavior. However, the number and type of symptoms included in these symptom clusters differed from study to study. In addition, numerous predictors of symptom clusters were tested. According to

the literature, age, race, hormone levels, metastasis, treatment modality, and hospitalization may predict some symptom clusters. However, many of these predictors were studied only once.

In addition, many predictors known to influence symptom experiences in the general population, such as severity of pre-treatment symptoms, body mass index (BMI), activity level, QOL before starting treatment, and Hb level, have not yet been studied. Furthermore, no study evaluated how symptom clusters changed between the baseline and after the end of the treatment. Four patient outcomes (QOL, functional status, nutritional status, and psychological distress) were studied. All but psychological distress were negatively affected by the symptom clusters. Finally, the clusters were experienced differently among women. The women can be divided into two or more subgroups according to their experiences in the sickness behavior cluster. The subgroups' severity ranged from experiencing no symptoms in the cluster to having high levels of all symptoms in the cluster. Considering all of these gaps in knowledge, this dissertation research aims to identify symptom clusters, predictors of symptom clusters, and changes over time in a sample of women with breast cancer undergoing their first four cycles of CTX.

# CHAPTER III

# METHODOLOGY

The overall purpose of this descriptive study was to explore the presence and characteristics of symptom clusters among women undergoing intravenous CTX for breast cancer. The specific aims were to: (1) identify symptom clusters using different symptom dimensions (frequency, severity, and distress); (2) identify which personal, health and illness, and treatment-related variables best predict severity of the symptom clusters; and (3) evaluate how symptom clusters (clustered by the severity dimension) change over time. This chapter presents the methodology for this secondary analysis of data collected from 220 women undergoing CTX in Nebraska between 2002 and 2006 who were enrolled in a randomized clinical trial. Permission for access to the data was granted before any analysis was begun. The components of this chapter include design, setting, sample, data collection variables and measures, data collection procedure and interventions, selection of measures from the original study; selection of time points for current study data analysis, rationale for combining experimental and control groups, methods of the current data analysis, and current study human subject ethics considerations.

## Research Design

The overall purpose and research questions for this dissertation were derived from the literature review and data available from a randomized controlled clinical trial entitled, *Fatigue in Breast Cancer: A Behavioral Sleep Intervention* (Berger et al., 2009). This trial was funded by the National Institutes of Health and National Institute of Nursing Research (5R01NR007762-05). The purpose of the clinical trial was to evaluate the effectiveness of behavioral sleep therapy (BST), which includes stimulus control, sleep restriction, relaxation therapy, and sleep hygiene,

compared to a healthy eating control (HEC) condition in women with breast cancer before, during, and after breast cancer adjuvant CTX.

The current study involved both cross-sectional and longitudinal data analysis. The research questions are: (1) What symptom clusters are present among women with breast cancer undergoing intravenous CTX? (2) What personal, health and illness, and treatment-related characteristics best predict severity of symptom clusters? (3) How do symptom clusters (clustered by severity dimension) change over time? The first question was answered by cross-sectional descriptive design. The second and third questions were answered by longitudinal design. The independent variables (predictors) for the second question were measured at baseline and the dependent variable (severity of symptom cluster) was measured one week after the third cycle of CTX. For the third question, symptom clusters were assessed for change at four time points: baseline, during third and fourth cycles of CTX, and one month after finishing CTX.

## Setting

Patients were recruited from two cancer centers and 10 community oncology clinics in the Midwestern United States. They were stratified by site and randomized at each site to one of two groups (BST or HEC) based on their sleeping history (good/poor) and the number of CTX cycles prescribed (four or more than four). The number of women recruited from each site ranged from one to 72.

## Sample

Between 2002 and 2006, 534 women were screened for eligibility. Inclusion criteria were: (a) women 19 years and older; (b) initial diagnosis of stages I to IIIA breast cancer; (c) post-modified radical mastectomy or lumpectomy; (d) scheduled to begin four anthracycline-based (A/C) intravenous CTX treatments with or without four additional taxane treatments; and

(e) Karnofsky Performance Scale (KPS) score greater than 60. Exclusion criteria included self-reported history of diagnosis of co-morbidities associated with poor sleep and fatigue (including chronic insomnia, chronic fatigue syndrome, unstable heart, lung or neuromuscular disease, insulin-dependent diabetes, sleep apnea, chronic oral steroid therapy, and night-shift employment).

Of the women screened, 314 were excluded from the study; 95 refused to participate because they were not interested (*n* = 78), too overwhelmed (*n* = 12), or without reason (*n* =5), and 219 did not meet the inclusion criteria. The remaining women (*n* = 220) were consented and randomized to either the BST (*n* = 113) or HEC group (*n* = 106) based on good or poor sleeping history and the number of CTX cycles prescribed. At the end of the study, an additional 18 women were excluded because they did not complete any measurements (*n* = 16) or because of screening error (*n* = 2).

## Data Collection Variables and Measures

See Table 3.1 for the selected current study variables and their definitions. The ten symptoms included in the current study for secondary data analysis are anxiety, depression, nausea, pain, appetite, sleep disturbance, fatigue, bowel pattern, concentration, and appearance. In the parent study, four measurements were used to assess symptoms: the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), the revised version of Piper Fatigue Scale (PFS) (Piper, et al., 1998), and the Symptom Experience Scale (SES) (Saramel et al., 1996). In addition, baseline questionnaires were used to gather demographic information about participants; the KPS (Karnofsky & Burchenal, 1949) was used to assess participant's

performance status and the Medical Outcomes Study Short-Form General Health Survey (MOS SF-36) (Ware & Sherbourne, 1992) was used to assess participants' QOL.

Table 3.1 *Definition of Study Variables*

| Variable | Type of Measure | Definition or measure |
|---|---|---|
| Symptoms Included in the Analysis: | | |
| Nausea, pain, appetite, sleep disturbance, fatigue, bowel pattern, concentration, and appearance | Ordinal | Symptom Experience Scale (SES) |
| Anxiety and depression | Continuous | Hospital Anxiety Depression Scale (HADS). |
| Severity of Symptom Cluster | Continuous | Sum of standardized symptoms (measured by severity dimension) that were part of a specific symptom cluster. |
| Other Variables: | | |
| Activity Level | Ordinal | 1) Non-active: sedentary (sitting most of the time).<br>2) Moderate-active: moderate to physically active (on feet most of the time). |
| Age | Ratio | in years $\geq 19$ |
| Body mass index (BMI) | Ratio | Mass (kg) / (height (m))$^2$ |
| Cancer Stage | Ordinal | 1) I<br>2) II + IIIA |
| Education | Ordinal | 1) High school graduate or less<br>2) Some college or more |
| Employment | Nominal | 1) Employed: working or student.<br>2) Non-employed: homemaker, retired, and unemployed. |

| Variable | Type of Measure | Definition or measure |
|---|---|---|
| Ethnicity | Nominal | 1) Hispanic or Latino.<br>2) Non-Hispanic |
| Hemoglobin level | Ratio | at baseline (day 1) |
| Performance Status | Ordinal | Karnofsky Performance Scale (KPS). Score is from 100 to 0, where 100 is "perfect" health and 0 is death. The score was divided into:<br>1) 60-70 and 2) 80-100 |
| Marital Status | Nominal | 1) Married<br>2) Non-married included single, separated, divorced, widowed. |
| Menstrual Status | Nominal | 1) Regular<br>2) Irregular included irregular past 6 months or stopped. |
| Quality of Life (QOL) | Continuous | Quality of life was measured by two summary measures from MOS SF-36:<br>1) Physical Component Summary (PCS)<br>2) Mental Component Summary (MCS) |
| Race | Nominal | 1) White<br>2) Non-White included American Indian / Alaskan Native, Asian, Black or African American, Pacific Islander. |
| Research Group | Nominal | 1) Behavioral sleep therapy (BST) group<br>2) Healthy eating control (HEC) group |
| Surgical Procedure | Nominal | 1) Lumpectomy<br>2) Modified mastectomy included modified mastectomy and modified mastectomy with reconstruction. |

**Nausea, Pain, Appetite, Sleep Disturbance, Fatigue, Bowel Pattern, Concentration, and Appearance.** These eight symptoms were assessed with the SES, which was designed to measure women's symptomatic experiences associated with treatment for breast cancer in three

dimensions (frequency, severity, and distress) (Saramel et al., 1996) (see Appendix C). The scale consists of 24 items, rated on a five-point Likert scale that ranges from 0 (most positive result) to 4 (most negative result). Each point in the scale is connected with descriptive words to facilitate understanding. The descriptors allow for total absence of the symptom in all three symptom dimensions. The SES is administered as a 3-page self-report questionnaire and takes approximately 10 minutes to complete. It assesses symptoms present during the past week. To obtain the total symptom experience score, all items are summed. Scores can range from 0 to 96.

Originally, the SES was tested on 252 women diagnosed with breast cancer (Saramel et al., 1996). The mean age of the women was 57.4 years, and 92% were White. Data were collected approximately five months after surgery (18% lumpectomy, 69% mastectomy, 13% unknown). Only 43% of the women were undergoing treatment during the study (30% CTX, 7% RT, and 6% CTX and RT).

The SES is valid and reliable for measuring symptom experience in oncology patients (Saramel et al., 1996). Content and construct validity were used to evaluate the scale. Content validity was confirmed by a panel of expert oncologists. Construct validity was tested by comparing total symptom experience scores between women receiving CTX ($n$ = 74) and women who were not receiving any adjuvant treatment ($n$ = 143). Scores were significantly higher for women receiving CTX. Internal consistency reliability was estimated with Cronbach's alpha and was .94 for the total scale (Saramel et al., 1996).

**Anxiety and Depression.** The HADS is a 14-item scale that assesses anxiety and depression in medically ill patients (Zigmond & Snaith, 1983) (see Appendix D). The severity of each symptom is measured by seven items using a four-point Likert scale. The total score for

each symptom ranges from 0 to 21 and is interpreted as normal (0-7), mild (8-10), moderate (11-14), or severe (15-21).

The HADS is widely used to assess anxiety and depression among cancer patients (Bjelland, Dahl, Haug, & Neckelmann, 2002). It has well established validity and reliability (Bjelland et al., 2002; Herrmann, 1997). Concurrent validity was measured by comparing the HADS to commonly used anxiety and depression questionnaires such as the Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Clinical Anxiety Scale (CAS), and Symptom Checklist 90 scale (SCL-90). There were medium to strong correlations between the HADS subscales and other related scales (Bjelland et al., 2002). Cronbach's alpha for the HADS anxiety subscale varied from .68 to .93 ($M$ = .83) and for the HADS depression subscale from .67 to .90 ($M$ = .82) among different studies (Bjelland et al., 2002; Costantini et al., 1999; Moorey et al., 1991).

**Performance Status.** Performance status was measured by the KPS, a widely used scale that evaluates the functional status of cancer patients. The performance status of the patient is rated by observers on a numerical scale from 0 to 100, in increments of 10. The scale represents the observer's assessment of the ability of the patient to perform normal activities. A score of 100 indicates that a patient is able to carry out normal activities and work with no special assistance. A score of 60 indicates that a patient requires occasional assistance, but is able to look after his or her personal needs. A score of zero indicates that a patient is dead.

The KPS scale is both valid and reliable (Mor, Laliberte, Morris, & Wiemann, 2006; Schag, Heinrich, & Ganz, 1984; Yates, Chalmer, & McKegney, 1980). Construct validity was demonstrated by strong correlations between the KPS and variables related to functional status such as "difficulty with balance," "problems with eating and grooming," and "difficulty

walking." Inter-rater reliability was evaluated by comparing the KPS scores measured by oncologists and psychologists (Schag et al., 1984) and nurses and social workers (Yates et al., 1980). The results showed high inter-rater reliability.

**Quality of Life.** QOL was measured by the MOS SF-36 scale. The MOS SF-36 is a scale that assesses patients' perceived health status (Ware & Sherbourne, 1992) and is considered one of the most common instruments for assessing health-related QOL (HRQOL). The scores of the scale range from 0 to 100, with 100 representing the highest level of health. The MOS SF-36 assesses eight health concepts, namely physical functioning, role-physical functioning, role-emotional functioning, bodily pain, general health, vitality, social functioning, and mental health. In addition, two summary measures: the physical component summary (PCS) and the mental component summary (MCS), can be computed. The MOS SF-36 is a self-report questionnaire for patients 14 years or older and takes less than 10 minutes to complete (Byar, Berger, Bakken, & Cetak, 2006; Ware & Sherbourne, 1992).

The PCS is highly related to the physical functioning, role-physical functioning, and bodily pain domains, and moderately related to the general health, vitality, and social functioning domains (Ware, Snow, & Kosinski, 2000). A low score on the PCS indicates that a patient is limited in his or her daily activities, may have pain and fatigue, and has problems in work and social life as a result of his or her physical limitations. Conversely, a high score on the PCS indicates that a patient evaluates his or her health as excellent, has a lot of energy and minimal pain, performs physical activity, and has no problems in work or social activities due to physical problems.

The MCS is highly related to the role-emotional functioning, social functioning, and mental health domains, and moderately related to the general health and vitality domains (Ware,

Snow, & Kosinski, 2000). A low score on the MCS indicates that a patient evaluates his or her personal health as poor, has problems in work or social activities that are caused by emotional problems, and feels depressed and nervous most of the time. Conversely, a high score on the MCS indicates that a patient evaluates his or her health as excellent, has no problems in work or social activities related to emotional problems, and feels peaceful, happy and calm.

The MOS SF-36 is valid and reliable (Ware & Sherbourne, 1992). The content validity was demonstrated through comparison of the scale with other health surveys. The construct validity was established by discrimination of eight subscales of the MOS SF-36 between medical outcome study groups differing in physical mobility. In addition, seven subscales of the MOS SF-36 were sensitive to clinically defined differences in mental health (Ware & Sherbourne, 1992). Reliability coefficients ranged from .62 to .96 for different subscales, with a median of .80 (McHorney, Ware, Lu, & Sherbourne, 1994).

## Data Collection Procedure and Interventions

Women who had undergone surgery for breast cancer and scheduled an appointment to receive their first CTX were introduced to the original study by the physician or clinic nurse who briefly explained the study to them and asked if they would be willing to speak to the research nurse (Berger et al., 2009). The research nurse contacted potential participants, to further explain the study and check for eligibility criteria. If the woman met the inclusion criteria and agreed to participate in the study, she was given an informed consent to sign, and was randomized to one of the study groups. She was then given a baseline questionnaire to complete before beginning her initial treatment.

Each woman in the BST group developed an individualized sleep promotion plan based on her answers to different questionnaires related to sleep problems. The program was started

prior to the initial CTX and was reinforced after one week of each CTX, and 30, 60, and 90 days after the last CTX. The women from the HEC group received equal time and attention as the BST group. However, they were given healthy eating information and general support instead of a sleep support plan. If the topic of sleep or fatigue was raised by a woman from the HEC group, the research nurse instructed the woman to contact her clinic (Berger et al., 2009).

Each woman was followed 12 times throughout the study. Table 3.2 summarizes the data collection time points during CTX. There were three CTX regimens; 90 women (43.3%) received A/C without Taxane, 103 women (49.5%) received A/C (four or six cycles) followed by Taxane, and 15 women (7.2%) received A/C with Taxane or Adriamycin and Taxane (AT). In addition, 89 women (42.8%) were receiving dose dense CTX (every two weeks) and 119 women (57.2%) were receiving standard CTX (every three weeks). The symptoms were assessed during all CTX cycles. The PFS was used to assess fatigue on the third day after each CTX. The PSQI was used at cycles four and eight to assess sleep quality. The HADS was used at cycles three, four, six, and eight to assess psychological distress. Finally, the SES was used at all cycles to assess additional symptoms such as nausea and concentration. All measurements except the PFS were administered on the seventh day after CTX. All symptoms were measured at baseline and 30, 60, and 90 days after finishing the last CTX. Personal, health and illness, and treatment characteristics were measured at the beginning of the study, before starting the treatment.

Table 3.2 *Parent Study Data Collection Timetable from T1 to 30 Days after Treatment*

| Variable | Measure | T1<br>Days<br>-2 to 7 | T2<br>Days<br>-2 to 7 | T3<br>Days<br>-2 to 7 | T4<br>Days<br>-2 to 7 | T5<br>Days<br>-2 to 7 | T6<br>Days<br>-2 to 7 | T7<br>Days<br>-2 to 7 | T8<br>Days<br>-2 to 7 | 30 days after last T 7 |
|---|---|---|---|---|---|---|---|---|---|---|
| Fatigue | PFS<br>Fatigue Intensity Item | (-2, 3)<br>(D) | (3)<br>(D) | (3)<br>(D) | (3)<br>(D) | (3)<br>(D) | (3)<br>(D) | (3)<br>(D) | (3)<br>(D) | (1)<br>(D) |
| Sleep/ wake | Diary<br>PSQI | (D)<br>(-2) | (D)<br>-- | (D)<br>-- | (D)<br>(7) | (D)<br>-- | (D)<br>-- | (D)<br>-- | (D)<br>(7) | (D)<br>(1) |
| Psycholog-ical Distress | HADS | (-2) | -- | (7) | (7) | -- | (7) | -- | (7) | (1) |
| Symptom | SES | (-2,7) | (-2,7) | (-2,7) | (-2,7) | (-2,7) | (-2,7) | (-2,7) | (-2,7) | (1) |

*Note.* T = treatment -2 = two days before treatment D = daily

## Selection of Measures from the Parent Study

The ten symptoms included in the analysis were anxiety, depression, nausea, pain, appetite, sleep disturbance, fatigue, bowel pattern, concentration, and appearance. Anxiety and depression were measured by the HADS. Other symptoms, including fatigue and sleep disturbance, were measured by the SES. Fatigue was not measured by the PFS because this scale uses a different time frame than the SES and HADS. The SES and HADS ask about symptoms experienced in the week of the scale administration and were administered one week after each CTX; the PFS asks about fatigue on the day of administration of the scale and was administered on the third day after each CTX. Sleep disturbance was not measured by the PSQI for the same

reason. The PSQI measures sleep quality over the previous month. As stated previously in the literature review chapter, symptoms must be related and co-occur in a cluster; therefore, it is important that all symptoms are measured within the same time-frame.

### Time Point Selection

Four time points were used for analysis in the current study; baseline, cycles three and four of CTX, and 30 days after the last CTX. These time points were used because they were the points at which all symptoms were measured; anxiety and depression were not measured during the second, fifth, and seventh cycles of CTX. In addition, all women underwent cycles one to four, but approximately half of the women underwent cycles five to eight.

### Combining Experimental and Control Groups to Increase Sample Size

The experimental and control groups were combined in the current study after demonstrating that there were no significant differences between the two groups on any of the independent variables at baseline and no differences on any of the symptoms, including sleep, measured in all dimensions at all time points. Table 3.3 shows differences in independent variables between the two groups. Table 3.4 summarizes *p*-values for group differences in symptoms by time point. The primary reason for combining the groups was to increase the sample size.

Table 3.3 *Differences in Independent Variables between the Experimental and Control Groups* ($n$ = 175)

| **Variable** | **Categories** | **BST Group Mean (*SD*) (*N* = 113)** | **HEC Group Mean (*SD*) (*N* = 106)** | ***p*-value** |
|---|---|---|---|---|
| Age (years) | | 52.1 (9.8) | 52.2 (10.3) | .98 |
| BMI | | 28.1 (6.7) | 29.1 (5.4) | .16 |
| Hb level at baseline | | 13.1 (1.2) | 13.2 (1.2) | .65 |
| PCS | | 45.1 (10.3) | 44.1 (8.8) | .45 |
| MCS | | 46.7 (10.6) | 48.3 (10.1) | .30 |
| Ethnicity | Hispanic<br>Non-Hispanic | 3 (3%)<br>110 (97%) | 5 (5%)<br>101 (95%) | .49 |
| Race | White<br>Non-White | 109 (97%)<br>4 (4%) | 100 (94%)<br>6 (6%) | .53 |
| Marital Status | Married<br>Non-Married | 79 (70%)<br>34 (30%) | 79 (75%)<br>27 (26%) | .45 |
| Employment | Employed<br>Non-Employed | 82 (73%)<br>31 (27%) | 83 (78%)<br>23 (22%) | .33 |
| Education | Up to High School<br>Some College or more | 29 (26%)<br>84 (74%) | 26 (25%)<br>80 (76%) | .85 |
| Surgical Procedure | Lumpectomy<br>Modified Mastectomy | 44 (39%)<br>69 (61%) | 51 (49%)<br>54 (51%) | .15 |
| Cancer Stage | I<br>II + IIIA | 33 (29%)<br>80 (71%) | 39 (38%)<br>65 (63%) | .20 |
| Menstrual Status | Regular<br>Irregular | 33 (30%)<br>77 (70%) | 36 (35%)<br>66 (65%) | .41 |
| Karnofsky Score | 60-70<br>80-100 | 6 (5%)<br>107 (95%) | 4 (4%)<br>102 (96%) | .75 |
| Activity Level | Moderate-Active<br>Non-Active | 101 (89%)<br>12 (11%) | 94 (89%)<br>12 (11%) | .87 |

*Note.* Differences in continuous variables were measured by *t*-test and differences in nominal variables were measured by Chi-square.

