

RELATIONSHIPS AMONG SYMPTOMS, BRAIN-DERIVED NEUROTROPHIC FACTOR
(BDNF), DAILY ACTIVITIES, SELF-CARE, AND QUALITY OF LIFE IN BREAST
CANCER SURVIVORS

BY

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Abstract

Background: Breast cancer survivors confront ongoing symptoms following diagnosis and treatment. Studies examining the relationship between biomarkers and symptoms are scarce.

Purpose: To explore symptom occurrence and severity as reported by breast cancer survivors and their relationship to the BDNF Val66Met SNP (a biomarker), daily activities, quality of life and other selected subject characteristics and health variables. In addition, self-care methods used by survivors to alleviate symptoms and perceptions of the methods' usefulness were considered.

Methods: Breast cancer survivors (6 months or more post-treatment) were invited by a coalition from a Mid-Atlantic state to participate in an online survey in **Phase 1** ($N = 195$). The survey results provided the basis for a purposive sub-sampling. In **Phase 2**, two groups were identified from their scores on the Therapy-Related Symptoms Checklist (TRSC; low-scoring [≤ 14 , $n = 26$] and high-scoring [≥ 23 , $n = 25$]) for BDNF genotyping (by the Taqman probe assay) and exploration of self-care. All self-report tools have good psychometric properties: the TRSC, Daily Activities Rating (DAR), Health-Related Quality of Life-Linear Analogue Scale Assessment (HRQOL-LASA), and Symptom Alleviation: Self-Care Methods (SA: SCM). Fisher's exact test, logistic and multiple regression, and descriptive and content analyses were conducted.

Findings: (a) The presence of the BDNF Val66Met SNP biomarker was related to lower symptom scores, but effect size was small and the relationship did not persist when controlling for confounders; (b) TRSC scores were not impacted by time since completion of treatment; (c) high total scores on the TRSC (high symptom occurrence and severity) were significantly related to high scores on the DAR (difficulty with activities of daily life) and to lower quality of life on

the HRQOL-LASA; (d) the odds of a low TRSC score increased with increased education and increased age, and diminished if treatment included chemotherapy; (e) the self-care method used most commonly was diet/nutrition/lifestyle; the least common was herbs/vitamins/complementary therapy, and the methods that were used were perceived as effective.

Clinical Implications and Need for Further Research: Beginning evidence that the BDNF Val66Met SNP may have a protective effect for ongoing symptoms in breast cancer survivors.

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“I know the plans I have for you, declares the Lord, plans to prosper you and not to harm you, plans to give you a hope and a future” (Jer. 29:11, New International Version).

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Chapter I

Introduction

Breast cancer is the second leading cause of cancer death in women in the United States (American Cancer Society, 2007). One out of eight women will be diagnosed with breast cancer in her lifetime; thus, millions of women are living with this disease and the sequelae of treatment. Ongoing symptoms are a considerable problem for breast cancer survivors. Little information is available about possible objective physiological markers that might predict the occurrence and severity of these symptoms. To date, researchers have not investigated the impact of brain-derived neurotrophic factor (BDNF) in breast cancer survivors. Low levels of BDNF have been associated with reactive oxygen species (ROS) that result in oxidative stress leading to cell death (apoptosis) processes that have been linked to a variety of symptoms (Kim, Barsevick, & Tulman, 2009). The presence of a biological indicator, such as the BDNF Val66Met single nucleotide polymorphism (SNP), could be predictive of symptoms that would facilitate targeting effective nursing care to specific at-risk individuals or groups. This would be an important step toward improved care for millions of women suffering from the effects of breast cancer. For example, a recently published pilot intervention study with 20 newly diagnosed cancer patients, mostly females with breast cancer, yielded some preliminary evidence in support of an educational intervention in decreasing symptom occurrence and severity (P. D. Williams, Williams, LaFaver-Rolling, Johnson, & Williams, 2011d).

The original plan was to conduct this study in one Mid-Atlantic state having one of the highest incidences of breast cancer in the United States, with 139.2 cases per 100,000 people (American Cancer Society, 2007). Due to a need for further recruitment of subjects, the study was expanded to include breast cancer survivors in neighboring states.