Table 3.4 *Significant Group Differences in Symptoms by Time Point* (*n* = 179)

| **Symptom Dimension** | ***p*-values** | | | |
|---|---|---|---|---|
| | T1 (Baseline) | T2 (CTX 3) | T3 (CTX 4) | T4 (One month after CTX) |
| Nausea Frequency | .96 | .35 | .84 | .96 |
| Nausea Intensity | .61 | .37 | .92 | .93 |
| Nausea Distress | .99 | .92 | .93 | .86 |
| Pain Frequency | .71 | .12 | .51 | .31 |
| Pain Intensity | .75 | .09 | .63 | .54 |
| Pain Distress | .49 | .15 | .77 | .75 |
| Appetite Frequency | .38 | .59 | .69 | .96 |
| Appetite Intensity | .53 | .80 | .99 | .93 |
| Appetite Distress | .50 | .72 | .87 | .76 |
| Sleep Disturbance Frequency | .76 | .31 | .07 | .68 |
| Sleep Disturbance Intensity | .51 | .42 | .09 | .86 |
| Sleep Disturbance Distress | .89 | .61 | .18 | .83 |
| Fatigue Frequency | .13 | .92 | .44 | .81 |
| Fatigue Intensity | .72 | .94 | .70 | .59 |
| Fatigue Distress | .09 | .50 | .59 | .56 |
| Bowel Pattern Frequency | .40 | .88 | .21 | .83 |
| Bowel Pattern Intensity | .35 | .71 | .23 | .79 |
| Bowel Pattern Distress | .62 | .49 | .18 | .67 |
| Concentration Frequency | .58 | .36 | .49 | .60 |
| Concentration Intensity | .93 | .27 | .64 | .67 |
| Concentration Distress | .86 | .32 | .45 | .90 |
| Appearance Frequency | .65 | .48 | .51 | .81 |
| Appearance Intensity | .68 | .79 | .67 | .88 |
| Appearance Distress | .63 | .97 | .61 | .87 |
| Anxiety Intensity | .58 | .91 | .72 | .82 |
| Depression Intensity | .76 | .47 | .62 | .51 |

*Note*. Differences in continuous variables were measured by *t*-test and differences in ordinal variables were measured by Mann-Whitney U. T = Treatment.

## Methods of Data Analysis

Data were analyzed using SPSS for Windows software version 17.0.1 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to describe the demographics, clinical characteristics, and symptom dimensions, as well as to assess study variables for any violation of statistical assumptions. Descriptive statistics included the mean, standard deviation (*SD*), and

range for continuous variables and frequencies and percentages for categorical variables. A *p*-value ≤ .05 was considered statistically significant. All tests were two-tailed.

Potential differences in symptoms as well as personal and treatment-related variables between the HEC group and the BST group were assessed using the Mann-Whitney *U* test to analyze ordinal variables, chi-square for nominal variables, and *t*-tests for continuous variables. Because there were no statistically significant differences found between the two groups in all symptom dimensions and other characteristics, the study groups were combined in the analysis.

**Research Question # 1. Symptom Clusters**

**Exploratory Factor Analysis (EFA**). EFA was used to identify the number and types of symptom clusters during the first week of the third cycle of CTX. This cycle was chosen because there was an optimal number of symptoms present and an optimal number of women were assessed at this time point. Symptoms from the SES were clustered by different dimensions (frequency, severity, and distress). In addition, symptoms from the HADS were clustered with symptoms measured by the severity dimension from the SES. After evaluating different symptom clusters by using specific criteria, the best fit was reported.

The best fit of symptom grouping was determined according to the following criteria: (1) simple structure, i.e., variables load strongly on only one factor and each factor is represented by a number of strongly loading variables (Pallant, 2007); (2) total variance explained by the symptom clusters; (3) internal reliability of the symptom clusters measured by Cronbach's alpha; and (4) clinical plausibility of the grouping.

To increase clinical significance symptoms with a prevalence of less than 20% were excluded from the analysis (Gleason et al., 2007; Kim et al. 2009). Symptom prevalence was measured by identifying cumulative percentages of women who answered *never* (0) on each

symptom of the SES scale, or scored 0 to 7 on the depression and anxiety subscales of the HADS. In addition, variability of symptom severity level was evaluated when assessing symptom clusters by severity dimension.

**Data factorability (DF)**. Symptom data were screened for outliers and missing values (using frequencies). No outliers were found on the SES 1 to 4 scale or HADS 0 to 21 scale. The missing values were excluded from the analysis using the listwise deletion technique. To verify if the data set was suitable for EFA, the correlation matrix and Kaiser-Meyer-Olkin (KMO) were examined. Bivariate correlations between variables were computed using the Spearman correlation coefficient. According to Tabachnick and Fidell (2007), the correlation matrix should show at least some coefficients of .3 or greater to be suitable for EFA. The KMO, which is an overall measure of sampling adequacy, is accepted if the value is greater than .60, which indicates that the assessed symptoms share common factors (Kaiser & Rice, 1974). Initial communalities were assessed before including the symptoms in the model. Any value less than .20 was seriously considered before addition.

Because the EFA is a component of inferential statistics, the statistical significance is not tested and the concept of power does not apply. However, a ratio of at least 10 subjects to each variable (symptom) is desirable to generalize the results (Munro, 2005, p. 327). The current study had approximately 20 subjects for each variable (symptom).

**Factor extraction.** The sample structure was estimated using the method of Principal Axis Factoring (PAF). In PAF, each factor is extracted to account for the maximum amount of common variance. The strength of this method is that it can be used for normal as well as non-normal data (Skerman, Yates, & Battistutta, 2012). In addition, it is an approach used for cancer symptom cluster identification (Fan, Filipczak, & Chow, 2007). The number of factors included

in the analysis was determined by an eigen-value greater than one and evaluation of a scree plot. The oblique factor rotation, Promax, was conducted, as it was expected that the factors were correlated.

If more than one cluster was identified, each symptom was included in the cluster in which it had a higher factor loading. A minimum cut-off value of .30, which is 9% of the shared variance between a factor and a symptom was required (Skerman et al., 2012). The symptoms with a factor loading less than .30 were excluded from a cluster.

Cronbach's alpha was measured using standardized variables. A symptom cluster was accepted if it had a Cronbach's alpha of .60 or greater, with symptom-total correlations greater than .25. According to Ferketich (1991), the corrected item-total correlations should range between .30 to .70 for a good reliability.

**Research Question #2. Predictors of Symptom Clusters**

Simple linear regression and standard multiple linear regression were used to identify predictors of the severity of the symptom clusters clustered by severity dimension that were found in research question #1. Standard multiple regression explores how well each independent variable predicts the dependent variable, controlling for the other independent variables. First, assumptions of the regression were evaluated. Normality of the dependent variables was assessed by histograms, normal probability plots, residual plots, skewness, and kurtosis. In addition, residual plots were used to check homoscedasticity and linearity. The presence of outliers was checked by collinearity diagnostics and Cook's distance. Furthermore, independent variables were checked for multicollinearity; any bivariate correlation of .7 or more between independent variables led to exclusion one of them form the analysis (Pallant, 2007).

Symptom clusters were treated as dependent variables, and each cluster was entered separately into the regression model. The symptoms in each cluster were standardized [*z*-score = *(x - M)/ SD*] to equalize the influence of variables and then summed to compute a combination score. Because the distribution of the symptom clusters was slightly skewed, the cluster scores were converted to the percentile and then to *t*-scores.

Independent variables that are not continuous or dichotomous, such as race, marital status, education, or activity level, were recoded into dichotomous variables. Bivariate correlations between variables were computed using the Pearson correlation coefficient. If the correlations between dependent and independent variables were less than .10 they were excluded from the analysis. Bivariate correlations between independent variables were tested and if any two variables had a correlation greater than .70, one of them was excluded from the standard multiple linear regression. Independent variables were entered simultaneously into the regression analysis. Multicollinearity was assessed by checking tolerance values, and any independent variables with values less than .10 were excluded from the analysis. The amount of variance ($R^2$) explained by the independent variables, as well as the variables that significantly predicted the severity of symptom clusters, were reported. A *p*-value of $\leq .05$ was considered statistically significant.

Nunnally and Bernstein (1994) recommend that there be at least 10 subjects per predictor in order to have a stable predictor equation. In this study, listwise deletion was used to address missing values, which decreased the sample size to 150. From 16 independent variables, only six had correlations greater than .10 and were included in the regression analysis. This means that there were 25 subjects per independent variable.

**Research Question # 3. Symptom Clusters Change Over Time**

To evaluate a symptom cluster's trajectory over time, data were analyzed at baseline, two times during CTX, and one month after finishing the last CTX. First, symptom prevalence was assessed at each time point. Symptoms that presented in more than 20% of the women were included in further analysis. To determine symptom clusters, an EFA was conducted at each time point. Again, the sample structures were estimated using the method of PAF with promax (oblique) rotation. Symptoms were clustered based on symptom severity ratings. Changes in symptom clusters during different time points were evaluated manually because the best factor models from factor analyses were very different during time points.

## Ethical and Human Research Considerations

The clinical trial of the primary parent study was approved by the Institutional Review Board at the University of Nebraska Medical Center (UNMC). Before receiving the dataset, the memorandum of understanding for data sharing was signed between Professor Ann Berger at UNMC and Professor Catherine Waters and Ph.D. student Randa Albusoul at University of California, San Francisco (UCSF) (see Appendix E). The dataset was de-identified, making it impossible to identify any individual participant. Research involving only unidentifiable information is not considered for review by the UCSF Committee of Human Research (see Appendix F). Data were kept securely on an encrypted hard drive and password-protected laptop and used only for the stated research purposes. Copies of the SES and the HADS are included with permissions from the authors (see Appendix G).

# CHAPTER IV

# RESULTS

This chapter is divided into two main sections: the descriptive results pertaining to demographic and clinical variables, and results that address the three research questions. To answer the three research questions, symptom clusters at cycle three of CTX, predictors of severity of symptom clusters, and trajectory of symptom clusters (clustered by severity dimension) over time will be described.

## Initial Analyses of the Sample Characteristics

### Demographic Characteristics

The demographic characteristics of the sample are presented in Table 4.1. All participants in the study were female with breast cancer (n = 220). However, the sample size used for answering the questions was smaller than 220 because of missing data. The mean age of the women was 52 years (*SD* = 10) and ranged from 29 to 83. The majority of the women were White (95.4%), married (72.1%), and had at least a college education (74.9%). In addition, most were employed (75.3%), worked on average 28.3 hours per week (*SD* = 19), and had a household income of over $40,000 per year (68.7%).

Table 4.1 *Demographic Characteristics of the Sample*

| **Characteristic** | **Mean (*SD*)** | **Range** | **N** |
|---|---|---|---|
| Age (years) | 52.2 (10) | 29-83 | 219 |
| Working Hours | 28.3 (19) | 0-65 | 217 |
| | **Categories** | ***N* (%)** | **N** |
| Ethnicity | Hispanic<br>Non-Hispanic | 8 (3.7)<br>211 (96.3) | 219 |
| Race | White<br>Non-White | 209 (95.4)<br>10 (4.6) | 219 |
| Education | Up to High School<br>Some College or more | 55 (25.1)<br>164 (74.9) | 219 |
| Marital Status | Married<br>Non-Married | 158 (72.1)<br>61 (27.9) | 219 |
| Employment | Employed<br>Non-Employed | 165 (75.3)<br>54 (24.7) | 219 |
| Household Income ($)<br>(year) | Less than 20,000<br>20,000 - 40,000<br>Over 40,000 | 21 (10)<br>45 (21.3)<br>145 (68.7) | 211 |

*Note*. N: total sample size.

**Clinical Characteristics**

The clinical characteristics of the sample are summarized in table 4.2. Thirty-three percent of the women had first stage breast cancer and 67% had second or third stage. The majority of the women had breast cancer with positive estrogen receptors (75.5%) and progesterone receptors (66.3%). Approximately half of the women (52.5%) had no lymph node involvement. All women had surgery for breast cancer approximately three to four weeks prior to beginning of CTX; 56.4% underwent modified mastectomy and 43.6% underwent lumpectomy.

The mean BMI was 28.7 (*SD* = 6.1) and ranged from 16 to 53. More than 95% of the women had Karnofsky score 80 or greater and had a moderate-to-active lifestyle (89%). However, most had PCS (*M* = 44.6; *SD* = 9.6) and MCS (*M* = 47.5; *SD* = 10.4) values that were lower than national norms for females aged 45 to 54 (Ware et al., 2000).

Table 4.2 *Clinical Characteristics of the Sample*

| **Characteristic** | **Mean (*SD*)** | **Range** | **N** |
|---|---|---|---|
| BMI* | 28.7 (6.1) | 16-53 | 216 |
| Hemoglobin level (baseline) | 13.1 (1.2) | 10.3-16.4 | 175 |
| PCS* | 44.6 (9.6) | 17.2-63.5 | 194 |
| MCS* | 47.5 (10.4) | 13.4-65.2 | 194 |
| | **Categories** | ***N* (%)** | **N** |
| Surgical Procedure | Lumpectomy<br>Modified Mastectomy | 95 (43.6)<br>123 (56.4) | 218 |
| Cancer Stage | I<br>II + IIIA | 72 (33.2)<br>145 (66.8) | 217 |
| Lymph Node Status | Positive, 1 to 3<br>Positive, 4 to 9<br>Negative | 78 (35.6)<br>26 (11.9)<br>115 (52.5) | 219 |
| Estrogen Receptor Status | Positive<br>Negative | 160 (75.5)<br>52 (24.5) | 212 |
| Progesterone Receptor Status | Positive<br>Negative | 106 (66.2)<br>54 (33.8) | 160 |
| Menstrual Status | Regular<br>Irregular | 69 (32.5)<br>143 (67.5) | 212 |
| Karnofsky Score | 60-70<br>80-100 | 10 (4.6)<br>209 (95.4) | 219 |
| Activity Level | Moderate-Active<br>Non-Active | 195 (89.0)<br>24 (11.0) | 219 |

*Note*. BMI: Body Mass Index; PCS: Physical Component Summary; MCS: Mental Component Summary; N: total sample size.

**Symptoms at Cycle Three of CTX**

The symptom frequency, severity, and distress mean scores for the 10 symptoms are summarized in table 4.3. The women who did not have symptoms were still included in calculating mean symptom severity and distress scores. All symptoms occurred in more than 20% of the women and were included in further analysis. However, most of the symptoms occurred with low frequency. The mean symptom frequency scores for the SES ranged from 0.80 for pain to 2.18 for fatigue on a scale of 0 to 4.

Table 4.3 *Means and Standard Deviations for Symptoms at the Cycle Three of CTX* (*n* = 186)

| **Symptoms** | **Symptom Dimensions** | | |
|---|---|---|---|
| | Frequency Mean (*SD*) | Severity Mean (*SD*) | Distress Mean (*SD*) |
| Nausea* | 1.35 (1.04) | 1.30 (0.94) | 1.35 (0.89) |
| Pain* | 0.80 (0.82) | 0.85 (0.87) | 0.95 (0.92) |
| Appetite* | 1.49 (1.04) | 1.26 (0.94) | 1.20 (0.78) |
| Sleep Disturbance* | 1.41 (1.01) | 1.41 (0.95) | 1.36 (0.83) |
| Fatigue* | 2.18 (0.99) | 1.85 (0.76) | 1.57 (0.70) |
| Bowel Pattern* | 1.41 (1.10) | 1.24 (0.92) | 1.35 (0.94) |
| Concentration* | 1.07 (0.88) | 1.03 (0.84) | 1.10 (0.85) |
| Appearance* | 0.94 (1.05) | 0.78 (0.88) | 0.98 (1.00) |
| Anxiety** | NA | 5.94 (3.82) | NA |
| Depression** | NA | 6.10 (4.21) | NA |

*Note*. * The scores range from 0 (most positive result) to 4 (most negative result), **The scores range from 0 to 21, NA; not available, *SD*; standard deviation. The women who did not have symptoms were included in calculating severity and distress scores.

The overall score for symptom distress was relatively mild-to-moderate. The mean symptom distress score for the SES symptoms ranged from 0.95 for pain to 1.57 for fatigue on a scale of 0 to 4. The four symptoms that caused the most distress from the SES were fatigue ($1.57 \pm 0.70$), sleep disturbance ($1.36 \pm 0.83$), nausea ($1.35 \pm 0.89$), and bowel pattern ($1.35 \pm 0.94$).

The overall score for symptom severity was relatively mild-to-moderate. The mean symptom severity score for the SES symptoms ranged from 0.78 for appearance to 1.85 for fatigue on a scale of 0 to 4. The four most severe symptoms from the SES were fatigue ($1.85 \pm 0.76$), sleep disturbance ($1.41 \pm 0.95$), nausea ($1.30 \pm 0.94$), and appetite ($1.26 \pm 0.94$). The HADS scores are for the symptom severity dimension only; mean symptom severity scores for anxiety and depression were $5.94 \pm 3.82$ and $6.10 \pm 4.21$, respectively. It is important to note that scores for the three different symptom dimensions were similar. For example, women who had severe symptoms also had more symptom distress.

**Symptom Prevalence and Severity Across Time Points**

The symptom prevalence (% of the sample) and severity (mean ± standard deviation) across the four time points are presented in Table 4.4. The most prevalent symptom was fatigue, which ranged from 89.2 % to 98.3%, followed by sleep disturbance, pain, and concentration problems all with prevalence above 50% at each time point. The least prevalent symptoms were anxiety and depression, rated under 50% at all time points. In general, symptoms were more prevalent during CTX (T2 and T3). However, pain was more prevalent before and after CTX, and anxiety was most prevalent at baseline. During CTX, all symptoms had a prevalence greater than 20% and therefore were included in further analysis. At T1, depression was excluded because of low prevalence (10.8%). At T4, both depression (13.3%) and nausea (13.7%) were excluded.

During CTX, mean symptom severity scores for the SES symptoms ranged from 0.71 for appearance to 1.90 for fatigue. Six symptoms, namely nausea, appetite, sleep disturbance, fatigue, bowel pattern, and concentration, had mean symptom severity scores greater than one during both CTX cycles. However, no symptom exceeded a mean severity score of two on the 0 to 4 scale. Pain, which had a mean severity score less than one during CTX, was the most severe symptom reported at T1. In addition, fatigue was the only symptom from the SES with a severity greater than one across all time points.

The mean severity score for both anxiety and depression was less than seven, which is the cut point for normal symptom severity on the HADS. Anxiety was most severe at T1, and decreased gradually over time. Depression was most severe during CTX and least severe during T1.

Table 4.4 *Symptom Prevalence and Severity Across Time Points* (*n* = 178)

| Symptoms | T1 | | T2 | | T3 | | T4 | |
|---|---|---|---|---|---|---|---|---|
| | Prevalence % | Severity Mean (*SD*) | Prevalence % | Severity Mean (*SD*) | Prevalence % | Severity Mean (*SD*) | Prevalence % | Severity Mean (*SD*) |
| Nausea* | **22.1** | 0.32 (0.68) | **79.1** | 1.30 (0.94) | **80.4** | 1.32 (0.95) | 13.7 | 0.16 (0.44) |
| Pain* | **84.8** | 1.28 (0.79) | **58.8** | 0.85 (0.87) | **59.8** | 0.86 (0.89) | **61.0** | 0.88 (0.86) |
| Appetite* | **41.2** | 0.45 (0.62) | **82.9** | 1.26 (0.94) | **82.1** | 1.25 (0.93) | **28.6** | 0.34 (0.63) |
| Sleep Disturbance* | **76.0** | 1.25 (0.91) | **84.0** | 1.41 (0.95) | **80.0** | 1.28 (0.95) | **64.8** | 0.90 (0.90) |
| Fatigue* | **89.2** | 1.21 (0.64) | **97.9** | 1.85 (0.76) | **98.3** | 1.90 (0.81) | **94.5** | 1.32 (0.64) |
| Bowel Pattern* | **37.7** | 0.46 (0.69) | **80.2** | 1.24 (0.92) | **77.8** | 1.18 (0.88) | **29.1** | 0.37 (0.64) |
| Concentration* | **54.7** | 0.66 (0.69) | **73.1** | 1.03 (0.84) | **72.2** | 1.08 (0.91) | **59.9** | 0.74 (0.71) |
| Appearance* | **25.5** | 0.26 (0.49) | **57.0** | 0.78 (0.88) | **52.8** | 0.71 (0.84) | **33.5** | 0.42 (0.70) |
| Anxiety** | **38.2** | 6.58 (3.87) | **30.6** | 5.93 (3.82) | **26.7** | 5.51 (3.73) | **22.2** | 4.62 (3.75) |
| Depression** | 10.8 | 3.25 (3.00) | **32.8** | 6.10 (4.21) | **36.7** | 6.16 (4.06) | 13.3 | 4.00 (3.28) |

*Note*. *The scores severity range from 0 (most positive result) to 4 (most negative result), **The scores range from 0 to 21. *** Prevalence in bold face type were included in the factor analysis. The women who did not have symptoms were included in calculating mean symptom severity score.

## Key Analyses of the Three Research Questions

### Research Question 1: Symptom Clusters at Cycle Three of the CTX (T2)

**Symptom clusters measured by frequency dimension.** The eight symptoms from the SES were included in the analysis. Scores were screened for outliers and missing values. No outliers were found on the 0 to 4 SES scale. With 186 women included in this analysis, there were approximately 23 women per symptom. The *SD* ranged from 0.82 for pain to 1.10 for bowel pattern, indicating some variability in symptom frequency among the women (Table 4.3). Variability in items is an important assumption in factor analysis (Munro, 2005, p. 327).