In one study of breast cancer survivors, Ferrans (1994) emphasized the role of nursing in managing symptoms: “To help alleviate these problems, nurses first need to find out what the problems are and who is suffering from them. This sort of problem identification should become a routine part of follow-up care for survivors of cancer” (p. 1650). Women who do not have the support they need often find that a nurse acting as an understanding confidant may be a critical element in their cancer-related quality of life (Halyard & Ferrans, 2008).

Documentation of symptoms in a survivorship care plan has recently begun to appear in the literature. Oncology nurses play a key role in a developing model of survivorship care planning for patients with breast cancer (Miller, 2008). There are increasing numbers of people being successfully treated for cancer, and there are an estimated 11.4 million cancer survivors in the United States, with 23% of those survivors (2.6 million) being female survivors of breast cancer (National Cancer Institute, 2006). Doyle (2008) indicated that millions of women globally are survivors of breast cancer. For example, 87% of the women diagnosed with breast cancer can expect to be alive five years later (University of Texas, 2009). In view of these facts, the need for a preliminary study to explore the linkage between BDNF and symptom occurrence and severity to allow for a more personalized approach to nursing for breast cancer patients is deemed to be a timely and important endeavor.

Societal, Organizational, and Governmental Goals

The American College of Surgeons Commission on Cancer has added survivorship care as a new standard for accreditation beginning in 2012 (Commission on Cancer, 2011). One of the seven Oncology Nursing Society (ONS; 2008) research priorities for 2009-2013 is quality of life. Goals from a national breast cancer research agenda published in 1998 by prominent members of the scientific, medical, advocacy, and industrial communities organized by the

National Cancer Institute (NCI) recommended a renewed focus on psychosocial factors and patient outcomes across a continuum of ages and race/ethnicity groups (American Cancer Society, 2007). The American Society of Clinical Oncology (ASCO) has considered quality of life issues, such as symptom management, second in importance only to survival as a research outcome for nearly two decades (Halyard & Ferrans, 2008). This study is particularly timely due to the American Academy of Nursing's identification of nurse sensitive outcomes, which has put improvement in self-care, symptom management, and quality of life in the forefront of nursing initiatives (Richard & Shea, 2011).

Background

The most recent Oncology Nursing Society statement on the scope and standard of oncology nursing practice refers to the process of care as being based on a “continuous healing relationship” (Boyle, Bruce, Iwamoto, & Summers, 2004, p. 3). Evidence-based symptom management and skilled assessments are emphasized in this publication. This study builds on a research program of symptom assessment and management by P. D. Williams and colleagues, described in the next chapter, and provides further development of evidence-based practice in symptom assessment and management.

Nursing is a key discipline assisting cancer survivors with ongoing symptoms. Better understanding of symptoms and self-care in breast cancer survivors served by a state coalition may provide information that could be applied to oncology nursing and the shaping of health care in the United States and beyond. There currently are no reliable, objective markers to indicate which breast cancer patients will continue to have debilitating symptoms after the conclusion of their initial treatment regime. BDNF is emerging as a possible indicator of resiliency (Krueger et al., 2011). Low levels of BDNF production have been related to the

BDNF Val66Met SNP. Based on a survey of the literature, it is possible that such lowered levels of BDNF production could be indicative of increased symptom burden. This preliminary feasibility study provides groundwork on which further investigations with cancer survivors could be based. Knowledge of which individuals are positive for the BDNF Val66Met SNP could allow nurses to proactively schedule follow-up appointments for at-risk patients, as well as tailor and target nursing interventions appropriately.

Aims and Research Questions

The primary aim of the study was to examine the relationship between self-reported symptom occurrence and severity, as measured by the Therapy-Related Symptom Checklist (TRSC) total scores, and the presence or absence of the BDNF Val66Met SNP in breast cancer survivors. Secondary aims were investigated using three additional self-reported measures: Daily Activities Rating Scale (DARS), Health-Related Quality of Life - Linear Analogue Self Assessment (HRQOL-LASA), and the Symptom Alleviation: Self-Care Methods (SA: SCM) scale, as well as selected demographic and other variables (age, ethnicity, education, treatment method, and time since treatment).

Primary Research Question

Is there a significant relationship between symptom occurrence and severity in breast cancer survivors and the presence or absence of the BDNF Val66Met SNP?

Secondary Research Questions

1. What are the occurrence and severity of symptoms among breast cancer survivors as reported on the TRSC after the completion of their cancer therapy regimen?
2. Are there significant relationships among symptom occurrence and severity, daily activities ratings, and health-related quality of life and selected demographic and other

variables (age, ethnicity, education, treatment method, and time since treatment)?

3. What self-care methods are used by survivors to alleviate symptoms, and what are the survivors' perceptions of the usefulness of these self-care methods?

Design Overview

This study had a cross-sectional design with two phases. Phase 1 enabled participant selection for Phase 2. Phase 2 addressed the primary study RQ. The purposive Phase 2 subsample ($n = 51$) addressed the BDNF Val66Met SNP as a genetic indicator of cancer symptoms, using two groups based on the Therapy-Related Symptom Checklist (TRSC) scores (low ≤ 14 , $n = 25$; high ≥ 23 , $n = 26$). The self-report tools have had good psychometric properties in previous uses, and the results from this study will be discussed in later chapters.

Conceptual Framework

The Oncology Nursing Society (2008) has prioritized symptom management for all aspects of nursing practice. A symptom is defined in many ways, but there is a consensus in most sources that it is a persistent, subjective, physical or emotional phenomenon that accompanies a pathological condition.

Brain-derived neurotrophic factor, also known as brain-dependent neurotropic factor (BDNF), is required for the differentiation and survival of specific neuronal subpopulations in both the central and the peripheral nervous system. The Val66Met SNP gene variant for BDNF controls the expression and quantity of BDNF active within an individual. In many studies, the method used for the analysis of the circulating biological indicators is the enzyme-linked immunosorbent (ELISA) assay (Leng et al., 2008). For this study, genetic testing was completed to establish the presence or absence of the BDNF Val66Met SNP, but there was no testing for circulating BDNF. The Conceptual Framework Diagram (see Figure 1) demonstrates the process

of investigating how the relationship between the BDNF Val66Met SNP and symptoms was conceptualized in this study.