A correlation matrix was created to examine the relationships between the symptoms (Table 4.5). The correlations between symptoms were weak to moderate in strength, with many correlations greater than .3, indicating that data were suitable for FA (Tabachnick & Fidell, 2007). In addition, the KMO was .82 indicating that the symptoms share common variance (Kaiser & Rice, 1974). Initial communalities ranged from .13 for pain to .40 for concentration. Although pain frequency had low communality, it was still included in the analysis because of its high prevalence and clinical importance

Table 4.5 *Bivariate Correlations for Symptoms in Frequency Dimension at T2* (*n* = 187)

| Symptoms | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 1-Nausea | -- | | | | | | |
| 2-Pain | .13 | -- | | | | | |
| 3-Appetite | .45** | .15* | -- | | | | |
| 4-Sleep Disturbance | .31** | .18* | .32** | -- | | | |
| 5-Fatigue | .36** | .14 | .39** | .40** | -- | | |
| 6-Bowel Pattern | .19** | .24** | .24** | .21** | .29** | -- | |
| 7-Concentration | .21** | .19* | .25** | .28** | .47** | .42** | -- |
| 8-Appearance | .27** | .23** | .35** | .26** | .35** | .30** | .44** |

*Note*. Spearman correlation coefficient was used to correlate the symptoms.
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

The number of factors was determined by evaluation of eigenvalues and a scree plot. Both methods suggested including two factors. The two factors were extracted, and accounted for 39.39 % of variance explained in all the symptoms. The pattern matrix showed that five symptoms were loaded on factor one (Table 4.6). The symptoms were pain, fatigue, bowel pattern, concentration, and appearance. Factor loadings ranged from .30 for pain to .84 for concentration. Cronbach's alpha was .71, with symptom-total correlations ranging from .31 for pain to .58 for concentration, indicating good internal reliability of the factor. The factor explained 33.5% of the variance.

Table 4.6 *Symptom Clusters Measured by Frequency Dimension at T2* (*n* = 186)

| Symptoms | Factor 1 | Factor 2 | Item-total *r* Factor 1 | Item-total *r* Factor 2 | Initial Communalities |
|---|---|---|---|---|---|
| Nausea | -.03 | **.67** | | .51 | .30 |
| Appetite | -.07 | **.77** | | .50 | .35 |
| Sleep Disturbance | .25 | **.37** | | .39 | .27 |
| Pain | **.30** | .08 | .31 | | .13 |
| Fatigue | **.38** | .35 | .46 | | .39 |
| Bowel Pattern | **.60** | -.04 | .49 | | .26 |
| Concentration | **.84** | -.12 | .58 | | .40 |
| Appearance | **.46** | .24 | .52 | | .35 |
| **Total:** | | | | | |
| Cronbach's alpha | | | .71 | .65 | |
| Variance Explained (%) | 33.5 | 5.9 | | | |

*Note. r,* correlation.

The second factor included three symptoms: nausea, appetite, and sleep disturbance (Table 4.6). The factor loading of the symptoms ranged from .37 for sleep disturbance to .77 for appetite. Cronbach's alpha was .65, with symptom-total correlations ranging from .39 for sleep disturbance to .51 for nausea, which indicates acceptable-to-good internal reliability. The factor explained 5.9% of the variance.

Two symptoms loaded on more than one factor. Fatigue and sleep disturbance had factor loading greater than .25 on both factors, indicating that the relationship between these symptoms and both factors is not clear. Other symptoms clearly loaded on one factor. Some symptoms such as nausea and bowel pattern had negative weak correlations with the other factor. Finally, there was moderate correlation between the two factors ($r$ = .64).

**Symptom clusters measured by severity dimension for SES only (1).** The eight symptoms from the SES were included in the analysis. Symptoms were screened for outliers and missing values. No outliers were found on the 0 to 4 scale. With 185 women included in the

analysis, there were approximately 23 women per symptom. The *SD* ranged from 0.76 for fatigue to 0.95 for sleep disturbance, indicating some variability in symptom severity among the women (see Table 4.3).

A correlation matrix was created to examine the relationships among the symptoms (Table 4.7). The correlations between symptoms ranged from .08 to .47, with some correlations greater than .3, indicating that using FA is appropriate (Tabachnick & Fidell, 2007). In addition, the KMO was .80, indicating that the symptoms share common variance (Kaiser & Rice, 1974). Initial communalities ranged from .13 for pain to .38 for concentration. Although pain severity had low communality, it was included in the analysis because of its high prevalence and clinical importance.

Table 4.7 *Bivariate Correlations for Symptoms in Severity Dimension at T2(1)* (*n* = 187)

| Symptoms | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 1-Nausea | -- | | | | | | |
| 2-Pain | .12 | -- | | | | | |
| 3-Appetite | .43** | .13 | -- | | | | |
| 4-Sleep Disturbance | .29** | .13 | .22** | -- | | | |
| 5-Fatigue | .29** | .14 | .31** | .32** | -- | | |
| 6-Bowel Pattern | .08 | .17* | .12 | .18* | .21** | -- | |
| 7-Concentration | .19** | .19** | .28** | .26** | .47** | .32** | -- |
| 8-Appearance | .20** | .19** | .26** | .21** | .24** | .18* | .43** |

*Note*. Spearman correlation coefficient was used to correlate the symptoms.
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

The number of factors was determined by evaluation of eigenvalues and a scree plot. Both methods suggested including two factors. The two factors were extracted and accounted for 35.22% of variance explained by all the symptoms. The pattern matrix showed that six symptoms were loaded on factor one (Table 4.8). The symptoms were sleep disturbance, pain,

fatigue, bowel pattern, concentration, and appearance. The factor loading of these symptoms ranged from .35 for sleep disturbance to .75 for concentration. Cronbach's alpha was .71, with symptom-total correlations ranging from .33 for pain to .55 for concentration, indicating good internal reliability of the factor. The factor explained 29.77% of the variance.

The second factor included two symptoms; nausea and appetite. The factor loadings were .58 for appetite and .79 for nausea. Cronbach's alpha was .62 and symptom-total correlations .45, indicating acceptable internal reliability. The factor explained 5.45% of the variance.

Table 4.8 *Symptom Clusters Measured by Severity Dimension at T2(1)* (*n* = 185)

| Symptoms | Factor 1 | Factor 2 | Item-total *r* Factor 1 | Item-total *r* Factor 2 | Initial Communalities |
|---|---|---|---|---|---|
| Nausea | -.13 | **.79** | | .45 | .26 |
| Appetite | .08 | **.58** | | .45 | .29 |
| Sleep Disturbance | **.35** | .23 | .43 | | .23 |
| Pain | **.37** | -.02 | .33 | | .13 |
| Fatigue | **.48** | .20 | .49 | | .34 |
| Bowel Pattern | **.52** | -.12 | .37 | | .15 |
| Concentration | **.75** | -.05 | .55 | | .38 |
| Appearance | **.52** | .12 | .48 | | .31 |
| **Total:** | | | | | |
| Cronbach's alpha | | | .71 | .62 | |
| Variance Explained (%) | 29.77 | 5.45 | | | |

*Note. r*; correlation. Only the SES symptoms were included.

As with frequency, fatigue and sleep disturbance severity scores loaded on more than one factor. However, both symptoms were clearly more related to factor 1. Other symptoms clearly loaded on one factor. Some symptoms, such as pain and concentration, had negative weak correlations for factors in which they were not included. Finally, there was moderate correlation between the two factors ($r$ = .64).

**Symptom clusters measured by severity dimension for both SES and HADS (2).** In this analysis, both symptoms from the SES and the HADS were included. Symptoms were screened for outliers and missing values. Severity of the HADS symptoms ranged from 0 to 17 for anxiety and 0 to 18 for depression. With 184 women included in the analysis, there were approximately 19 women per symptom. The *SD* ranged from 0.76 to 0.95 for the SES symptoms and from 3.82 to 4.21 for the HADS symptoms, indicating variability in symptom severity (see Table 4.3).

A correlation matrix was created to examine the relationships among the symptoms (Table 4.9). The correlations between symptoms ranged from .08 to .64. Many correlations were greater than .3, indicating that using FA is appropriate (Tabachnick & Fidell, 2007). In addition, the KMO was .85, indicating that the symptoms share common variance (Kaiser & Rice, 1974). Initial communalities ranged from .12 for pain to .57 for depression. Although pain severity had low communality, it was included in the analysis because of its high prevalence and clinical importance.

Table 4.9 *Bivariate Correlations for Symptoms in Severity Dimension at T2 (2)* (*n* = 187)

| Symptoms | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1-Nausea | -- | | | | | | | | |
| 2-Pain | .12 | -- | | | | | | | |
| 3-Appetite | .43** | .13 | -- | | | | | | |
| 4-Sleep Disturbance | .29** | .13 | .22** | -- | | | | | |
| 5-Fatigue | .29** | .14 | .31** | .32** | -- | | | | |
| 6-Bowel Pattern | .08 | .17* | .12 | .18* | .21** | -- | | | |
| 7-Concentration | .19** | .19** | .28** | .26** | .47** | .31** | -- | | |
| 8-Appearance | .20** | .19** | .26** | .21** | .24** | .18* | .43** | -- | |
| 9-Anxiety | .25** | .18* | .29** | .24** | .42** | .24** | .44** | .35** | -- |
| 10-Depression | .33** | .19** | .41** | .31** | .52** | .19* | .49** | .47** | .64** |

*Note*. Spearman correlation coefficient was used to correlate the symptoms.
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

The number of factors was determined by evaluation of eigenvalues and a scree plot. Both methods suggested including two factors. The two factors were extracted and accounted for 38.02% of the variance explained by all the symptoms. The pattern matrix showed that eight symptoms loaded on factor one (Table 4.10). The symptoms were anxiety, depression, sleep disturbance, pain, fatigue, bowel pattern, concentration, and appearance. The factor loading of these symptoms ranged from .33 for sleep disturbance to .73 for depression. Cronbach's alpha was .80, with symptom-total correlations ranging from .32 for pain to .67 for depression, indicating good internal reliability of the factor. The factor explained 33.38% of the variance.

The second factor included two symptoms; nausea and appetite (Table 4.10). The factor loadings were .56 for appetite and .80 for nausea. Cronbach's alpha was .62 and symptom-total correlation was .45, indicating acceptable internal reliability. The factor explained 4.64% of the variance.

This time only sleep disturbance severity loaded on more than one factor. Other symptoms clearly loaded on one factor. Some symptoms, such as pain and nausea, had negative correlations with the factor in which they were not included. Finally, there was moderate correlation between the two factors ($r$ = .66).

Table 4.10 *Symptom Clusters in Severity Dimension at T2(2)* (*n* = 184)

| Symptoms | Factor 1 | Factor 2 | Item-total *r* Factor 1 | Item-total *r* Factor 2 | Initial Communalities |
|---|---|---|---|---|---|
| Nausea | -.13 | **.80** | | .45 | .26 |
| Appetite | .11 | **.56** | | .45 | .31 |
| Sleep Disturbance | **.33** | .22 | .44 | | .23 |
| Pain | **.34** | .01 | .32 | | .12 |
| Fatigue | **.54** | .15 | .56 | | .40 |
| Bowel Pattern | **.44** | -.09 | .34 | | .14 |
| Concentration | **.72** | -.06 | .60 | | .41 |
| Appearance | **.56** | .08 | .54 | | .38 |
| Anxiety | **.72** | -.04 | .59 | | .45 |
| Depression | **.73** | .09 | .67 | | .57 |
| **Total:** | | | | | |
| Cronbach's alpha | | | .80 | .62 | |
| Variance Explained (%) | 33.38 | 4.64 | | | |

*Note. r,* correlation. Analysis included symptoms from the SES and the HADS.

**Symptom clusters measured by distress dimension.** The eight symptoms from the SES were included in the analysis. Symptoms were screened for outliers and missing values. No outliers were found on the 0 to 4 scale. With 186 women in this analysis, there were approximately 23 women per symptom. The *SD* ranged from 0.70 for fatigue to 1.00 for appearance, indicating variability in symptom distress (see previous Table 4.3).

A correlation matrix was created to examine relationships among symptoms (Table 4.11). The correlations between symptoms ranged from .17 to .53; many correlations were greater than .3, indicating that using FA is appropriate (Tabachnick & Fidell, 2007). In addition, KMO was .83, indicating that symptoms share common variance (Kaiser & Rice, 1974). Initial communalities ranged from .20 for bowel pattern to .41 for appetite.

Table 4.11 *Bivariate Correlations for Symptoms in Distress Dimension at T2* (*n* = 187)

| Symptoms | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 1-Nausea | -- | | | | | | |
| 2-Pain | .34** | -- | | | | | |
| 3-Appetite | .53** | .24** | -- | | | | |
| 4-Sleep Disturbance | .36** | .19** | .40** | -- | | | |
| 5-Fatigue | .43** | .27** | .42** | .44** | -- | | |
| 6-Bowel Pattern | .19* | .24** | .17* | .26** | .29** | -- | |
| 7-Concentration | .28** | .31** | .29** | .25** | .45** | .35** | -- |
| 8-Appearance | .24** | .27** | .33** | .25** | .24** | .22** | .36** |

*Note*. Spearman correlation coefficient was used to correlate the symptoms.
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

The number of factors was determined by evaluation of eigenvalues and scree plot. Eigenvalues suggested including one factor and the scree plot suggested including one to two factors (Figure 4.1). The model with two factors was chosen because it explained more total variance (39.65%) than the one factor model (32.98%). The pattern matrix showed that three symptoms were loaded on factor one (Table 4.12). The symptoms were sleep disturbance, nausea, and appetite. Factor loading of these symptoms ranged from .41 for sleep disturbance to .87 for appetite. Cronbach's alpha was .70, with symptom-total correlations ranging from .43 for sleep disturbance to .58 for appetite, indicating good internal reliability. The factor explained 33.91% of the variance.

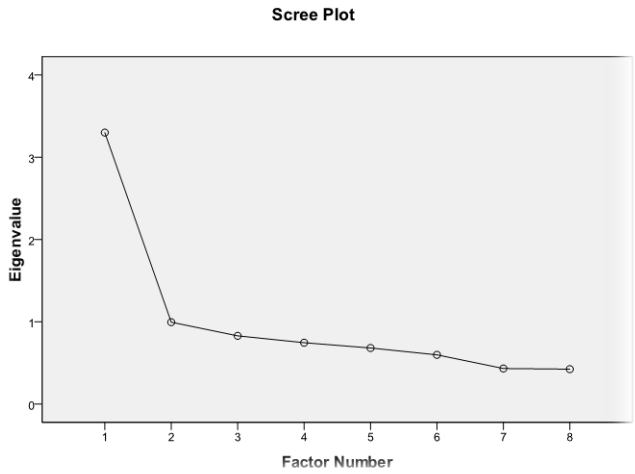


*Figure 4.1* Scree Plot for Symptom Clusters by Distress Dimension at T2.

Table 4.12 *Symptom Clusters in Distress Dimension at T2* (*n* = 186)

| Symptoms | Factor 1 | Factor 2 | Item-total *r* Factor 1 | Item-total *r* Factor 2 | Initial Communalities |
|---|---|---|---|---|---|
| Nausea | **.67** | .01 | .53 | | .36 |
| Appetite | **.87** | -.10 | .58 | | .41 |
| Sleep Disturbance | **.41** | .20 | .43 | | .28 |
| Pain | .14 | **.40** | | .43 | .22 |
| Fatigue | .31 | **.42** | | .48 | .39 |
| Bowel Pattern | -.07 | **.58** | | .43 | .20 |
| Concentration | -.06 | **.74** | | .57 | .34 |
| Appearance | .19 | **.37** | | .42 | .25 |
| **Total:** | | | | | |
| Cronbach's alpha | | | .70 | .71 | |
| Variance Explained (%) | 33.91 | 5.74 | | | |

*Note. r*, correlation

The second factor included five symptoms; pain, fatigue, bowel pattern, concentration, and appearance. The factor loadings ranged from .37 for appearance to .74 for concentration. Cronbach's alpha was .71, with symptom-total correlations ranging from.42 for appearance and

bowel pattern to .57 for concentration, indicating good internal reliability. The factor explained 5.74% of the variance.

Fatigue and sleep disturbance in the distress dimension had factor loadings greater than .20 on both factors, indicating that the relationship between these symptoms and both factors is not clear. Other symptoms clearly loaded on one factor. Some symptoms such as bowel pattern and concentration had negative weak correlations with the factor in which they were not included. Finally, there was moderate correlation between the two factors ($r$ = .65).

**Summary of symptom clusters measured by different dimensions.** Based on the results of FA, there were minimal differences in symptom clusters measured by different dimensions (Table 4.13). Two symptom clusters were identified: the GI symptom cluster and the treatment-related symptom cluster. The GI symptom cluster included two symptoms (nausea and appetite) when measured by severity dimension, and three symptoms (nausea, appetite, and sleep disturbance) when measured by other dimensions. The treatment-related symptom cluster included five symptoms (pain, fatigue, concentration, bowel pattern, and appearance) when measured by frequency and distress dimensions and six (SES) to eight (SES and HADS) symptoms (pain, fatigue, concentration, bowel pattern, appearance, anxiety, depression, and sleep disturbance) when measured by severity dimension. The symptom clusters were able to explain from 35.22% to 39.65% of the total variance. The symptom clusters were stable with Cronbach alpha coefficients ranging from .62 to .80.

Table 4.13 *A Summary of Symptom Clusters by Dimension at T2* (*n* = 184)

| Symptom Clusters | Frequency | Severity[a] | Severity[b] | Distress |
|---|---|---|---|---|
| Cluster 1 | Pain<br>Fatigue<br>Bowel Pattern<br>Concentration<br>Appearance | Sleep[c]<br>Pain<br>Fatigue<br>Bowel Pattern<br>Concentration<br>Appearance | Sleep[c]<br>Pain<br>Fatigue<br>Bowel Pattern<br>Concentration<br>Appearance<br>Anxiety<br>Depression | Pain<br>Fatigue<br>Bowel Pattern<br>Concentration<br>Appearance |
| Cluster 2 | Nausea<br>Appetite<br>Sleep[c] | Nausea<br>Appetite | Nausea<br>Appetite | Nausea<br>Appetite<br>Sleep[c] |
| Total Variance (%) | 39.39 | 35.22 | 38.02 | 39.65 |

*Note*. [a]Only symptoms from SES were included. [b]Symptoms from SES and HADS.
[c] Sleep = sleep disturbance.

The correlations between the two symptom clusters were moderate and ranged from .64 to .66. Two symptoms, fatigue and sleep disturbance, loaded strongly on both clusters, indicating they were related to both clusters.

There was a small difference between clusters when including eight or ten symptoms in the analysis. Symptom clusters formed from ten symptoms seems to be slightly more stable and explained more variance. They were used to answer the second and third research questions.

**Research Question 2: Predictors of Severity of Symptom Clusters During CTX**

To answer this question, simple and multiple regressions were conducted. The assumptions were checked and there were no violations. Symptoms from the GI and treatment-related symptom clusters, clustered based on severity dimension at T2, were standardized and summed to compute a combination score. Because the distribution of the combination scores was

slightly skewed, they were converted to a percentile. Then percentile scores were standardized as *t*-scores with a mean of 50 and *SD* of 10.

Three types of independent variables were evaluated: personal (age, race, ethnicity, marital status, employment, education, menstrual status, and activity level), health and illness (hemoglobin level, BMI, Karnofsky score, QOL [PCS, MCS], cancer stage, and severity of pre-treatment symptoms), and treatment-related (surgical procedure). Any independent variable correlated less than .10 with the dependent variable was excluded from further analysis. The remaining independent variables were analyzed by simple and multiple regression. Independent variables were entered simultaneously using the enter technique. The coding system for binary variables is in Table 4.14.

Table 4.14 *Coding System for Binary Variables*

| Variables | Coding |
|---|---|
| Education | Some college or more = 0<br>Up to high school = 1 |
| Employment | Employed = 0<br>Non-employed = 1 |
| KPS | 60-70 = 0<br>80-100 = 1 |
| Surgical Procedure | Lumpectomy = 0<br>Modified Mastectomy = 1 |

**Predictors of severity of the GI symptom cluster.** The relationships between dependent and independent variables are presented in Table 4.15. Eight independent variables (surgical procedure, age, hemoglobin level, PCS, MCS, severity of pre-treatment symptoms, employment, and education) were correlated greater than .10 and included in the analysis. Correlations between dependent and independent variables ranged from .10 to .27. In addition,

relationships between independent variables were checked, and ranged from .01 to .66. There were no correlations above .70 among independent variables and therefore no further exclusion of variables was necessary.

Table 4.15 *Bivariate Correlations among Predictors of Severity of GI Symptom Cluster* (*n* = 151)

| Variables | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| 1- Cluster Severity[a] | -- | | | | | | | |
| 2- Surgical Procedure | .10 | -- | | | | | | |
| 3- Age | -.18* | -.04 | -- | | | | | |
| 4- Hemoglobin | -.18* | -.27** | .23** | -- | | | | |
| 5- PCS | -.11 | -.18* | -.16 | .15 | -- | | | |
| 6- MCS | -.26** | -.08 | .29** | .05 | -.03 | -- | | |
| 7- SBS | .27** | .19* | -.16* | -.17* | -.40** | -.66** | -- | |
| 8- Employment | -.11 | -.06 | .46** | .06 | -.30** | .07 | -.01 | -- |
| 9- Education | -.10 | .01 | .01 | .02 | -.02 | -.10 | -.05 | .07 |

*Note*. Listwise deletion. Pearson correlation coefficient was used to correlate variables. [a]cluster severity, severity of symptoms in GI symptom cluster;
*Correlation significant at .05 level (2-tailed).
**Correlation significant at .01 level (2-tailed).
MCS, mental component summary; PCS, physical component summary; SBS, severity of pre-treatment symptoms.

The summary of this regression analysis is in Table 4.16. According to univariate analysis, patient's age, hemoglobin level, MCS score, and severity of pre-treatment symptoms significantly predicted severity of GI symptom cluster during CTX. Patients who were younger, had lower hemoglobin levels, had more severe symptoms at the baseline, or had lower scores on MCS, had a more severe symptom cluster.

In the multiple regression analysis, the eight independent variables explained 14% of the variance in the GI symptom cluster during CTX. However, no variable independently predicted the severity of this symptom cluster when the effects of other variables in the model were controlled.

Table 4.16 *Summary of Regression Analysis for Variables Predicting Severity of GI Symptom Cluster* (*n* = 151)

| Predictors | **Univariate** | | | **Multivariate** | | | |
|---|---|---|---|---|---|---|---|
| | B | S.E. | *t* | B | S.E. | *t* | Part$^2$ |
| Age | -0.16 | 0.08 | -2.14* | -0.06 | 0.10 | -0.60 | .00 |
| Surgical Procedure | 2.17 | 1.47 | 1.48 | 0.08 | 1.64 | 0.05 | .00 |
| Hemoglobin level | -1.57 | 0.67 | -2.36* | -1.06 | 0.72 | -1.47 | .01 |
| PCS | -0.12 | 0.08 | -1.49 | -0.12 | 0.10 | -1.18 | .01 |
| MCS | -0.27 | 0.07 | -3.82*** | -0.22 | 0.11 | -1.88 | .02 |
| SBS | 0.53 | 0.12 | 4.43*** | 0.06 | 0.22 | 0.25 | .00 |
| Employment | -2.70 | 1.75 | -1.55 | -2.13 | 2.21 | -0.96 | .01 |
| Education | -2.37 | 1.80 | -1.32 | -2.95 | 2.01 | -1.47 | .01 |
| | | | | $R^2$ | | .14 | |
| | | | Multivariate: | Adjusted $R^2$ | | .09 | |
| | | | | *F* change | | 2.81** | |

*Note.* Listwise deletion was used.
*Correlation is significant at the .05 level.
**Correlation is significant at the .01 level.
***Correlation is significant at the .001 level.
Education, some college or more vs. up to high school; Employment, employed vs. non-employed; MCS, mental component summary; Part$^2$, unique contribution of the variable to the total $R^2$; PCS, physical component summary; SBS, severity of pre-treatment symptoms; S.E., standard error.

**Predictors of severity of the treatment-related symptom cluster.** The relationships between dependent and independent variables are presented in Table 4.17. Six independent variables (hemoglobin level, employment, KPS, PCS, MCS, and intensity of pre-treatment symptoms) had correlations greater than .10 and were included in the analysis. The correlations between dependent and independent variables ranged from .12 to .57. In addition, the relationships between independent variables were checked and ranged from .01 to .67. There were no correlations greater than .70 among independent variables and therefore no further exclusion of variables was necessary.

Table 4.17 *Bivariate Correlations among Predictors of Severity of Treatment-related Symptom Cluster* (*n* = 150)

| Variables | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1- Cluster severity[a] | -- | | | | | |
| 2- Hemoglobin | -.12 | -- | | | | |
| 3- SBS | .57** | -.16* | -- | | | |
| 4- PCS | -.30** | .15 | -.41** | -- | | |
| 5- MCS | -.46** | .05 | -.67** | -.02 | -- | |
| 6- KPS | -.14 | .06 | -.13 | .31** | .09 | -- |
| 7- Employment | -.14 | .06 | .01 | -.29** | .06 | -.12 |

*Note*. Listwise deletion. Pearson correlation coefficient was used to correlate variables.
[a] cluster severity, severity of symptoms in the treatment-related symptom cluster;
*Correlation is significant at the .05 level (2-tailed). **Correlation is significant at the .01 level (2-tailed). KPS, Karnofsky performance scale; MCS, mental component summary; PCS, physical component summary; SBS, severity of pre-treatment symptoms.

The regression analysis is presented in Table 4.18. According to univariate analysis, KPS performance status, PCS and MCS scores, and severity of pre-treatment symptoms significantly predicted severity of treatment-related symptom cluster during CTX. Women with more severe symptoms at baseline or lower scores on the PCS or MCS, had a more severe symptom cluster. In addition, women who had more limited performance status (KPS, 60-70) at baseline had a more severe symptom cluster than patients who had better performance status (KPS, 80-100).

In the multiple regression analysis, the six independent variables were able to explain 39% of the variance in the treatment-related symptom cluster during CTX. Employment status, PCS and MCS scores, and severity of pre-treatment symptoms were independent predictors of this symptom cluster. Patients who had more severe symptoms at the baseline or lower PCS and MCS scores had a more severe symptom cluster. In addition, patients who were employed had a more severe symptom cluster when compared to patients who were not employed. Although the KPS was a significant predictor in the simple regression, it was no longer significant after controlling for the effects of other variables on this symptom cluster.

Table 4.18 *Summary of Regression Analysis Predicting Severity of Treatment-related Symptom Cluster* (*n* = 150)

| Predictors | **Univariate** | | | **Multivariate** | | | |
|---|---|---|---|---|---|---|---|
| | B | S.E. | *t* | B | S.E. | *t* | Part$^2$ |
| Hemoglobin | -0.87 | 0.68 | -1.27 | -0.08 | 0.58 | -0.14 | .00 |
| SBS | 0.92 | 0.11 | 8.80*** | 0.56 | 0.19 | 2.96** | .04 |
| PCS | -0.29 | 0.08 | -3.84*** | -0.23 | 0.09 | -2.49* | .03 |
| MCS | -0.44 | 0.07 | -6.79*** | -0.22 | 0.09 | -2.37* | .02 |
| KPS | -7.37 | 3.58 | -2.06* | -1.56 | 3.31 | -0.47 | .00 |
| Employment | -3.05 | 1.76 | -1.73 | -4.79 | 1.70 | -2.82** | .03 |
| | | | | $R^2$ | | .39 | |
| | | | Multivariate: | Adjust $R^2$ | | .36 | |
| | | | | *F* change | | 15.14*** | |

*Note.* Listwise deletion was used.
*Correlation is significant at the .05 level.
**Correlation is significant at the .01 level.
***Correlation is significant at the .001 level.
Employment, employed vs. non-employed; KPS, Karnofsky performance scale; KPS, 60-70 vs. 80-100; MCS, mental component summary; Part$^2$, unique contribution of the variable to the total $R^2$; PCS, physical component summary; SBS, severity of pre-treatment symptoms; S.E., standard error.

**Research Question 3: Symptom Clusters Trajectory over Time**

**Symptom clusters at baseline (T1).** Both SES and HADS symptoms were included in the analysis. All symptoms were measured by the severity dimension. After checking prevalence of the symptoms, depression was excluded from the analysis because it was present in less than 20% of the women. Other symptoms were screened for outliers and missing values. No outliers were found on the 0 to 4 SES scale or on the 0 to 21 HADS scale. With 202 women included in the analysis, there were approximately 22 women per symptom. The *SD* ranged from .49 to .91for the SES symptoms and was 3.9 for anxiety, indicating variability in symptom severity.

A correlation matrix was created to examine the relationships among the severity of symptoms (Table 4.19). The correlations between symptoms ranged from .09 to .51; many correlations were greater than .3, indicating that using FA is appropriate (Tabachnick & Fidell,

2007). In addition, the KMO was .81, indicating that the symptoms share common variance (Kaiser & Rice, 1974). Initial communalities ranged from .16 for nausea to .36 for concentration. Two symptoms, nausea and bowel pattern, had initial communalities less than .2. After comparing FA results with and without these symptoms, the best model was chosen.

Table 4.19 *Bivariate Correlations for Symptom Severity Dimension at Baseline* (*n* =203)

| Symptoms | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| 1-Nausea | -- | | | | | | | |
| 2-Pain | .22** | -- | | | | | | |
| 3-Appetite | .33** | .28** | -- | | | | | |
| 4-Sleep Disturbance | .12 | .29** | .23** | -- | | | | |
| 5-Fatigue | .26** | .40** | .35** | .36** | -- | | | |
| 6-Bowel Pattern | .19** | .23** | .20** | .26** | .27** | -- | | |
| 7-Concentration | .09 | .23** | .34** | .38** | .34** | .18** | -- | |
| 8-Appearance | .14* | .31** | .25** | .26** | .32** | .28** | .35** | -- |
| 9-Anxiety | .10 | .21** | .19** | .44** | .30** | .13 | .51** | .34** |

*Note*. Spearman correlation coefficient was used to correlate the symptoms.
*Correlation is significant at the .05 level (2-tailed).
**Correlation is significant at the .01 level (2-tailed).

The number of factors was determined by evaluating eigenvalues and a scree plot. Both methods suggested including two factors. Two factors were extracted and accounted for 34.66% of variance explained. The pattern matrix showed that four symptoms loaded on factor 1 (Table 4.20). The symptoms were sleep disturbance, concentration, anxiety, and appearance. The factor loading of these symptom severity scores ranged from .30 for appearance to .79 for anxiety. Cronbach's alpha was .70, with symptom-total correlations ranging from .38 for appearance to .56 for anxiety, indicating good internal reliability of the factor. The factor explained 27.91% of the variance.

Table 4.20 *Symptom Clusters by Severity Dimension at Baseline (T1)* (*n* = 202 )

| Symptoms | Factor 1 | Factor 2 | Item-total *r* Factor 1 | Item-total *r* Factor 2 | Initial Communalities |
|---|---|---|---|---|---|
| Nausea | -.18 | **.59** | | .39 | .16 |
| Appetite | .04 | **.48** | | .40 | .21 |
| Bowel Pattern | .04 | **.44** | | .35 | .18 |
| Pain | .03 | **.56** | | .45 | .24 |
| Fatigue | .16 | **.55** | | .50 | .32 |
| Sleep Disturbance | **.54** | .11 | .47 | | .30 |
| Concentration | **.70** | .01 | .55 | | .36 |
| Anxiety | **.79** | -.15 | .56 | | .34 |
| Appearance | **.30** | .29 | .38 | | .24 |
| **Total:** | | | | | |
| Cronbach's alpha | | | .70 | .66 | |
| Variance Explained (%) | 27.91 | 6.75 | | | |

*Note. r,* correlation.

The second factor included five symptoms: nausea, appetite, bowel pattern, pain, and fatigue. The factor loadings ranged from .44 for bowel pattern to .59 for nausea. Cronbach's alpha was .66 with symptom-total correlations ranging from .35 for bowel pattern to .50 for fatigue, indicating acceptable internal reliability. The factor explained 6.75% of the variance.

In general, the model showed simple structure. However, appearance severity loaded on both factors with a difference of .01 between them. In addition, nausea, sleep disturbance, anxiety, and fatigue had correlations of more than .10 with the factor in which they were not included. Finally, there was moderate correlation between the two factors ($r$ = .59).

**Symptom clusters during CTX (T2).** Symptom clusters measured at time 2 were described in detail when answering the first research question.

**Symptom clusters during CTX (T3).** Both SES and HADS symptoms were included in the analysis. All symptoms occurred in more than 20% of the women. Symptoms were screened for outliers and missing values. With 178 women in this analysis, there were approximately 18

women per symptom. The *SD* ranged from .81 to .95 for SES symptoms and from 3.73 to 4.06 for HADS symptoms, indicating variability in symptom severity among the women at T3.

A correlation matrix was created to examine the relationships among the symptom severity scores at T3 (Table 4.21). The correlations between symptoms ranged from .08 to .57; some correlations were greater than .3, indicating that FA can be used (Tabachnick & Fidell, 2007). In addition, the KMO was .82, indicating that the symptoms share common variance (Kaiser & Rice, 1974). Initial communalities ranged from .15 for sleep disturbance to .53 for depression.

Table 4.21 *Bivariate Correlations for Symptom Severity Dimension During CTX (T3)* ($n$ = 180)

| Symptoms | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1-Nausea | -- | | | | | | | | |
| 2-Pain | .33** | -- | | | | | | | |
| 3-Appetite | .35** | .11 | -- | | | | | | |
| 4-Sleep disturbance | .24** | .19* | .15* | -- | | | | | |
| 5-Fatigue | .26** | .08 | .32** | .08 | -- | | | | |
| 6-Bowel Pattern | .19* | .24** | .24** | .21** | .22** | -- | | | |
| 7-Concentration | .28** | .17* | .24** | .22** | .36** | .39** | -- | | |
| 8-Appearance | .27** | .18* | .32** | .13 | .33** | .21** | .32** | -- | |
| 9-Anxiety | .26** | .26** | .13 | .30** | .27** | .19* | .33** | .37** | -- |
| 10-Depression | .25** | .21** | .41** | .16* | .51** | .28** | .36** | .51** | .57** |

*Note*. Spearman correlation coefficient was used to correlate symptoms.
*Correlation is significant at the .05 level (2-tailed).
**Correlation is significant at the .01 level (2-tailed).

The number of factors was determined by evaluation of eigenvalues and a scree plot. Both methods suggested including two factors. The two factors were extracted and accounted for 34.06% of the variance explained by all the symptoms. The pattern matrix showed that six symptoms were loaded on factor 1 (Table 4.22). The symptoms were fatigue, concentration, appearance, appetite, anxiety, and depression. The factor loading of these symptoms ranged from

.37 for concentration to .92 for depression. Cronbach's alpha was .77, with symptom-total correlations ranging from .39 for appetite to .70 for depression, indicating very good internal reliability of the factor. The factor explained 29.33% of the variance.

Table 4.22 *Symptom Clusters by Severity Dimension During CTX (T3)* (*n* = 178)

| Symptoms | Factor 1 | Factor 2 | Item-total *r* Factor 1 | Item-total *r* Factor 2 | Initial Communalities |
|---|---|---|---|---|---|
| Nausea | .13 | **.49** | | .37 | .28 |
| Bowel pattern | .18 | **.30** | | .29 | .18 |
| Sleep Disturbance | -.08 | **.53** | | .31 | .15 |
| Pain | -.06 | **.55** | | .37 | .19 |
| Fatigue | **.70** | -.13 | .52 | | .32 |
| Appetite | **.40** | .10 | .39 | | .25 |
| Concentration | **.37** | .23 | .46 | | .29 |
| Appearance | **.52** | .12 | .53 | | .31 |
| Anxiety | **.40** | .30 | .52 | | .42 |
| Depression | **.92** | -.12 | .70 | | .53 |
| **Total:** | | | | | |
| Cronbach's alpha | | | .77 | .55 | |
| Variance Explained (%) | | | | | |
| | 29.33 | 4.73 | | | |

*Note. r,* correlation.

The second factor included four symptoms: nausea, bowel pattern, sleep disturbance, and pain. The factor loadings ranged from .30 for bowel pattern to .55 for pain. Cronbach's alpha was .55 with symptom-total correlations ranging between .29 and .37, indicating poor internal reliability. The factor explained 4.73% of the variance. This factor was excluded from the model because of poor internal reliability.

The model structure was complex. Bowel pattern, anxiety, and concentration loaded on more than one factor. In addition, nausea, fatigue, appetite, appearance, and depression had correlations of greater than .10 with the factor in which they were not included. Finally, there was moderate correlation between the two factors ($r$ = .63).

**Symptom clusters after CTX.** After checking prevalence of the symptoms, nausea and depression were excluded from the analysis because they were present in less than 20% of the women. With 180 women in this analysis, there were approximately 23 women per symptom. The *SD* ranged from .63 to .90 for the SES symptoms and was 3.75 for anxiety, indicating variability in symptom severity among the women.

A correlation matrix was created to examine the relationships among the symptoms (Table 4.23). The correlations between symptoms ranged from .02 to .42; with some correlations greater than .3, indicating that using FA is appropriate (Tabachnick & Fidell, 2007). In addition, the KMO was .78, indicating that the symptoms share common variance (Kaiser & Rice, 1974). Initial communalities ranged from .14 for appearance and appetite to .31 for fatigue.

Table 4.23 *Bivariate Correlations for Symptoms Severity Dimension after CTX (T4)* (*n* = 180)

| Symptoms | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 1-Pain | -- | | | | | | |
| 2-Appetite | .07 | -- | | | | | |
| 3-Sleep Disturbance | .28** | .18* | -- | | | | |
| 4-Fatigue | .42** | .26** | .28** | -- | | | |
| 5-Bowel Pattern | .15* | .29** | .12 | .24** | -- | | |
| 6-Concentration | .27** | .13 | .31** | .37** | .23** | -- | |
| 7-Appearance | .09 | .23** | .02 | .21** | .18* | .26** | -- |
| 8-Anxiety | .36** | .16* | .32** | .32** | .26** | .39** | .29** |

*Note*. Spearman correlation coefficient was used to correlate the symptoms.
*Correlation is significant at the .05 level (2-tailed).
**Correlation is significant at the .01 level (2-tailed).

The number of factors was determined by evaluation of eigenvalues and the scree plot (Figure 4.2). Both methods suggested three factors. The three factors were extracted and accounted for 38.46% of variance explained in all the symptoms. The pattern matrix showed that three symptoms loaded on factor 1 (Table 4.24). The symptoms were sleep disturbance, pain, and

fatigue. The factor loading of these symptoms ranged from .60 for fatigue to .68 for pain. Cronbach's alpha was .62, with symptom-total correlations ranging from .39 for sleep disturbance to .48 for fatigue, indicating acceptable internal reliability of the factor. The factor explained 26.78% of the variance.

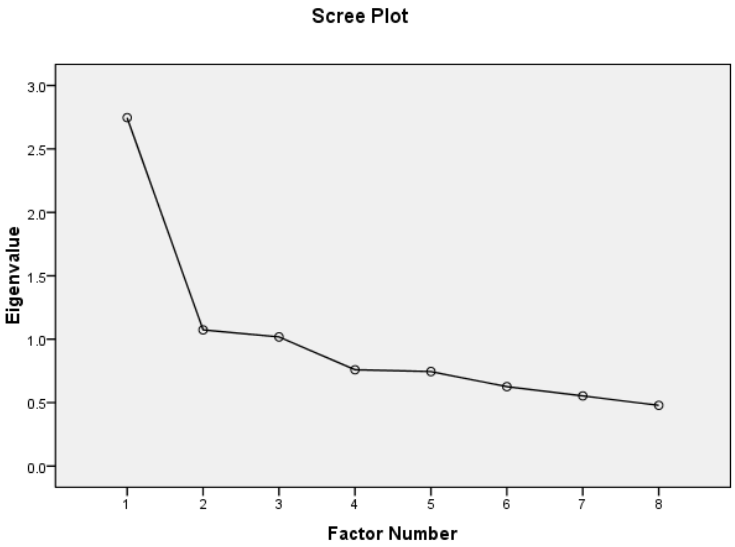


*Figure 4.2* Scree plot for Symptom Cluster by Severity Dimension at T4.

The second factor included three symptoms: appearance, anxiety, and concentration. The factor loadings ranged from .39 for concentration to .66 for appearance. Cronbach's alpha was .59, with symptom-total correlations ranging from .32 for appearance to .46 for anxiety, indicating poor internal reliability. The factor explained 6.39% of the variance. This factor was excluded from the model due to poor internal reliability.

The third factor included one symptom, namely appetite, and explained 5.29% of the variance. This factor was excluded from the model because it has less than two symptoms, the minimum number to compose a symptom cluster. In addition, bowel pattern was excluded from the analysis because of its low factor loading (< .30).

Table 4.24 *Symptom Clusters by Severity Dimension after CTX (T4)* (*n* = 180)

| Symptoms | Factor 1 | Factor 2 | Factor 3 | Item-total *r* Factor 1 | Item-total *r* Factor 2 | Initial Communalities |
|---|---|---|---|---|---|---|
| Fatigue | **.60** | -.00 | .09 | .48 | | .31 |
| Sleep Disturbance | **.62** | -.11 | .05 | .39 | | .23 |
| Pain | **.68** | -.13 | -.04 | .43 | | .25 |
| Concentration | .37 | **.39** | -.11 | | .42 | .29 |
| Appearance | -.25 | **.66** | .09 | | .32 | .14 |
| Anxiety | .29 | **.46** | -.05 | | .46 | .29 |
| Appetite | .02 | .04 | **.73** | | | .14 |
| Bowel Pattern | .28 | .08 | .27 | | | .18 |
| **Total:** | | | | | | |
| Cronbach's alpha | | | | .62 | .59 | |
| Variance Explained (%) | 26.78 | 6.39 | 5.29 | | | |

*Note. r*; correlation.

Concentration and anxiety severity scores loaded on more than one factor, indicating no clear relationship between these symptoms and factors. Other symptoms had small correlations with factors they were not part of. Inter-factor correlations were .25 between factors 2 and 3, .32 between factors 1 and 3, and .61 between factors 1 and 2.

**Summary of symptom cluster trajectories over time.** Based on the results of FA, there were moderate differences in symptom clusters among different time points (Table 4.25). To describe the differences the results are divided into three parts: (1) Differences between symptom clusters before and after initiating of CTX; (2) Stability of symptom clusters during CTX; and (3) Differences between symptom clusters during and after CTX.

Table 4.25 *A Summary of Symptom Clusters Measured at Different Time Points*

| Symptom Clusters | T1 | T2 | T3 | T4 |
|---|---|---|---|---|
| Cluster 1 | Nausea<br>Appetite<br>Bowel Pattern<br>Pain<br>Fatigue | Nausea<br>Appetite | *Nausea*<br>*Bowel pattern*<br>*Sleep*<br>*Pain* | Pain<br>Fatigue<br>Sleep |
| Cluster 2 | Sleep<br>Concentration<br>Appearance<br>Anxiety | Sleep<br>Concentration<br>Appearance<br>Anxiety<br>Bowel Pattern<br>Pain<br>Fatigue<br>Depression | Concentration<br>Appearance<br>Anxiety<br>Fatigue<br>Appetite<br>Depression | *Concentration*<br>*Appearance*<br>*Anxiety* |
| Total Variance (%) | 34.66 | 38.02 | 29.33 | 26.78 |

*Note*. The italicized symptom clusters had reliability less than .60.