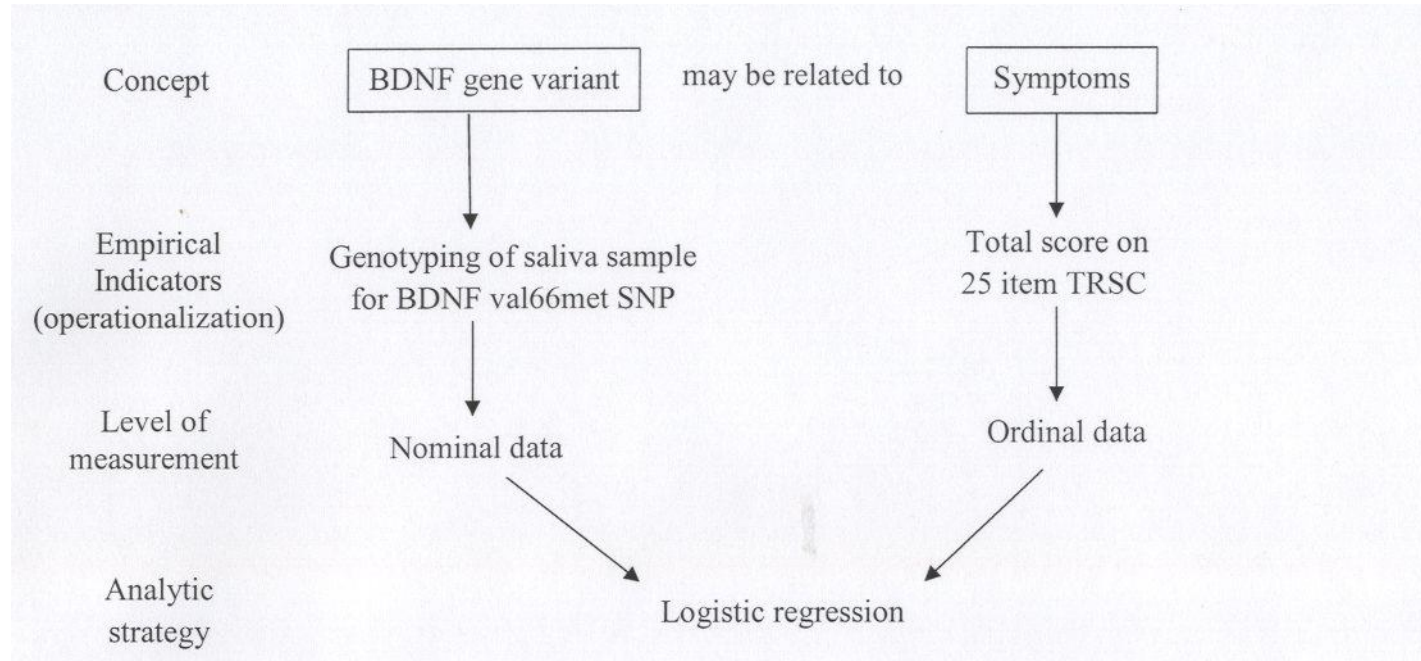


Figure 1. Conceptual framework diagram for the primary research question.

The study aims (primary and secondary) focus on several concepts: self-reported symptom occurrence and severity, daily activities performance, self-care, health-related quality of life, and the biological marker (presence/absence of the BDNF Val66Met SNP). Figure 2 illustrates the physiological relationships, such as how BDNF levels may impact symptoms. These are further described in the literature presented in Chapter 2. The model was developed by Ken Kirschner, Research Associate at the University of Delaware neuroendocrine laboratory. Previous work was conducted in cooperation with this laboratory by this researcher as an amendment to the study by P. D. Williams (2009) entitled *Symptom Alleviation and Self-Care Methods During Cancer Treatment* (KUMC-HSC #12048). Biomarkers provided important information on the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-

adrenomedullary (SAM) system, which were important in the development of the following model (Heinze, 2010b).