***Differences between symptom clusters before and after initiating of CTX.*** Two symptom clusters were found when clustering nine to ten symptoms before and after initiating CTX (Table 4.25). The first cluster consisted of five symptoms at the baseline: nausea, appetite, bowel pattern, pain, and fatigue. After initiating CTX, the cluster consisted of nausea and appetite at T2 and nausea, bowel pattern, pain, and sleep disturbance at T3. However, because of its poor internal reliability ($\alpha = .55$), the cluster at T3 was not retained.

The second symptom cluster consisted of four symptoms, namely sleep disturbance, concentration, anxiety and appearance. At T2, the same symptoms remained in the cluster. In addition, four new symptoms were added; bowel pattern, pain, and fatigue, which were part of the first symptom cluster at the baseline, and depression, which was not included at the baseline because of its low prevalence. At T3, the cluster consisted of all symptoms from the second

symptom cluster at the baseline, except sleep disturbance, in addition to fatigue, appetite, and depression.

Some differences were found between symptom clusters before and after initiating CTX. At both time points two symptom clusters were formed. However, the number and type of symptoms included in each cluster differed. Concentration, anxiety, and appearance were the only symptoms that remained in the same cluster during all three time points.

***Stability of symptom clusters during CTX.*** Two time points (T2 and T3) were assessed to evaluate stability of symptom clusters during CTX. All symptoms occurred in more than 20% of the women and were included in the analysis. At T2, two symptom clusters were found: cluster 1 consisted of nausea and appetite, and cluster 2 consisted of all other eight symptoms. At T3, cluster 1 had poor internal reliability and therefore was not retained. Cluster 2 consisted of six symptoms; five of the six symptoms (fatigue, concentration, appearance, anxiety, and depression) were part of cluster 2 at T2 (Table 4.25). Appetite, the sixth symptom of cluster 2 at T3, was part of cluster 1 at baseline and T2. Although at T3 appetite was clearly loading on symptom cluster 2, it is important to note that it has the lowest item-total correlation in the cluster and would not affect the Cronbach's alpha level if it were deleted. In addition, according to the bivariate correlation matrix (see Table 4.21), appetite had a high correlation with nausea ($r$ = .35).

***Symptom cluster differences during and after CTX.*** After CTX, two symptoms, nausea and depression, were excluded from the analysis because of low prevalence. As nausea was one of the main symptoms in the symptom cluster 1, this cluster no longer existed after CTX. Symptom cluster 2 consisted of three symptoms: pain, fatigue, and sleep disturbance. Additionally, a new symptom cluster was found and included three symptoms; appearance,

anxiety, and concentration. However, because of its low internal reliability ($\alpha = .59$), it was not included. Nonetheless, it is interesting to note that appearance, anxiety, and concentration clustered together at all time points (Table 4.25).

# CHAPTER V

# DISCUSSION

This dissertation research focused on symptom clusters, their predictors, and changes over time among women with breast cancer undergoing CTX. The aims of the study were to identify symptom clusters in this population, to identify predictors of severity of the symptom clusters, and to evaluate how symptom clusters (clustered by severity dimension) change over time. To my knowledge, this is the most comprehensive study done to date on symptom clusters among women with breast cancer undergoing CTX. The biggest strength of the study was its homogeneous sample; all women had early stage breast cancer and were having only CTX treatment. From the review of literature in Chapter 2, most other studies included mixed cancer diagnoses or treatment modalities, which make them less specific in evaluating symptom cluster experiences among women with breast cancer undergoing CTX.

The current study is the first to use three symptom dimensions (frequency, severity, and distress) to explore symptom clusters among women with breast cancer undergoing treatment. Furthermore, the all-possible symptom approach was used, resulting in more accurate and comprehensive symptom clusters. In only one previous study (Suwisith et al., 2010) was the all-possible symptom approach used to cluster symptoms by severity and distress dimensions in this population. In two previous studies (Kim, et al., 2009c; Molassiotis, et al., 2012) the all-possible symptom approach was used to cluster symptoms by severity and occurrence dimensions in women with breast cancer during treatment. However, the first study (Kim, et al., 2009c) included breast and prostate cancer and was specific to RT, and the second study (Molassiotis, et al., 2012) used a mixed cancer sample (breast cancer = 80.6%) and addressed only nausea-related symptom clusters.

The current study comprehensively assessed predictors of severity of symptom clusters among women with breast cancer undergoing CTX. Many possible predictors such as hemoglobin level, BMI, QOL, and activity level were studied for the first time. In addition, the previous studies that assessed predictors included many cancer diagnoses or treatment modalities, and therefore were not specific to a population of women with breast cancer.

Finally, the study evaluated symptom cluster (clustered by severity dimension) changes over time by comparing the symptom clusters before, during, and after CTX. Only one previous study (Molassiotis et al., 2012) evaluated symptom clusters (clustered by severity dimension) over time in this population. However, their study was not specific to breast cancer and included only a nausea-related symptom cluster. In addition, no study compared symptom cluster trajectory from baseline to the end of the treatment.

Discussion of the study's findings are presented in the following sections: (1) characteristics of the study sample; (2) symptom occurrence and severity; (3) symptom clusters during CTX; (4) predictors of severity of the symptom clusters; (5) symptom cluster change over time; (6) limitations of the study; (7) implications for nursing research; (8) implications for nursing practice; and (9) recommendations for future research.

**Characteristics of the Study Sample**

There were some differences in characteristics of the study sample compared to other studies in the literature. According to nationwide statistics, from the years 2005 to 2009, the median age of a breast cancer diagnosis was 61 years old (Howlader et al., 2012). The mean age of the current sample was 52.2, relatively low compared to the nationwide statistics and the literature reviewed in Chapter 2, where mean ages were above 55 years in 10 of the 18 studies.

Another difference in this sample was related to race. For the studies that reported race and were done in the United States, the most common race was White and ranged from 72.8% to 93.5% of the samples. However, in the current study 95.6% of the sample was White, which is the highest among the studies. The high percentage of White women in this study may be related to the geographic location where the data were collected. In 2011, 90.1% of people in Nebraska were White, compared to 78.1% in the USA in general (U.S. Census Bureau). In addition, according to the Centers for Disease Control and Prevention (CDC; 2009), White women had the highest incidence of breast cancer. The small number of non-White women in the sample made it difficult to assess race as a predictor of the severity of symptom clusters.

The biggest difference between other studies and the current study, however, is its sample homogeneity; all women in this study had newly diagnosed breast cancer and were undergoing CTX. Only one study in the literature (Suwisith et al., 2010) was specific to women with breast cancer undergoing CTX. Other studies included mixed diagnoses, different cancer treatments, or just RT or HT treatments. Exploration of symptom clusters in oncology is a newer area of research and it is important to have a homogeneous sample (Molassiotis et al., 2012). The differences among the published studies may have resulted in a variety of symptom clusters found in the literature.

No differences were found in surgical procedures and cancer stages that were included among the studies. Most of the studies included early stages of breast cancer and the same surgical procedures.

**Symptom Occurrence and Severity**

During treatment, all symptoms occurred in more than 20% of the women. However, most symptoms occurred occasionally and had mild-to-moderate severity. Similar results were

found in other studies (Kim et al., 2006; Suwisith et al., 2010). Suwisith et al. reported that most symptoms occurred occasionally, and mean severity scores ranged from 1.32 to 2.66 on a 1- 4 scale. Furthermore, studies that explored subgroups in sickness behavior and GI symptom clusters (Dodd et al., 2010; Given et al., 2001; Golan-Vered & Pud, 2012; Kim et al., 2012; Miaskowski et al., 2006; Pud et al., 2008) reported that 19% to 62.5% of patients were in the low symptom subgroup, which indicates that most patients experienced low symptom severity.

The causes of low symptom severity in this study may be related to some inclusion criteria (i.e., KPS $\geq$ 60, early breast cancer) or the method by which the mean score was calculated (including all patients regardless of whether they had a symptom or not). In addition, patients with more severe symptoms may have been less likely to enroll in the study or more likely to drop out from the study.

One interesting result is that pain had its highest frequency and severity at the baseline. This result was supported by Kim (2006). The high frequency and severity of pain at baseline may be due to surgical procedures that the women underwent one month prior to beginning CTX.

**Symptom Clusters during CTX**

Two symptom clusters were found when clustering symptoms by different dimensions. The GI symptom cluster consisted of nausea and appetite when clustered by severity dimension, and nausea, appetite, and sleep disturbance when clustered by frequency and distress dimensions. The GI symptom cluster is common and specific to CTX treatment. All studies that included women with CTX treatment and used all-possible approach have found this cluster. The cluster was less common in the studies that included only RT treatment. Only Matthews et al. (2011)

reported a GI symptom cluster in a sample specific to RT, when they clustered symptoms according to the distress dimension.

Symptoms included in the GI symptom cluster widely vary among the studies. Most studies included nausea in the cluster. Other common symptoms found in the cluster were vomiting, loss of appetite, lack of energy, and feeling bloated. Less common symptoms found were dizziness, feeling drowsy, shortness of breath, pain, and bowel patterns. This is the first study that included sleep disturbance in the GI symptom cluster and it is not clear why sleep disturbance clustered with the GI symptoms when clustering symptoms using frequency and distress dimensions. However, it is important to note that sleep disturbance loaded on both clusters with higher loading on GI cluster when clustering by frequency and distress dimension. Sleep disturbance item-total correlations were strong, ranging from .39 to .43. In addition, Cronbach's alpha ranged from .65 to .70 for the GI symptom cluster that included sleep disturbance, and was .62 for the cluster with nausea and loss of appetite alone.

Most of the GI symptom clusters in the literature included three or more symptoms. The low number of symptoms included in the GI symptom cluster in the current study may be related to the total number of symptoms that were assessed in the study. Symptoms such as vomiting, feeling bloated, dizziness, and shortness of breath were not assessed in the current study, and therefore it is not possible to explore their association with the GI symptom cluster.

The second symptom cluster that was found in the current study was the treatment-related symptom cluster. This cluster consisted of eight symptoms when clustered by the severity dimension (pain, fatigue, bowel pattern, concentration, appearance, sleep disturbance, anxiety, depression) and five symptoms when clustered by frequency or distress dimensions (pain, fatigue, bowel pattern, concentration, appearance). The treatment-related symptom cluster had

different names in the literature such as sickness behavior or psycho-neurological symptom cluster. It is a common cluster found in almost all studies that explored symptom clusters during treatment. The number of symptoms in the cluster differs among the studies. In studies that used common symptom approach the cluster consisted of three to four symptoms, most commonly pain, fatigue, and insomnia. In studies that used all possible symptom approach the cluster consisted of three to six symptoms.

Two studies (Kim et al., 2008; So et al., 2009) included depression in the treatment-related symptom cluster. In other studies, emotional symptoms (e.g., depression, worrying, feeling irritable, feeling nervous) were clustered alone or with cognitive symptoms (e.g., concentration). One study (Kim et al., 2008) supported clustering of pain, fatigue, and insomnia with emotional and cognitive symptoms such as in the current study. Conversely, in the Suwisith et al. (2010) study, the three key symptoms were in different clusters; insomnia was a part of emotional cluster, fatigue was a part of GI cluster, and pain was a part of pain cluster that consisted of pain, numbness, and dry mouth. It is unclear why the same symptoms clustered differently among the studies. Some reasons may include: 1) using different symptom dimensions when clustering the symptoms, 2) including heterogeneous samples, 3) different number and types of symptoms among the studies, or 4) using different methods to extract the number of factors.

Two additional clusters were found in the literature. The first cluster was called menopausal symptom cluster, and consisted of hot flashes, tiredness, vaginal dryness, weight gain, and decreased sexual interest. The cluster was found in women with breast cancer undergoing HT. The second symptom cluster was called image-related cutaneous symptom

cluster and consisted of hair loss, changes in food taste, mouth sores, skin changes, and difficulty swallowing.

There were many differences among the studies in terms of symptom clusters identified and symptom component of each cluster. The differences in symptom clusters may be related to many factors such as using different scales with different dimensions and time frames among the studies, clustering symptoms in different dimensions, using different analytic approaches, using different symptom cluster approaches, measuring symptoms at different time points, and using a sample that was heterogeneous in term of disease or treatment type.

Using an appropriate scale is important when exploring symptom clusters. The scale should be comprehensive and include all symptoms that are frequently experienced by women with breast cancer. Only one study (Glaus et al., 2006) included menopausal symptoms when studying symptom clusters in women with breast cancer receiving HT. However, it is possible that this symptom cluster is also present among women undergoing CTX. Liu and colleagues (2012) assessed difference in menopausal status among women with breast cancer before and during cycle four of CTX. They found that 38.1% of the women were pre-menopausal at the baseline but only 4.6% were pre-menopausal at the end of cycle four of the treatment. The results show that menopausal symptom cluster may be common among women with breast cancer, however it was under-assessed.

It is unclear clustering in which dimension is more comprehensive and beneficial. In the current study there were minimal differences between symptom clusters when clustered by the three symptom dimensions. In the literature, three studies (Kim et al., 2009c; Molassiotis et al., 2012; Suwisith et al., 2010) compared symptoms clustered by different dimensions and found mild-to-moderate differences, and it is not clear which dimension is better to use. According to

Kim et al. (2009c), severity dimension fits the data better. However, in the current study, clustering by distress dimension had better reliability and explained more variance.

**Predictors of Severity of the Symptom Clusters**

The current study evaluated the ability of 16 variables to predict severity of GI and treatment-related symptom clusters. Seven of the variables, namely BMI, race, ethnicity, menstrual status, activity level, marital status, and cancer stage were excluded because of their low correlation with the severity of these clusters. Baseline age, hemoglobin level, symptom severity, and the MCS score were significant predictors of the severity of GI symptom cluster during CTX. Employment status and baseline KPS, MCS, PCS, and symptom severity scores were significant predictors of the severity of treatment-related symptom cluster.

Seven variables, namely BMI, menstrual status, activity level, surgical procedure, PCS and MCS scores, and baseline symptom severity were studied for the first time in the literature. BMI, menstrual status, and activity level had correlations less than .10 with the severity of both symptom clusters, and therefore were not evaluated further. Surgical procedure was evaluated as a predictor of severity of the GI symptom cluster. However, it was non-significant on the univariate and multivariate level. Severity of pre-treatment symptoms and patients' MCS score were significant predictors of severity of the GI and treatment-related symptom clusters at the univariate level. However, when other variables in the model were controlled, the two variables significantly predicted only the treatment-related symptom cluster. The patient's PCS score was a significant predictor of the severity of treatment-related symptom cluster at both the univariate and multivariate level. However, the patient's PCS score was not predictive of the severity of GI symptom cluster. As all these variables were studied only in the current study, it is recommended to further evaluate them before concluding their ability to predict severity of symptom clusters.

In the current study, race, ethnicity, marital status, and cancer stage were excluded because of their low correlations with the severity of GI and treatment-related symptom clusters. Race was examined in one longitudinal study (Kim et al., 2009a), which found race to predict severity of GI symptom cluster, however, only at one time point. It also did not predict the severity of treatment-related symptom cluster at any time point. Low correlation between race and severity of symptom clusters in the current study may be related to uneven distribution of the race subgroups, as only 4.4% of the sample was non-White. The correlation between ethnicity and severity of treatment-related symptom cluster was examined in two studies (Miaskowski et al., 2006; Pud et al., 2008). Neither study found a significant difference in ethnicity between study subgroups that were divided according to symptom severity experience.

The correlation between marital status and severity of treatment-related symptom cluster was examined in three studies (Kim et al., 2012; Miaskowski et al., 2006; Pud et al., 2008). However, only Miaskowski et al. found a significant difference in marital status between the subgroups; patients from the high severity subgroup in that study were less likely to be married.

Finally, correlations between cancer stage and severity of treatment-related (Chen & Lin, 2007; Miaskowski et al., 2006; Pud et al., 2008) and GI (Chen & Lin, 2007) symptom clusters were examined. All three studies divided the cancer stage into two groups: metastatic and non-metastatic. Only Chen & Lin found any correlation between cancer stage and severity of symptom clusters; patients who had metastatic disease had higher scores on both clusters. The differences between the published literature and the current study may be related to the difference in symptoms and number of symptoms included in each symptom cluster. In addition, in the current study the cancer stage variable was not divided into metastatic and non-metastatic cancer, as all women had early-stage breast cancer.

In the current study, age was a significant predictor of the severity of GI symptom cluster, however, only at the univariate level. Women who were younger had a more severe GI symptom cluster. In the literature, age was examined in three studies (Kim et al., 2009a; Miaskowski et al., 2006; Pud et al., 2008). In the Kim et al. study, age was a significant predictor of the severity of GI and treatment-related symptom clusters. Again, younger women had more severe symptom clusters. In the Miaskowski et al. study, there was a significant difference in age between the study subgroups; women who were in high severity treatment-related symptom cluster subgroup were younger. Finally, Pud et al. did not find significant differences in age among the subgroups. It is unclear why age did not predict the severity of treatment-related symptom cluster in this sample which contradicts the findings from the Miaskowski et al. and Kim et al studies. One reason may be related to differences between the studies. For example, Miaskowski et al. included a mixed cancer sample and different treatment modalities. In addition, there was a difference in number of symptoms in the symptom cluster.

In the current study, baseline performance status measured by the KPS was a significant predictor of severity of treatment-related symptom cluster, however, only at the univariate level. Women who had lower performance status (KPS, 60-70) at the baseline had a more severe treatment-related symptom cluster. In the literature, performance status was examined in one study (Kim et al., 2009a) using the Eastern Cooperative Oncology Group Performance Status (ECOG) scale. The researchers found that women with lower physical performance had more severe symptoms in the treatment-related symptom cluster over the entire treatment time. Furthermore, lower physical performance increased severity of symptoms in the GI cluster, but only at the end of treatment.

In the current study, hemoglobin level was a significant predictor of the severity of GI symptom cluster at the univariate level. However, it was not a significant predictor of the severity of treatment-related symptom cluster. In the literature, only Miaskowski et al. (2006) examined the correlation between hemoglobin level and severity of treatment-related symptom cluster. They did not find any significant differences in hemoglobin level between subgroups divided according to symptom severity.

Employment was found to be significant predictor of the severity of treatment-related symptom cluster after controlling for other variables (i.e., KPS scores, MCS scores, PCS scores, hemoglobin level, severity of pre-treatment symptoms). Women who were employed had a more severe symptom cluster compared to women who were not employed. It is unclear why working women had more severe symptom clusters, however, it may be related to work burden. In the literature, three studies (Kim et al., 2009a; Miaskowski et al., 2006; Pud et al., 2008) reported that employment status had no significant effect on severity of symptom clusters.

Finally, in the current study, education was not a significant predictor of the severity of symptom clusters. This result supports other studies (Miaskowski et al., 2006; Pud et al., 2008).

Studying predictors of severity of symptom clusters is important in order to determine what variables should be controlled or included in a study. The effects of many predictors on symptom clusters were examined across the studies. However, most predictors were examined only once or among heterogeneous samples, which has led to inconclusive results. More studies need to be conducted before we can conclude what predictors may affect severity of GI and treatment-related symptom clusters. Furthermore, severity of other symptom clusters should be evaluated.

**Symptom Cluster Change Over Time**

The current study evaluated symptom cluster changes over time by comparing symptom clusters before, during, and after CTX. At baseline, two symptom clusters were found. The first cluster consisted of five symptoms: nausea, appetite, bowel pattern, pain, and fatigue. The cluster was found during CTX, however, it contained only nausea and appetite. From the review of the literature in Chapter 2, two studies evaluated symptom cluster changes between baseline and treatment time (Kim et al., 2008; Molassiotis et al., 2012). In the Kim et al. study, the GI symptom cluster was found only during treatment. Molassiotis and colleagues examined nausea-related symptom clusters and found that cluster at both baseline and treatment time when they clustered symptoms by occurrence and severity dimensions. Their clusters differed in number and type of symptoms at different time points.

The results from Molassiotis et al. (2012) and the current study show that GI related symptoms, such as nausea and loss of appetite, are present in cancer patients even before beginning CTX, therefore the GI symptom cluster may be found at the baseline. However, there are differences in GI symptom clusters before and during CTX. At baseline, nausea correlated with many symptoms, especially pain and fatigue. During CTX, nausea most commonly correlated with GI symptoms such as bowel problems and loss of appetite. More studies need to be done before accurate differences can be concluded.

The second symptom cluster found in the current study consisted of sleep disturbance, concentration, appearance, and anxiety. After initiating CTX, the four symptoms stayed approximately the same, however, three to four new symptoms namely pain, fatigue, appetite, bowel pattern, and depression entered the cluster. In the literature, one study (Kim et al., 2008) found pain, fatigue, insomnia, depressed mood, and cognitive disturbance cluster remained

approximately the same before and after initiating treatment. More studies are needed to evaluate changes between baseline and CTX symptom clusters among women with breast cancer.

Two studies (Kim et al., 2008; Kim et al., 2009b) evaluated stability of symptom clusters during treatment. In both studies symptom clusters remained stable. In the current study, however, the symptom clusters seemed to be dynamic. The GI symptom cluster (i.e., nausea, loss of appetite) found at T2, had different symptoms and low reliability at T3. In addition, there were some differences in number and type of symptoms included in the treatment-related symptom cluster.

The current study is the first study to show that symptom clusters may be dynamic during treatment, even within a homogeneous sample. This may be related to many factors: first, symptoms are dynamic and their severity may change during treatment; second, there are complex relationships among symptoms within a cluster; and third, there are relationships between different clusters. In the current study, there were moderate correlations between the clusters, which was also supported by Kim and colleagues (2006). The correlations among clusters indicate that the symptoms from each cluster are correlated with the symptoms from another cluster, which increases the probability of clustering these symptoms together at different times. For example, appetite, which was a part of the GI symptom cluster at T2, became part of the treatment-related symptom cluster at T3. Other studies supported this result; Molassiotis et al. (2012) found nausea and appetite to be clustered together before treatment. However, after initiating CTX, appetite was no longer part of their nausea-related cluster. Furthermore, both Suwisith et al. (2010) and Kim et al. (2008) included appetite as a part of a GI cluster, while Chen and Lin (2007) included appetite as part of the treatment-related (sickness behavior) symptom cluster.

At the end of CTX, a cluster was found and consisted of pain, fatigue, and sleep disturbance. In addition, another cluster (appearance, anxiety, and concentration) was found but was not included because of its low reliability ($r$ = .59). The change in symptom clusters may be related to the change in number of symptoms that were included in the analysis. In the current study nausea and depression were excluded from the final analysis due to their low prevalence. In the literature, one study (Kim et al., 2009b) examined the difference between symptom clusters during and after RT and found differences in the number of symptom clusters and type of symptoms in each cluster. The clear difference between symptom clusters during and after treatment may be caused by a decreased number of symptoms after completing of the treatment, which may affect symptom clustering.

**Limitations of the Study**

The biggest limitation of the current study was in the number of symptoms included in the analysis. Although the SES is a valid measure that assesses symptoms in women with breast cancer undergoing treatment, some symptoms presented in this population were not included in the scale. In the Suwisith et al. (2010) study, which examined symptom clusters among women with breast cancer undergoing CTX, the researchers reported that women experienced between 2 and 32 symptoms, with a mean of 17.4 ($SD$ = 7.2). In another study, Molassiotis et al. (2012) assessed patients with breast (80.6%), bladder (9.7%), and ovarian (7.8%) cancer undergoing CTX. The researchers reported seven symptoms that had a prevalence above 40% and were not included in the database analyzed for the current study, namely hair loss (80.2%), feeling drowsy (57.7%), worry (50.5%), feeling nervous (44.3%), dry mouth (44.3%), sweats (41.2%), and taste changes (41.1%). Furthermore, menopausal symptoms, such as loss of libido, hot flashes, and vaginal dryness are common symptoms that could be related to either age or cancer treatments.

Lie et al. (2012) assessed menopausal status in women with breast cancer. They found that 23.7% of the sample were experiencing natural menopause at baseline, and that proportion increased to 62.2% after cycle four of the CTX. The results of the study indicated that treatment-induced menopause is common among women undergoing CTX. Other symptoms among women with breast cancer may include itching, memory problems, mucositis, rash, fever, and headaches. A comprehensive evaluation of symptoms is important to understand the patient's symptom experiences and interactions of symptoms within a symptom cluster.

Another limitation of the study is that most of the symptoms were measured by one item rated on five-point Likert scale ranging from zero (absence of symptom) to four (most negative symptom experienced). Using non-specific symptom scales can decrease the accuracy of the answers, as some symptom names may be confusing for patients (Watanabe, Nekolaichuk, Beaumont, & Mawani, 2009). Finally, information about women's comorbidities and methods they used to treat the symptoms was not available in the study, which may limit accuracy and interpretation of the data. All these limitations may affect symptom communalities and strength and stability of symptom clusters.

**Implications for Nursing Research**

The current study identifies symptom clusters in women with breast cancer undergoing CTX. Two symptom clusters were found and stayed approximately constant across different symptom dimensions. These results confirm the findings of previous studies (Kim et al., 2009c; Suwisith et al., 2010). We may conclude that evaluating one symptom dimension in future research studies is enough, as any dimension can give accurate and comprehensive findings. Symptom cluster research is complex research that requires many instruments to evaluate

complex relationships between symptoms, predictors, and outcomes. Making symptom scales more parsimonious will save the patient's time and effort and decrease patient burden.

Symptom clusters may be dynamic in nature. The current study showed that symptoms within the clusters may change during treatment. Therefore, it may be more accurate, when exploring symptom clusters, to study them at different time points during treatment. It is also important to analyze symptom clusters change over time to show when patients are most burdened and need support.

**Implications for Nursing Practice**

The current study identified common symptom clusters available in women with breast cancer undergoing CTX. Common symptom clusters include symptoms that are frequent, severe, or cause distress to patients. Although not all women experience symptom clusters in the same way, studying common symptom clusters may increase the likelihood of identifying common symptoms that are underreported or untreated. These symptom clusters can be included in assessment protocols in chemotherapy clinics, which will help in comprehensive understanding of women's symptom experiences.

Secondly, effects of symptoms in a symptom cluster overlap, therefore, the treatment of one symptom may have a positive effect on other symptoms in the cluster. This fact can lead to the discovery of new directions in symptom management. It can help in the development of more targeted intervention strategies, reduce polypharmacy, and decrease treatment side effects.

Finally, the current study identifies the predictors of severity of symptom clusters present among women with breast cancer undergoing CTX. Determining the predictors of the severity of symptom clusters will help in specifying women who should be further evaluated for presence of the symptom clusters to receive a more targeted and effective intervention for symptom

management. The findings from this study need to be replicated before definitive clinical practice recommendations can be made.

**Recommendations for Future Research**

The available literature provides beginning information about symptom clusters in women with breast cancer undergoing CTX. It lists common symptom clusters and their predictors and outcomes. However, because this topic is just beginning to be explored (Mollassiotis 2012), there are many gaps in the literature. Future research should focus on comprehensive identification of common symptom clusters present in homogeneous samples of women with breast cancer undergoing CTX. In particular, more research is needed to identify the symptom cluster experience among ethnic and racial minorities. In addition, more research should focus on symptoms clustered by the distress dimension. Second, predictors of severity of symptom clusters need further research to be confirmed. Third, the effects of common symptom clusters on outcomes such as cost, emotional status, and self-care should be studied. This exploration of symptom-related outcomes would aid in the testing of theories, such as the TSM, that includes these types of outcomes in addition to changes in symptom status or QOL.

In addition, more studies need to focus on the nature of the relationships among symptoms within symptom clusters. Because these relationships are complex, researchers might simplify the process and focus on the relationships among two or three symptoms in a cluster at a time. Furthermore, as known from the symptom clusters definition there may be correlations among different symptom clusters. This hypothesis should be tested in future studies. Finally, future research should explore how assessment and management of common symptom clusters have positive effects on women's outcomes. The number of studies exploring women with breast cancer undergoing CTX is still limited. Much more must be done before we comprehensively

and accurately identify and intervene to reduce common symptom clusters present in this population.

## Conclusions

This study aimed to identify common symptom clusters in women with breast cancer undergoing CTX. Two symptom clusters (GI and treatment-related) were found. However, symptoms in each cluster differed according to the assessment time. The symptom clusters stayed fairly constant when clustering by different symptom dimensions; this indicates that using any dimension should result in consistent, accurate and comprehensive results. Severity of pre-treatment symptoms, performance status, and QOL were common predictors of the severity of symptom clusters that women experienced during CTX. While conducting a patient's baseline assessment, clinicians may provide preparatory information to the patient regarding what to expect during treatment.

Although many findings from this study are preliminary, the findings have implications for further research and clinical practice. The findings will contribute to the comprehensive assessment, prevention, and management of symptoms involved in the common symptom clusters. Furthermore, the findings can encourage researchers to pursue longitudinal studies when trying to better understand symptom clusters.

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# APPENDIX A

## *Summary of Studies of Symptom Clusters in Women with Breast Cancer Undergoing Active Treatment*

| **First Author (Year), Purpose & Design** | **Sample Characteristics** | **Instruments & Methods** | **Major Findings** |
|---|---|---|---|
| Chen (2007)<br><br>To validate three symptom clusters (sickness, gastrointestinal, emotional) in a large cancer population.<br><br>To examine how diagnosis, disease stage, cancer treatment, hospitalization, and functional status are associated with available symptom clusters.<br><br>Cross-sectional | N = 321 patients with cancer from two university hospitals in Taipei.<br><br>*n* = 93 patients with breast cancer (29%).<br><br>More than seven cancer types were included.<br><br><u>Mixed Sample</u><br><br>Age: *M* = 60.7 years, range: 22 - 97 years.<br>Gender: Female (54.5%).<br><br>Metastasis: No (76%).<br>Treatment:<br>Surgery (61.4%), CTX (53%),<br>RT (72.6%)<br>Hospitalization:<br>No (77%) | <u>Instruments</u><br>MDASI-T and KPS.<br><br><u>Symptom Dimensions</u><br>Severity<br><br><u>Symptom Approach</u><br>All-possible<br><br>CFA | <u>Symptom Clusters</u><br>Three symptom clusters were confirmed:<br>1) Sickness (pain, fatigue, disturbed sleep, lack of appetite, drowsiness).<br>2) Gastrointestinal (nausea, vomiting).<br>3) Emotional (distress, sadness).<br><br><u>Predictors</u><br>Hospitalized patients had higher scores on three symptom clusters.<br>Patients who received both CTX and RT or had metastatic disease had higher scores on sickness and gastrointestinal symptom clusters.<br>There was no difference in symptom cluster severity among the different diagnoses.<br><br><u>Outcomes</u><br>Patient functional status was negatively associated with three symptom clusters. The strongest association was with the sickness symptom cluster (*r* = -.44). |
| Dodd (2010)<br><br>To determine whether subgroups of oncology outpatients can be identified based on a specific symptom cluster composed of pain, fatigue, depression, sleep disturbances.<br><br>To determine whether these subgroups differ in functional status and QOL.<br><br>To determine whether subgroup membership changes over time.<br><br>Longitudinal | *n* = 112 patients with breast cancer.<br><br>Age:<br>*M* = 50 years, *SD* = 9.3<br><br>Ethnicity:<br>White (74.1%), Black (10.7%), Asian-Pacific Islander (10.7%), and other (4.47%).<br><br>Menopausal status:<br>Premenopausal (38.8%), Perimenopausal (17.5%), and Postmenopausal (43.7%).<br><br>Stages of breast cancer:<br>1 (37.1%), 2 (47.7%), and 3 (15.2%).<br>Treatment: CTX with or without RT, HT, or biological therapy.<br>CTX types:<br>Adriamycin + Cytoxan (88.4%), other (12.6%). | <u>Instruments</u><br>The demographic profile, KPS, worst pain scale, PFS, GSDS, CES-D, MQOLS-CA.<br><br><u>Symptom Approach</u><br>Most-common<br><br>CA<br><br>The outcomes were measured at three points:<br>1) Baseline (T1): week before second cycle.<br>2) End of cancer treatment (T2).<br>3) Approximately one year after starting CTX (T3). | <u>Symptom Cluster</u><br>At T1 and T2 four subgroups were identified:<br>1) Low (< 2 symptoms greater than the cut score).<br>2) Mild (two symptoms greater than the cut score).<br>3) Moderate (three symptoms greater than the cut score).<br>4) High (four symptoms greater than the cut score).<br>At T3 three subgroups were identified:<br>1) Mild.<br>2) Moderate.<br>3) High.<br><br><u>Outcomes</u><br>Patients who were in the high group had poorer QOL and functional status.<br><br><u>Other Findings</u><br>Group membership changed over time. |
| Dodd (2001)<br><br>To determine the effect of a selected symptom cluster (pain, fatigue, sleep insufficiency) on functional status during three cycles of CTX. | N = 93 patients with cancer from 23 outpatient offices and clinics.<br>*n* = 41 patients with breast cancer (45%).<br><br>More than four cancer types were included. | <u>Instruments</u><br>Demographic questionnaire, disease and treatment questionnaire, three items from the QOL-CA and KPS. | <u>Symptom Clusters</u><br>The inter-correlations among the three symptoms were small (pain to fatigue, *r* = .22, *p* < .05; pain to sleep insufficiency, *r* = -.06, nonsignificant; fatigue to sleep insufficiency, *r* = -.13, nonsignificant). |

| First Author (Year), Purpose & Design | Sample Characteristics | Instruments & Methods | Major Findings |
|---|---|---|---|
| Longitudinal | Age: *M* = 55.4 years, *SD* = 14.6<br>Gender: Female (72%)<br>Ethnicity: White (87%)<br>KPS score (*M* / *SD*): at baseline 84.84 / 11.22, at completion 82.66 / 10.56<br>Presence of metastatic disease: (65%) | <u>Symptom Dimensions</u><br>Severity<br><br><u>Symptom Approach</u><br>Most-common<br><br>Data were collected at two time points: baseline (T1) and the end of third cycle (T2). | <u>Outcomes</u><br>The symptom cluster did not demonstrate a synergistic effect on functional status.<br>Pain explained 10.7% of the change in functional status (from T1 to T2). Fatigue explained 7.3% of the change in functional status. Sleep insufficiency was not significant in explaining change in function status. |
| Given (2001)<br><br>To determine if age, selected co-morbidities, stage of cancer, treatment, and symptom cluster (i.e., pain, fatigue, insomnia) explain changes in physical function between three months prior to and eight weeks following diagnosis.<br><br>Longitudinal | N = 826 patients with cancer from 24 community oncology settings.<br>*n* = 228 patients with breast cancer (27.6%).<br><br>Four cancer types were included.<br>Age ranged between 72 and 75 years.<br>Treatment (for breast cancer sample):<br>Lumpectomy or segmental mastectomy plus RT and CTX (30%), modified or radical mastectomy alone (24.1%), and modified or radical surgery plus RT or CTX (14.5%). | <u>Instruments</u><br>Subscale from the SF-36 to measure physical functioning. Symptom checklist written by authors.<br><br><u>Symptom Approach</u><br>Most-common<br><br>Physical functioning and symptoms were measured at baseline and within 8 weeks after initiation of treatment. | <u>Symptom Clusters</u><br>Four groups were identified (percentage of breast cancer patients according to breast cancer sample): all symptoms (18%), two symptoms (33%), one symptom (30%), no symptoms (19%).<br><br><u>Outcomes</u><br>The patients who had no symptoms had higher physical functioning compared to patients with one, two, or three symptoms six to eight weeks following diagnosis. |
| Glaus (2006)<br><br>To investigate presence of symptom cluster in women with breast cancer undergoing hormonal therapy.<br><br>Cross-sectional | *n* = 373 patients with breast cancer from eight outpatient departments in Eastern Switzerland.<br>Age:<br>≤ 50 years (20%)<br>51 - 65 years (41%)<br>> 65 years (39%)<br>Range: 28 - 88 years, *M* = 61 years.<br>Stage of breast cancer:<br>Early (81%)<br>Advanced (19%)<br>Hormonal treatment:<br>Antiestrogens, mainly Tamoxifin (72%)<br>Aromatase Inhibitors (11%)<br>Other anti-hormones (17%) | <u>Instruments</u><br>C-PET<br><br><u>Symptom Dimensions</u><br>Occurrence<br><br><u>Symptom Approach</u><br>All-possible<br><br>CA | <u>Symptom Clusters</u><br>One symptom cluster was identified (hot flashes, tiredness, vaginal dryness, weight gain, and decreased sexual interest). |
| Golan-Vered and Pud (2012)<br><br>To determine if subgroups of patients with breast cancer receiving Paclitaxel could be identified based on their experience of a specific symptom cluster (i.e., pain, fatigue, depression, sleep disturbance).<br><br>To examine the relationship between the symptom cluster and chemotherapy-induced | *n* = 40 patients with breast cancer<br><br>Age:<br>*M* = 45 years, *SD* = 9.3, Range: 21 - 65 years.<br><br>Breast cancer stages:<br>1 (2.5%), 2 (45%), and 3 (52%)<br><br>Comorbid conditions:<br>Migraine (22.5%), Asthma (15%), Irritable bowel (10%),<br>Hypertension (10%), | <u>Instruments</u><br>Demographic questionnaire, DN4, LFS, GSDS, CES-D, NRS for worst pain intensity.<br><br><u>Symptom Approach</u><br>Most-common<br><br>Data were collected at two time points: pre-treatment (demographics and CINP) and at least after second course of Paclitaxel (four | <u>Symptom Clusters</u><br>Two subgroups were found: low cluster group (62.5%) who reported low levels of four symptoms, and high cluster group (37.5%).<br><br><u>Other Findings</u><br>The patients in the high cluster group were more likely to have CINP. |

| First Author (Year), Purpose & Design | Sample Characteristics | Instruments & Methods | Major Findings |
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| neuropathic pain (CINP) in women with breast cancer undergoing Paclitaxel.<br><br>Longitudinal | Hypothyroidism (5%), DM2 (2.5%) | symptoms and CINP).<br><br>CA | |
| Kim (2012)<br><br>To investigate clinical subgroups using a psychoneurologic symptom cluster that consisted of five symptoms (i.e., pain, fatigue, insomnia, depressive mood, cognitive disturbance).<br><br>To examine the differences among subgroups in selected demographic and clinical variables and patient functional performance.<br><br>Longitudinal | *n* = 282 patients with breast cancer from two cancer centers in America.<br><br>Age:<br>*M* = 55.21 years, *SD* = 12.1,<br>Range: 30 - 83 years<br><br>Ethnicity: White: 92%<br><br>Breast cancer stages:<br>≤ 2 (87%)<br>Comorbid conditions:<br>One or more (56%)<br>Treatment:<br>CTX (44.3%) and/or RT (55.7%) | <u>Instruments</u><br>GFS, two subscales (depression and confusion) from POMS-SF, PSQI, side-effect checklist, which was derived from a self-care diary (Nail, Jones, Greene, Schipper, & Jensen, 1991), ECOG, and FPI.<br><br><u>Symptom Dimensions</u><br>Severity<br><br><u>Symptom Approach</u><br>All-possible<br><br>The outcomes were measured at baseline (T1) and at two follow-ups after treatment initiation (T2, T3). For CTX patients, T2 was 48 hours after the second dose of CTX and T3 48 hours after the third dose. For RT patients, T2 was after six weeks of RT and T3 one month after completion of RT.<br><br>Ward's minimum-variance method (1963) | <u>Symptom Clusters</u><br>At T1, four subgroups were identified (low symptoms, high fatigue and low pain, high pain, high symptoms).<br>At T2, five subgroups were identified (low symptoms, high fatigue and low pain, high pain, high symptoms, high depressed mood and cognitive disturbance).<br>At T3, six subgroups were identified (low symptoms, high fatigue and low pain, high pain, high symptoms, high depressed mood and cognitive disturbance, high fatigue and insomnia).<br><br><u>Predictors</u><br>Patients with poor performance status at T1 and high symptom burden had a higher probability of being in the high symptom subgroup.<br><br><u>Other Findings</u><br>Pain was the biggest contributor to subgroup separation at T1 and T2. Cognitive disturbance was the biggest contributor to subgroup separation at T3. |
| Kim (2009a)<br><br>To examine the influence of some demographics and clinical variables on the intensity of symptoms during treatment in two symptom clusters in women with breast cancer.<br><br>Longitudinal | *n* = 282 patients with breast cancer from two cancer centers in America.<br><br>Age:<br>*M* = 55.21 years,<br>*SD* = 12.1<br><br>Ethnicity: White: 91.5%<br>Breast cancer stages:<br>0 (8.9%), 1 (40.4%), 2 (37.6%), 3 (9.6%), and 4 (1.4%).<br><br>Comorbid conditions:<br>One or more (55.7%).<br><br>Treatment:<br>CTX (44.3%) or/and RT (55.7%). | <u>Instruments</u><br>GFS, two subscales (depression and confusion) from the POMS-SF, PSQI, and ECOG. In addition, pain and hot flashes were measured by the use of a single item from the side-effect checklist, which was derived from a self-care diary (Nail, Jones, Greene, Schipper, & Jensen, 1991).<br><br><u>Symptom Approach</u><br>All-possible<br><br>Demographic variables included: age, race, marital status, and employment status. | <u>Predictors</u><br>Physical performance status and age predicted intensity in symptoms in the psychoneurological cluster (pain, fatigue, insomnia, depressed mood, cognitive disturbance; cluster 1) at both T1 and T2.<br><br>Participants with poor physical performance and younger age had greater symptom intensity.<br><br>At T3, treatment modality and physical performance predicted intensity of symptoms in cluster 1. Women with CTX and poor physical performance had more intense symptoms.<br><br>Age and treatment modality predicted intensity of symptoms in the upper gastrointestinal cluster (nausea, vomiting, decreased appetite; cluster 2) at T2. Younger women and women receiving CTX had more |

| First Author (Year), Purpose & Design | Sample Characteristics | Instruments & Methods | Major Findings |
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| | | | intense symptoms.<br><br>Race, physical performance status, age, and treatment modality predicted intensity of symptoms in cluster 2 at T3. Caucasian ethnicity and poor physical performance status increased the intensity of the symptoms in the cluster. |
| Kim (2008)<br><br>To investigate treatment-related symptom clusters in women undergoing treatment for breast cancer.<br><br>To examine the influence of selected demographic and clinical variables on symptom clustering.<br><br>Longitudinal | *n* = 282 patients with breast cancer from two cancer centers in the US (different numbers of patients were included in the three time points because of missing data).<br><br>Age:<br>*M* = 55.21 years, *SD* = 12.1,<br>Range: 30 - 83 years.<br>Ethnicity: White: 91.5%<br><br>Breast cancer stages:<br>0 (8.9%), 1 (40.4%), 2 (37.6%), 3 (9.6%), and 4 (1.4%).<br><br>Comorbid conditions:<br>One or more (55.7%). Most frequently hypertension.<br>Treatment:<br>CTX (44.3%) or/and RT (55.7%). | Instruments<br>Fatigue intensity was measured by one item from the GFS (fatigue in the past week). Insomnia (for the past month) was measured by the PSQI. Depressive mood and cognitive disturbance (for the past 2-3 days) were measured by two subscales (depression and confusion) of the POMS-SF. The side effect checklist.<br><br>Symptom Dimensions<br>Severity<br><br>Symptom Approach<br>All-possible<br><br>The outcomes were measured at baseline (T1) and at two follow-up points after treatment initiation (T2, T3). For CTX patients, T2 was 48 hours after the second dose of CTX and T3 48 hours after the third dose. For RT patients, T2 was after six weeks of RT and T3 one month after completion of RT.<br><br>FA | Symptom Clusters<br>At T1, one symptom cluster was identified (pain, fatigue, insomnia, depressed mood, cognitive disturbances).<br>At T2, two symptom clusters were identified. Cluster 1 (nausea, vomiting, decrease appetite) (upper gastrointestinal cluster) and cluster 2 (pain, fatigue, insomnia, depressed mood, cognitive disturbance, hot flashes).<br>At T3, two symptom clusters were identified. Cluster 1 (nausea, vomiting, decrease appetite; upper gastrointestinal cluster) and cluster 2 (pain, fatigue, insomnia, depressed mood, cognitive disturbance).<br><br>Predictors<br>Demographic and clinical variables did not significantly influence symptom clustering.<br><br>Other Findings<br>The two symptom clusters remained nearly stable across the treatment trajectory.<br><br>Cronbach's α changed from .73 (T2) to .81 (T3) in cluster 1 and from .68 (T1) to .69 (T2) and then to .77 (T3) in cluster 2. |
| Kim (2009b)<br><br>To determine the number and types of symptom | N = 160 patients with cancer from a comprehensive cancer center and a community-based cancer | Instruments<br>MSAS, checklist of comorbidities, KPS, and demographic | Symptom Clusters<br>Three clusters were identified:<br>Mood-cognitive (difficulty concentrating, feeling sad, worrying, |

| First Author (Year), Purpose & Design | Sample Characteristics | Instruments & Methods | Major Findings |
|---|---|---|---|
| clusters at the middle, end, and one month after completion of RT.<br><br>To evaluate if these symptom clusters change over time.<br><br>Longitudinal | program.<br><br>*n* = 78 patients with breast cancer (48.7%).<br><br>Two types of cancer were included.<br><br>Age: *M* = 61.1 years, *SD* = 11.5.<br>Gender: Female (48.7%)<br>Ethnicity: Caucasian (72.8%).<br><br>Number of Comorbidities: *M* = 5, *SD* = 2.5<br>KPS score: *M* = 92.4, *SD* = 9.7<br>Presence of metastatic disease: (0%) | questionnaire.<br><br><u>Symptom Dimensions</u><br>Severity<br>Occurrence (≥20%)<br><br><u>Symptom Approach</u><br>All-possible<br><br>Data were collected at three time points: middle (T1), end (T2), and one month after (T3) RT.<br><br>EFA | feeling irritable, feeling nervous) at T1. At T2, "feeling nervous" was excluded from the cluster. At T3, "feeling irritable" was excluded. Cronbach's α ranged between .78 and .84.<br>Sickness-behavior (pain, lack of energy, feeling drowsy, difficulty sleeping, sweats) at T1 and T2. At T3, "pain" and "sweats" were removed and "feeling irritable" was added. Cronbach's α ranged between .68 and .73.<br>Treatment-related or pain that included problem with urination, diarrhea at T1; problem with urination, changes in skin at T2; and pain, numbness, tingling in hands/feet at T3. Cronbach's α ranged between .36 and .63.<br>The treatment-related symptom cluster was related most closely to patients with prostate cancer at T1 and T2 and to patients with breast cancer at T3.<br>Mood-cognitive and sickness-behavior symptom clusters remained approximately similar over time. |
| Kim (2009c)<br><br>To identify symptom clusters at the end of RT in patients with breast and prostate cancer.<br><br>To differentiate between symptom clusters identified using occurrence rate versus severity rate.<br><br>Cross-sectional | N = 160 patients with cancer from a comprehensive cancer center and a community-based cancer program.<br><br>*n* = 78 patients with breast cancer (48.7%).<br><br>Two types of cancer were included.<br><br>Age: *M* = 61.1 years, *SD* = 11.5<br>Gender: Female (48.7%)<br>Ethnicity: Caucasian (72.8%)<br><br>Number of comorbidities: *M* = 5, *SD* = 2.5<br>KPS score: *M* = 92.4, *SD* = 9.7<br>Presence of metastatic disease: (0%) | <u>Instruments</u><br>MSAS, checklist of comorbidities, KPS, and demographic questionnaire.<br><br><u>Symptom Dimensions</u><br>Severity<br>Occurrence (80% ≥ O ≥ 20%)<br><br><u>Symptom Approach</u><br>All-possible<br><br>EFA | <u>Symptom Clusters</u><br>Symptom clusters based on *occurrence*:<br>Mood-cognitive (difficulty concentrating, difficulty sleeping, feeling sad, worrying, feeling irritable, sweats, itching).<br>Sickness-behavior (pain, lack of energy, feeling drowsy).<br>Treatment-related (problems with urination, changes in skin).<br><br>Symptom clusters based on *severity*:<br>Mood-cognitive (difficulty concentrating, feeling sad, worrying, feeling irritable, itching). Cronbach's α was .78.<br>Sickness-behavior (pain, difficulty sleeping, lack of energy, sweats, feeling drowsy). Cronbach's α was .73.<br>Treatment-related (i.e., problems with urination, changes in skin). Cronbach's α was .36.<br><br>There were small differences between symptom clusters derived by occurrence and severity rates.<br>Symptom clusters derived from the severity rate fit the data better. |
| Matthews (2011)<br><br>To explore symptom clusters during RT in women with breast cancer.<br><br>Cross-sectional | *n* = 93 patients with breast cancer from mid-Atlantic region of United States.<br><br>Age:<br>*M* = 59.7, *SD* = 11.2<br>Range: 39 - 89<br>Ethnicity:<br>White (93.5%), African American (4.3%), other (2.2%) | <u>Instruments</u><br>SDS<br><br><u>Symptom Dimensions</u><br>Distress<br><br><u>Symptom Approach</u><br>All-possible<br><br>CFA | <u>Symptom Clusters</u><br>Three symptom clusters were found:<br>1) Pain - insomnia - fatigue cluster.<br>2) Cognitive disturbance - outlook (concentration, appearance, outlook).<br>3) Gastrointestinal (nausea, bowel). |

| First Author (Year), Purpose & Design | Sample Characteristics | Instruments & Methods | Major Findings |
|---|---|---|---|
| | Stage of breast cancer: 1 (66.7%), 2 (22.5%), 3 (9.7%), and 4 (1.1%)<br>Weeks in RT: 3 (39.8%), 4 (25.8%), 5 (18.3%), 6 (11.8%), and 7 (4.3%) | | |
| Miaskowski (2006)<br><br>To determine whether a subgroup of outpatients with cancer could be identified based on their ratings of the severity of the symptom cluster that consisted of fatigue, pain, sleep disturbance, and depression.<br><br>To determine whether the patients in the subgroups differed in selected demographics, disease and treatment characteristics.<br><br>To determine whether the patients in the subgroups differed in QOL and functional status.<br><br>Cross-sectional | N = 191 patients with cancer from four outpatient settings.<br><br>*n* = 52 patients with breast cancer (27%).<br><br>More than eight types of cancer included.<br><br>Age: *M* = 60.1, *SD* = 12.3<br>Ethnicity: White (82%)<br>Gender: Female (56%)<br><br>Presence of metastatic disease: (41%)<br>Treatment: CTX (57%), RT (41%), HT (15%), Biotherapy (5%), other (8%). | Instruments<br>Demographic questionnaire, KPS, LFS, GSDS, CES-D, MQOLS-CA, and a numeric rating scale of worst pain intensity (Jensen, 2003).<br><br>Symptom Dimensions<br>Severity<br><br>Symptom Approach<br>Most-common<br><br>HCA | Symptom Clusters<br>Patients were divided into four subgroups (percentage of breast cancer patients according to breast cancer sample): Low (low levels of all symptoms) (38% ), high fatigue and low pain (33%), low fatigue and high pain (17%), high (high levels of all symptoms) (12%).<br><br>Predictors<br>Age and marital status predicted the presence of patients in the low or high groups. Patients in the high group were younger and less likely to be married.<br>No differences were found in other demographic characteristics (education, gender, ethnicity, occupation, living alone), type of cancer, presence of metastasis, hemoglobin, hematocrit, or type of treatment.<br><br>Outcomes<br>The severity of a symptom cluster can affect patient functional status and QOL. Patients in the low subgroup reported higher KPS and QOL scores. No differences in KPS scores were found among the other three subgroups.<br>Patients in the high group reported lower QOL scores. No differences in QOL scores were found between the other two groups. |
| Molassiotis (2012)<br><br>To determine whether nausea exists as part of a symptom cluster.<br><br>To evaluate the symptom cluster's impact on patient's QOL, psychological distress, and nutritional status.<br><br>Longitudinal | N = 104 patients with cancer<br><br>*n* = 83 patients with breast cancer (80.6%).<br><br>Three types of cancer were included.<br><br>Age: *M* = 53.2 years, *SD* = 11.6<br>Gender: Female (90.3%)<br><br>Treatment: Anthracyclines (78.7%), taxanes (2.9%), and platinum-based (18.5%). | Instruments<br>MSAS, HADS, FACT, PG-SGA.<br><br>Symptom Dimensions<br>Severity<br>Occurrence<br><br>Symptom Approach<br>All-possible<br><br>Data were collected at three time points: the day of the first cycle of CTX (T1), end of cycle 1 (T2), and the end of cycle 2 (T3).<br><br>RFA | Symptom Clusters<br>Symptom clusters related to nausea were:<br>*Occurrence*:<br>At T1, nausea, loss of appetite, dry mouth, feeling drowsy, feeling bloated, vomiting.<br>At T2, nausea, pain, taste change, lack of energy, dizziness, appetite loss, and vomiting.<br>At T3, nausea, pain, and feeling bloated.<br>*Intensity*:<br>At T1, nausea, loss of appetite, dry mouth, feeling drowsy, lack of energy.<br>At T2, nausea, pain, lack of energy.<br>At T3, nausea, lack of energy, and feeling bloated.<br><br>Chemotherapy-induced nausea symptom clusters were dynamic during treatment and became more complex in nature with time. |

| First Author (Year), Purpose & Design | Sample Characteristics | Instruments & Methods | Major Findings |
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| | | | Outcomes<br>Chemotherapy-induced nausea symptom clusters have a greater negative impact on patients' QOL and nutritional status during CTX than does nausea alone. |
| So (2009)<br><br>To examine the symptom cluster of fatigue, pain, anxiety, and depression and its effect on the QOL of women with breast cancer undergoing CTX or RT.<br><br>Cross-sectional | *n* = 215 patients with breast cancer from the outpatient clinics of four public hospitals in Hong Kong.<br>Age:<br>*M* = 51.7, *SD* = 10.4<br>Range: 29 - 84<br>Ethnicity: Chinese<br>Stage of breast cancer:<br>1 (15%), 2 (52%), 3 (32%), and 4 (1%).<br>Current treatment:<br>CTX 60%<br>RT 40%<br>Comorbidity:<br>Ranged from 2 to 6 | Instruments<br>BFI -C, HADS, BPI-C, FACT-B, and MOS-SSS-C.<br><br>Symptom Dimensions<br>Severity<br><br>Symptom Approach<br>Most-common<br><br>Spearman's rho correlation | Symptom Clusters<br>Significant correlations among fatigue, anxiety, depression, and pain support the existence of the symptom cluster. The correlations ranged from .248 (pain- depression) to .627 (anxiety-depression).<br><br>Outcomes<br>The cluster had an effect on QOL.<br>The cluster with the covariates of social support and type of treatment explained 66% of the variance in QOL. |
| Suwisith (2010)<br><br>To explore symptom clusters across two symptom dimensions (severity and distress) and their influences on the functional status of women with breast cancer.<br><br>Cross-sectional | *n* = 320 patients with breast cancer from the outpatient cancer clinics of four hospitals in Bangkok.<br><br>Age:<br>Range: 17 to 68 years<br>*M* = 47.3, *SD* = 8.8<br><br>Ethnicity: Thai<br><br>Time since diagnosis:<br>Ranged from 1 to 168 months. *M* = 13.3 months, *SD* = 24.6<br><br>Diagnosis of breast cancer:<br>Newly diagnosed (73.4%); Recurrent (26.6%)<br><br>Stage of breast cancer:<br>1 (8.1%), 2 (51.6%), 3 (27.5%), and 4 (12.8%).<br><br>Current treatment: CTX | Instruments<br>MSAS and IFS-CA.<br><br>Symptom Dimensions<br>Severity<br>Distress<br><br>Symptom Approach<br>All-possible<br><br>FA | Symptom Clusters<br>Four symptom clusters were found in the dimension of symptom *severity*: emotional-related symptoms, gastrointestinal and fatigue-related symptoms, image-related cutaneous symptoms, and pain-related discomfort symptoms. The clusters were able to explain 50.1% of the variance in all of the symptoms. In addition, the clusters explained 19.8% of the variance in functional status.<br><br>Three symptom clusters were found in the dimension of symptom *distress*: emotional and pain-related discomfort symptoms, gastrointestinal and fatigue-related symptoms, and image-related cutaneous symptoms. The clusters were able to explain 50.7% of the variance in all the symptoms. In addition, the clusters explained 17.4% of the variance in functional status.<br><br>Outcomes<br>The gastrointestinal and fatigue symptom cluster was the strongest predictor of functional status in women with breast cancer undergoing CTX. |
| Pud (2008)<br><br>To determine whether subgroups of oncology outpatients receiving active treatment could be identified based on their experience of a specific symptom cluster (i.e., pain, fatigue, depression, sleep disturbance). | N = 228 patients with cancer from seven outpatient settings.<br><br>*n* = 86 patients with breast cancer (37.6%).<br><br>More than 9 types of cancer included.<br><br>Age: *M* = 54 years, *SD* = 12.7.<br>Gender: Female (70%). | Instruments<br>Demographic questionnaire, KPS, LFS, GSDS, CES-D, MQOLS-CA, and a numerical rating scale of worst pain intensity.<br><br>Symptom Dimensions<br>Severity<br><br>Symptom Approach<br>Most-common | Symptom Clusters<br>Patients were divided into four subgroups:<br>Low (low levels of all symptoms; 32.9%), high pain and moderate fatigue (42.5%), low pain and high fatigue (18%), high (high levels of all symptoms; 6.6%).<br><br>Predictors<br>No differences were found among the four subgroups on any of the demographic, disease, or treatment |

| First Author (Year), Purpose & Design | Sample Characteristics | Instruments & Methods | Major Findings |
|---|---|---|---|
| To determine whether patients in these subgroups differed in selected demo-graphic, disease, and treatment characteristics.<br><br>To determine whether patients in these subgroups differed in QOL and functional status.<br><br>Cross-sectional | KPS score: ≥ 50.<br>Presence of metastatic disease: (25%)<br>Treatment:<br>CTX (86.2%), RT (0.9%), HT (2.2%), other (10.7%) | HCA | characteristics.<br><br><u>Outcomes</u><br>Patients in the high subgroup reported lower KPS and QOL scores than the other three subgroups.<br>Patients in the low subgroup reported higher QOL scores than the other three subgroups. |
| Thornton (2010)<br><br>To test the hypothesis that the pain, fatigue, and depression (PDF) symptom cluster covaries with proposed biological mediators: hormones of the sympathetic nervous system (SNS) and the hypothalamic - pituitary - adrenal (HPA) axis.<br><br>Cross-sectional | *n* = 104 patients with breast cancer from medical oncology clinic in Ohio.<br>Age:<br>*M* = 53 years, *SD* = 11<br>Ethnicity:<br>Caucasian (89%)<br>African American (11%)<br>Stage of breast cancer:<br>Stage 4 (23%) and recurrent breast cancer (77%).<br>Current treatment:<br>Surgery (24%), CTX (61%), RT (15%), and/or HT (22%).<br>Patients were assessed a median of eight weeks after diagnosis. | <u>Instruments</u><br>BPI, FSI, CES-D, and KPS.<br>HPA activation was indicated by plasma levels of cortisol and adrenocorticotropic hormone, and SNS activation was indicated by plasma epinephrine and norepinephrine.<br><br><u>Symptom Approach</u><br>Most-common<br><br>SEM | <u>Predictors</u><br>Shared variance among hormone levels predicted shared variance among the PDF symptoms.<br><br>Norepinephrine levels predicted the PDF symptom cluster, while controlling for other variables such as diseases and demographics. |

*Instruments:* BFI-C, Brief Fatigue Inventory -Chinese version; BPI, Brief Pain Inventory; BPI-C, Brief Pain Inventory-Chinese version; CES-D, Center for Epidemiological Studies Depression Scale; C-PET, Checklist for Patients with Endocrine Therapy; DN4, Douleur Neuropathique 4 Questionnaire; ECOG, Eastern Cooperative Oncology Group Performance Status; FACT, Functional Assessment of Cancer Therapy-General Questionnaire; FACT-B, Functional Assessment of Cancer Therapy-Breast; FPI, Functional Performance Inventory; FSI, Fatigue Symptom Inventory; GFS, General Fatigue Scale; GSDS, General Sleep Disturbance Scale; HADS, Hospital Anxiety and Depression Scale; IFS-CA, Inventory Functional Status-Cancer; KPS, Karnofsky Performance Status; LFS, Lee Fatigue Scale; MDASI-T, Taiwanese M.D. Anderson Symptom Inventory; MOS-SSS-C, Medical Outcomes Study-Social Support Survey Chinese version; MQOLS-CA, Multidimentional Quality of Life Scale-Cancer; MSAS, Memorial Symptom Assessment Scale; NRS, Numeric Rating Scale; PFS, Piper Fatigue Scale; PG-SGA, Patient-Generated Subjective Global Assessment; POMS-SF, Profile of Mood States-Short Form; PSQI, Pittsburgh Sleep Quality Inventory; QOL-CA, Quality of Life-Cancer; SDS, Symptom Distress Scale; SF-36, Short Form Health Survey.
*Analysis:* CA, Cluster Analysis; CFA, Confirmatory Factor Analysis; EFA, Exploratory Factor Analysis; FA, Factor Analysis; HCA, Hierarchical Cluster Analysis; RFA, Random Forest Analysis; SEM, Structural Equation Model.
*Treatments:* CTX, Chemotherapy; RT, Radiation Therapy; HT, Hormonal Therapy.

APPENDIX B

*Summary of Symptom Clusters in Women with Breast Cancer Undergoing Active Treatment*

| **Author (Year) Symptom Approach** | **Type of Treatment** | **Symptom Dimension** | **Symptom Clusters** |
|---|---|---|---|
| Chen (2007) All-possible | RT, CTX, or both | Severity | Sickness (pain, fatigue, disturbed sleep, lack of appetite, and drowsiness).<br><br>Gastrointestinal (nausea and vomiting).<br><br>Emotional (stress and sadness). |
| Dodd (2001) Most-common | CTX | Severity | Fatigue, pain, and sleep insufficiency. |
| Glaus (2006) All-possible | HT | Occurrence | Hot flashes, tiredness, vaginal dryness, weight gain, and decreased sexual interest. |
| Kim (2008) All-possible | CTX, RT, or both | Severity | T2: Upper gastrointestinal (nausea, vomiting, and decreased appetite).<br><br>Pain, fatigue, insomnia, depressed mood, cognitive disturbance, and hot flashes.<br><br>T3: Upper gastrointestinal (nausea, vomiting, decreased appetite).<br><br>Pain, fatigue, insomnia, depressed mood, and cognitive disturbance. |
| Kim (2009b) All-possible | RT | Severity (after excluding symptoms present in < 20% of patients) | T1: Mood-cognitive (difficulty concentrating, feeling sad, worrying, feeling irritable, nervous).<br><br>Sickness-behavior (pain, lack of energy, feeling drowsy, difficulty sleeping, and sweats).<br><br>T2: Mood-cognitive (difficulty concentrating, feeling sad, worrying, and feeling irritable). |

| | | | |
|---|---|---|---|
| | | | Sickness-behavior (pain, lack of energy, feeling drowsy, difficulty sleeping, and sweats). |
| Kim (2009c) All-possible | RT | Occurrence | Mood-cognitive (difficulty concentrating, difficulty sleeping, feeling sad, worrying, feeling irritable, sweats, and itching).<br><br>Sickness-behavior (pain, lack of energy, and feeling drowsy). |
| | | Severity | Mood-cognitive (difficulty concentrating, feeling sad, worrying, feeling irritable, and itching).<br><br>Sickness-behavior (pain, lack of energy, difficulty sleeping, sweats, and feeling drowsy). |
| Matthews (2011) All-possible | RT | Distress | Pain-insomnia-fatigue.<br><br>Cognitive disturbance-outlook (concentration, appearance, and outlook).<br><br>Gastrointestinal (nausea and bowel patterns). |
| Molassiotis (2012) All-possible | CTX | Occurrence | T1: Nausea, pain, taste change, lack of energy, dizziness, appetite loss, and vomiting.<br><br>T2: Nausea, pain, and feeling bloated. |
| | | Severity | T1: Nausea, pain, lack of energy.<br><br>T2: Nausea, lack of energy, and feeling bloated. |
| Suwisith (2010) All-possible | CTX | Severity | Emotional-related symptom cluster (feeling sad, worrying, feeling irritable, feeling nervous, I don't look like myself, difficulty concentrating, sleeping difficulty, sweating, and constipation).<br><br>Gastrointestinal and fatigue-related symptom cluster (vomiting, lack of |

| | | | |
|---|---|---|---|
| | | | energy, lack of appetite, dizziness, feeling drowsy, shortness of breath, and feeling bloated).<br><br>Image-related cutaneous symptom cluster (hair loss, changes in food taste, mouth sores, skin changes, and difficulty swallowing). |
| | | Distress | Pain-related discomfort symptom cluster (numbness/tightness, pain, and dry mouth).<br><br>Emotional and pain-related discomfort symptom cluster (feeling nervous, difficulty concentrating, worrying, feeling sad, numbness/tingling, feeling irritable, sleeping difficulty, shortness of breath, feeling bloated, sweating, and pain).<br><br>Gastrointestinal and fatigue-related symptom cluster (nausea, vomiting, lack of appetite, lack of energy, dizziness, and feeling drowsy).<br><br>Image-related cutaneous symptom cluster (mouth sores, hair loss, skin changes, changes in food taste, difficulty swallowing, I don't look like myself, constipation, and dry mouth). |
| So (2009) Most-common | CTX or RT | Severity | Fatigue, pain, anxiety, and depression |

APPENDIX C

Symptom Experience Scale (SES)

**FORM 40**

Instructions:

This questionnaire asks you about several symptoms. Please rate the frequency, intensity, and distress you have experienced for each symptom DURING THE PAST 7 DAYS. Each statement is numbered from 0 to 4, with 0 indicating that you have not had the symptom, and 4 indicating the maximum frequency, intensity, or distress of the symptom. Please circle only one number for each question. Please answer all questions.

**NAUSEA DURING THE PAST 7 DAYS**

Frequency

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I never felt any nausea | I was occasionally nauseous | I was frequently nauseous | I was usually nauseous | I was nauseous almost always |

Intensity

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I never felt any nausea | When I had nausea, it was very mild | When I had nausea, I felt fairly sick | When I had nausea, I felt very sick | When I had nausea, I felt as sick as I could possibly be |

Distress

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I never felt any nausea | When I had nausea, I was not at all upset | When I had nausea, I was mildly upset | When I had nausea, I was very upset | When I had nausea, I was as upset as I could possibly be |

**PAIN DURING THE PAST 7 DAYS**

Frequency

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I never had pain | I occasionally had pain | I frequently had pain | I usually had pain | I almost always had pain |

Intensity

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I never had pain | When I had pain, it was very mild | When I had pain, it was fairly intense | When I had pain, it was very intense | When I had pain, it was as bad as it could possibly be |

Distress

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I never had pain | When I had pain, I was not at all upset | When I had pain, I was mildly upset | When I had pain, I was very upset | When I had pain, I was as upset as I could possibly be |

**APPETITE DURING THE PAST 7 DAYS**

Frequency

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I had my normal appetite | My appetite occasionally was not normal | My appetite frequently was not normal | My appetite usually was not normal | My appetite never was normal |

Intensity

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I had my normal appetite | My appetite was not quite as good as it used to be | My appetite was poor | My appetite was very poor | My appetite was as poor as it could possibly be |

Distress

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I had my normal appetite | When my appetite was not normal, I was not at all upset | When my appetite was not normal, I was mildly upset | When my appetite was not normal, I was very upset | When my appetite was not normal, I was as upset as I could possibly be |

**SLEEP DISTURBANCE DURING THE PAST 7 DAYS**

Frequency

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I slept as well as always | I occasionally had difficulty sleeping | I frequency had difficulty sleeping | I usually had difficulty sleeping | I had difficulty sleeping every single night |

Intensity

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I slept as well as always | I had difficulty sleeping, but it was very mild | I had a fair amount of difficulty sleeping | I had a lot of difficulty sleeping | I had an extreme amount of difficulty sleeping |

Distress

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I slept as well as always | When I had difficulty sleeping, I was not at all upset | When I had difficulty sleeping, I was mildly upset | When I had difficulty sleeping, I was very upset | When I had difficulty sleeping, I was as upset as I could possibly be |

**FATIGUE DURING THE PAST 7 DAYS**

Frequency

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I was never tired | I was occasionally tired | I was frequently tired | I was usually tired | I was always tired |

Intensity

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I was never tired | When I felt tired, I was just a little tired | When I felt tired, I was very tired | When I felt tired, I was extremely tired | I was as tired as I could possibly be |

Distress

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I was never tired | When I was tired, I was not at all upset | When I was tired, I was mildly upset | When I was tired, I was very upset | When I was tired, I was as upset as I could possibly be |

**BOWEL PATTERN DURING THE PAST 7 DAYS**

Frequency

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I had my normal bowel pattern | My bowel pattern occasionally was not normal | My bowel pattern frequently was not normal | My bowel pattern usually was not normal | My bowel pattern was never normal |

Intensity

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I had my normal bowel pattern | My abnormal bowel pattern caused me mild discomfort | My abnormal bowel pattern caused me moderate discomfort | My abnormal bowel pattern caused me severe discomfort | My abnormal bowel pattern caused me unbearable discomfort |

Distress

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I had my normal bowel pattern | I was not at all upset by my abnormal bowel pattern | I was mildly upset by my abnormal bowel pattern | I was very upset by my abnormal bowel pattern | I was as upset as I could possibly be by my abnormal bowel pattern |

**CONCENTRATION DURING THE PAST 7 DAYS**

Frequency

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I had my normal ability to concentrate | I occasionally had difficulty concentrating | I frequently had difficulty concentrating | I usually had difficulty concentrating | I always had difficulty concentratin g |

Intensity

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I had my normal ability to concentrate | I had difficulty concentrating, but it was very mild | I had a fair amount of difficulty concentrating | I had a lot of difficulty concentrating | I could not concentrate at all |

Distress

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| I had my normal ability to concentrate | When I had trouble concentrating, I was not at all upset | When I had trouble concentrating, I was mildly upset | When I had trouble concentrating, I was very upset | When I had trouble concentratin g, I was as upset as I could possibly be |

**APPEARANCE DURING THE PAST 7 DAYS**

Frequency

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| My appearance has basically not changed | My appearance was occasionally worse than usual | My appearance was frequently worse than usual | My appearance was usually worse than it used to be | My appearance was always worse than it used to be |

Intensity

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| My appearance has basically not changed | My appearance was a little worse than usual | My appearance was much worse than usual | My appearance was awful | My appearance was as awful as it could possibly be |

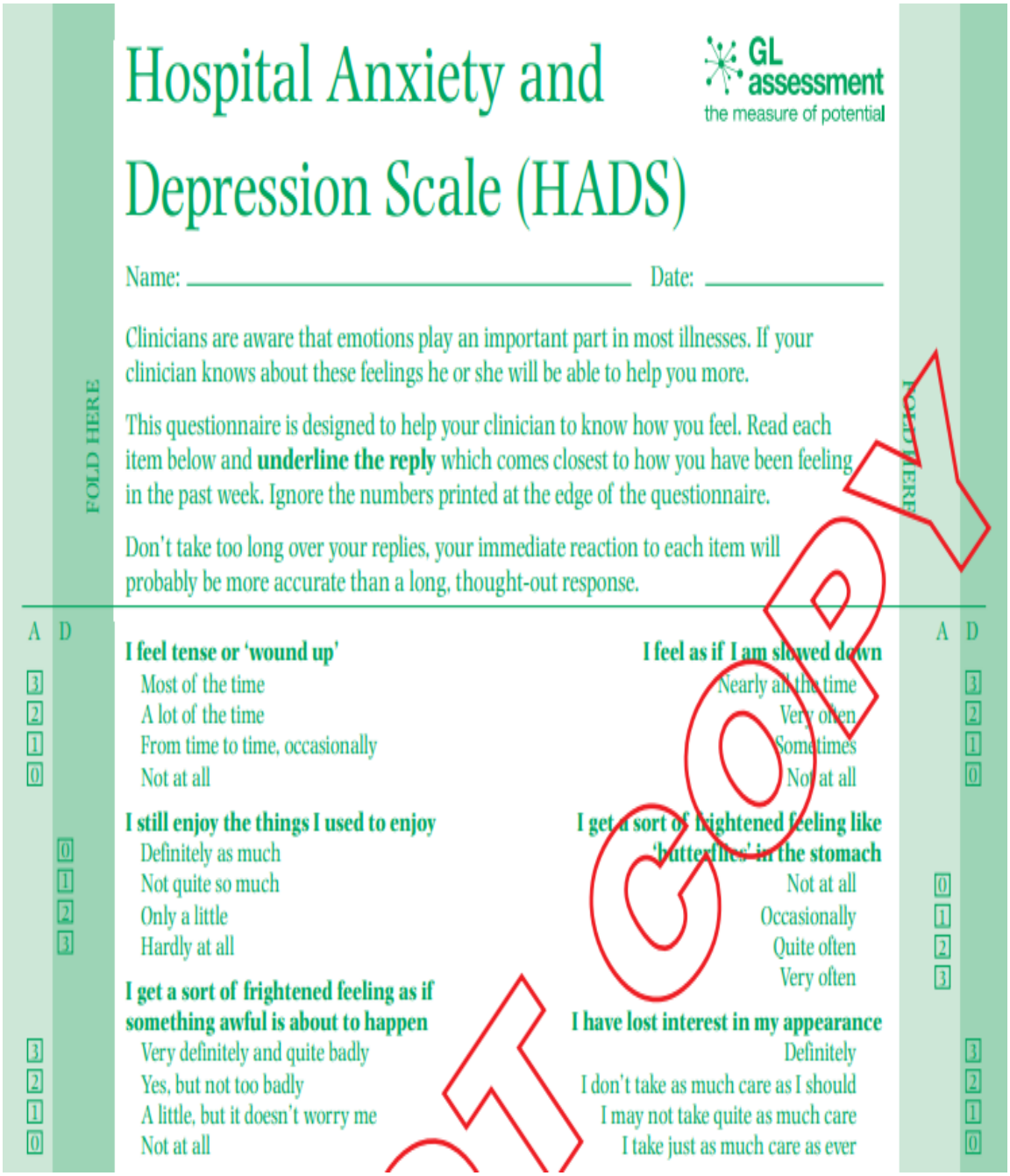
Distress

| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| My appearance has basically not changed | My changed appearance didn't upset me at all | My changed appearance upset me mildly | My changed appearance upset me very much | My changed appearance made me as upset as I could possibly be |

Samarel, N., Leddy, S. K., Greco, K., Cooley, M. E., Torres, S. C., Tulman, L., & Fawcett, J. (1996).

Appendix D

Hospital Anxiety and Depression Scale (HADS)



# Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Name: _____ Date: _____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A D

**I feel tense or 'wound up'**
- Most of the time
- A lot of the time
- From time to time, occasionally
- Not at all

**I still enjoy the things I used to enjoy**
- Definitely as much
- Not quite so much
- Only a little
- Hardly at all

**I get a sort of frightened feeling as if something awful is about to happen**
- Very definitely and quite badly
- Yes, but not too badly
- A little, but it doesn't worry me
- Not at all

**I feel as if I am slowed down**
- Nearly all the time
- Very often
- Sometimes
- Not at all

**I get a sort of frightened feeling like 'butterflies' in the stomach**
- Not at all
- Occasionally
- Quite often
- Very often

**I have lost interest in my appearance**
- Definitely
- I don't take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

**I can laugh and see the funny side of things**

- 0 As much as I always could
- 1 Not quite so much now
- 2 Definitely not so much now
- 3 Not at all

**Worrying thoughts go through my mind**

- 3 A great deal of the time
- 2 A lot of the time
- 1 Not too often
- 0 Very little

**I feel cheerful**

- 3 Never
- 2 Not often
- 1 Sometimes
- 0 Most of the time

**I can sit at ease and feel relaxed**

- 0 Definitely
- 1 Usually
- 2 Not often
- 3 Not at all

**I feel restless as if I have to be on the move**

- 3 Very much indeed
- 2 Quite a lot
- 1 Not very much
- 0 Not at all

**I look forward with enjoyment to things**

- 0 As much as I ever did
- 1 Rather less than I used to
- 2 Definitely less than I used to
- 3 Hardly at all

**I get sudden feelings of panic**

- 3 Very often indeed
- 2 Quite often
- 1 Not very often
- 0 Not at all

**I can enjoy a good book or radio or television programme**

- 0 Often
- 1 Sometimes
- 2 Not often
- 3 Very seldom

**Now check that you have answered all the questions**

A D

**TOTAL**

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Appendix E

**Memorandum of Understanding for Data Sharing**

Ann Berger, PI of the *Fatigue in Breast Cancer: A Behavioral Sleep Intervention* study (University of Nebraska Medical Center, NIH, R01 NR007762), agrees to share a de-identified dataset with Catherine Waters, PI, University of California, San Francisco (UCSF) School of Nursing on behalf of PhD student advisee, Randa Albusoul.

The data will be shared once approval to do so has been obtained from the appropriate Institutional Review Board at the University of Nebraska Medical Center.

Research involving only unidentifiable or coded private information is not human subject research and does not require review by UCSF Committee on Human Research (see attached self-certification form).

**The researchers agree to the following:**

(1) The data will be used only for research purposes related to preparing a doctoral dissertation and writing manuscripts for publication about symptom clusters among women with breast cancer undergoing adjuvant chemotherapy treatment.

(2) The dataset will be de-identified. It will not be possible to identify any individual participant.

(3) All data will be transmitted on a password-protected server at the UCSF and stored on an encrypted hard drive on a password-protected computer using appropriate computer technology.

(4) Dr. Berger will have the right to monitor and track use of the dataset and review all manuscripts on which her name will appear prior to submission for publications that result from the dataset.

(5) The dataset will be wiped permanently using appropriate computer technology after completion of the dissertation and manuscripts.

DocuSigned by:
Randa Albusoul
3DFF3087E308456...

10/11/2012

Randa Albusoul, PhD student DATE
University of California, San Francisco

Ann Berger 10-11-12

Ann Berger, PhD DATE
University of Nebraska Medical Center

Catherine M. Waters 10/11/2012

Catherine Waters, PhD advisor DATE
University of California, San Francisco

Appendix F



**University of California, San Francisco (UCSF)**
**Committee on Human Research (CHR)**

**Self-Certification for Determining Whether Human Subjects Are Involved In Research When Obtaining Coded Private Information (Data) and/or Biological Specimens**

**Instructions:**

1. If you need documentation for funding agencies, administrators, or collaborators, this self-certification form is provided for your use. Copies of this should be maintained in the PIs research files. Do **not** submit a copy of the form to the CHR.
2. If the following condition is met for your research, the use of coded private information (data) and/or biological specimens does not meet the definition of a *human subject* and does not require Exempt Certification or IRB review. The Determining Whether Human Subjects Are Involved in Research Decision Tree will help you make this determination.
3. More background information and CHR written guidance can be found at http://www.research.ucsf.edu/chr/Guide/chrExemptApp.asp
4. If you have questions on how to use this form contact the CHR at (415) 476-1814 or e mail: chr@ucsf.edu.

| **Principal Investigator:** | | |
|---|---|---|
| Name and Degree<br>Randa Albusoul (PhD Student)<br>Catherine Waters, PhD (Advisor) | Institution<br>Univ. of California, San Francisco | Department<br>Community Health Systems |
| Mailing Address<br>2 Koret Way, Box 0608; San Francisco, CA 94143-0608 | Phone Number<br>(415) 502-7995 | E-mail Address<br>catherine.waters@ucsf.edu |
| **Study/Grant Title/Award No.:** | | |
| Fatigue in Breast Cancer: A Behavioral Sleep Intervention. PI: Ann. Berger, PhD, U. of Nebraska Medical Cntr (NIH, R01NR007762) | | |

**Condition that must be met for the coded private information (data) or biological specimens:**

1. The research is not regulated by the Food and Drug Administration (FDA).
   AND
2. One or more of the following apply. Check all that apply:

- ☐ a. The key to decipher the code is destroyed before the researcher begins.
- ☑ b. PI and holder of the key enter into an agreement prohibiting the release of the key under any circumstances.
- ☐ c. There are IRB-approved written policies for the repository or data management that prohibit the release of the key.
- ☐ d. There are other legal requirements prohibiting the release of the key under any circumstances.

**Principal Investigator's Certification:**
I certify that the information provided in this application is complete and correct.

| | |
|---|---|
| Catherine M. Waters<br>DocuSigned by: Randa Albusoul<br>3DFF3867C380458...<br>**Principal Investigators Signature** | October 11, 2012<br>**Date** |

# Appendix G

## Permission Letters

### Permission for Using the Symptom Experience Scale (SES)

To: Albusoul, Randa

Friday, May 10, 2013 12:30 P

- You replied on 5/10/2013 6:08 PM.

Dear Ms Albusoul,

You have permission to place a copy of the SES in your dissertation. Please let me know if you need a copy of the scale.

Best wishes,
Nelda Samarel

**From:** School Info
**Sent:** Friday, May 10, 2013 10:34 AM
**To:** Nelda Samarel
**Subject:** Fwd: A question about professor Saramel contact info

---------- Forwarded message ----------
From: **Albusoul, Randa** <Randa.Albusoul@ucsf.edu>
Date: Thu, May 9, 2013 at 11:23 PM
Subject: A question about professor Saramel contact info
To: "schoolinfo@krotonainstitute.org" <schoolinfo@krotonainstitute.org>, "info@theosophical.org" <info@theosophical.org>

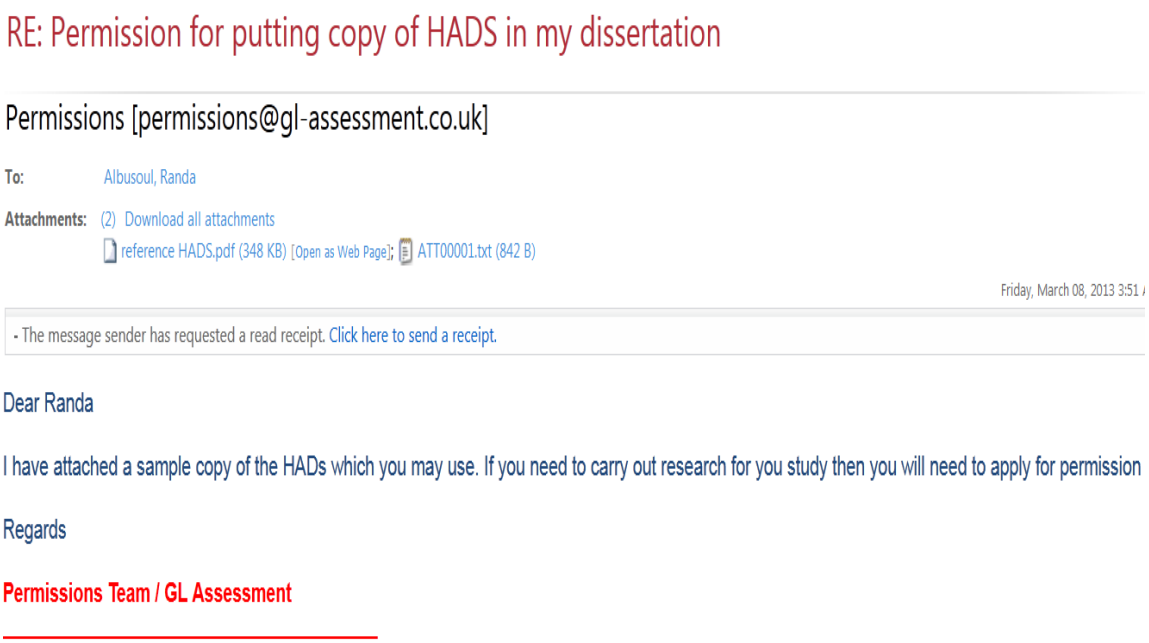
Hello,

I hope you are doing well.

My name is Randa Albusoul. I am 4th year PhD student at University of California, San Francisco (UCSF). I am looking for professor's Nelda Saramel email. I know that professor Saramel was director of the Krotona School of Theosophy, so I though I can ask you if you have any of her current contact info. I am currently writing my dissertation "symptom cluster among women with breast cancer undergoing chemotherapy" in which I am using secondary data analysis. The data set used the Symptom Experience Scale (SES) for measuring the patients symptoms. This scale was designed by professor Saramel. I am trying to ask for permission for putting copy of the scale in my dissertation paper, however, I am not able to find professor Samarel email.

thank you.

Permission for Using the Hospital Anxiety and Depression Scale (HADS)



RE: Permission for putting copy of HADS in my dissertation

Permissions [permissions@gl-assessment.co.uk]

To: Albusoul, Randa

Attachments: (2) Download all attachments

reference HADS.pdf (348 KB) [Open as Web Page]; ATT00001.txt (842 B)

Friday, March 08, 2013 3:51 A

- The message sender has requested a read receipt. Click here to send a receipt.

Dear Randa

I have attached a sample copy of the HADs which you may use. If you need to carry out research for you study then you will need to apply for permission

Regards

**Permissions Team / GL Assessment**

**Publishing Agreement**

It is the policy of the University to encourage the distribution of all theses, dissertations, and manuscripts. Copies of all UCSF theses, dissertations, and manuscripts will be routed to the library via the Graduate Division. The library will make all theses, dissertations, and manuscripts accessible to the public and will preserve these to the best of their abilities, in perpetuity.

I hereby grant permission to the Graduate Division of the University of California, San Francisco to release copies of my thesis, dissertation, or manuscript to the Campus Library to provide access and preservation, in whole or in part, in perpetuity.

Randa Albarsan

Author Signature

7/26/2013

Date