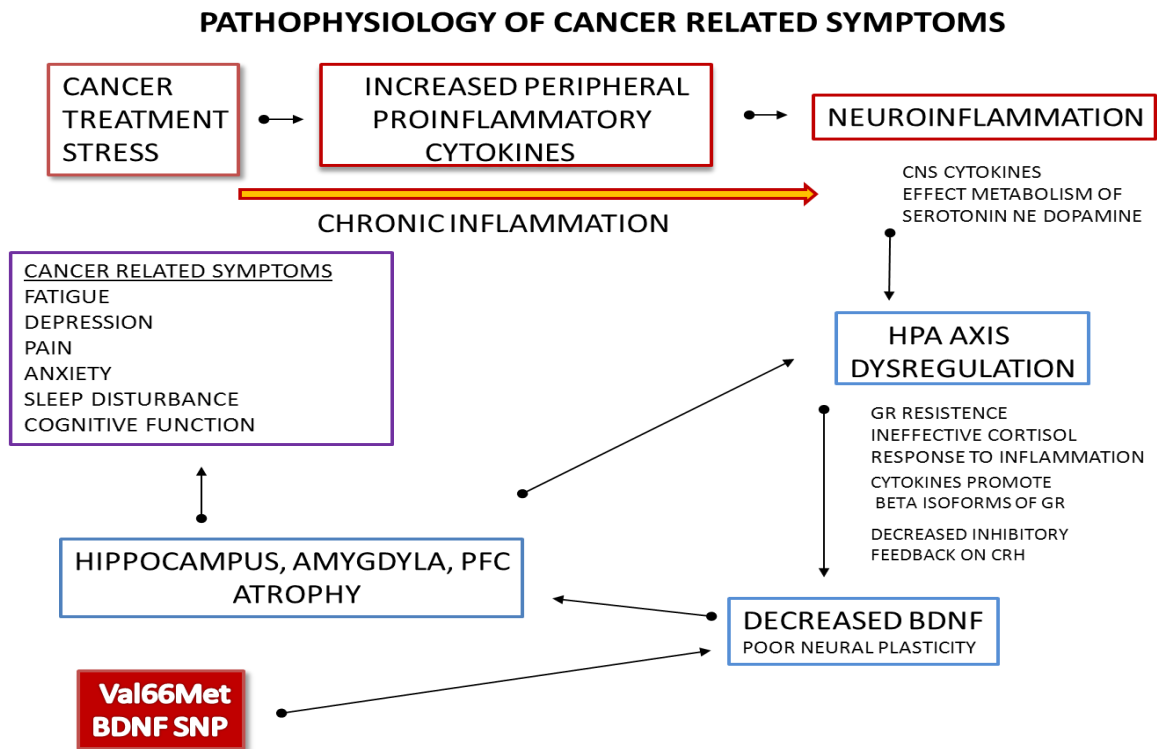


Figure 2. Proposed neuroimmunoendocrine model for the etiology of cancer-related symptoms. HPA = hypothalamic pituitary adrenal; CNS = central nervous system; BDNF = brain derived neurotrophic factor; NE = norepinephrine; GR = glucocorticoid receptor; CRH = corticotropin-releasing hormone; PFC = prefrontal cortex; SNP = single nucleotide polymorphism. (From Dantzer, 2001; Duman & Monteggia, 2006; Raison & Miller, 2003)

Although the model is complex, it was synthesized from the literature and provides a basis for how the effect of the BDNF Val66Met SNP, the variable under consideration in this study, relates to the physiological mechanisms that are influential in symptom etiology for the cancer patient. Chronic inflammation related to cytokines and other substances may be implicated in the development of clusters of adverse symptoms; this study focused on the BDNF Val66Met SNP as the primary mode of detection for the more general inflammatory pathway.

The BDNF Val66Met SNP that causes a lower circulating level of BDNF could be an underlying cause of symptoms.

Figure 3 shows the conceptual framework diagram for all three secondary research questions that explore the relationships of other variables to the cancer-related symptoms displayed in the pathophysiology model (Figure 2). The concepts and empirical indicators (Dulock & Holzemer, 1991) that further explicate the model are shown in Table 1.

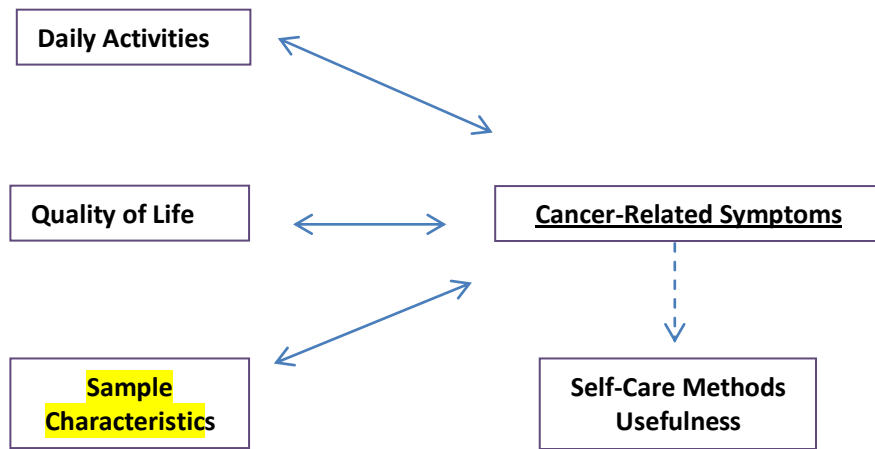


Figure 3. Conceptual framework diagram for the secondary research questions.

Table 1

Concepts and Empirical Indicators for the Secondary Research Questions

Concepts	Daily activities	Quality of Life	Symptoms	Sample characteristics
Empirical indicators (operationalization)	Daily Activities Rating Scale (DARS) 5-item scale	Health-Related Quality of Life-Linear Analog Self Assessment (HRQOL-LASA) 6-item scale	Therapy Related Symptom Checklist (TRSC) 25-item scale	Five self-reported: age, ethnicity, education, treatment type, and time since treatment completion
Level of measurement	Ordinal	Ordinal	Ordinal	Nominal/ordinal
Analytic strategy	Linear regression	Linear regression	Linear regression	Linear regression

The measures have been used in previous studies by P. D. Williams and colleagues, and strong relationships with HRQOL-LASA (inverse) and DARS (positive) scores are related to increased TRSC scores. The literature to fully illustrate these relationships is included in Chapters 2 and 3. The treatment type and time since treatment completion are of particular interest since ongoing symptoms in breast cancer survivors is the focus of this study.

Definition of Terms

Thirteen key terms have been selected and defined for the purpose of this study. The terms are bolded and are listed alphabetically in the paragraphs that follow. These are theoretical definitions; operational definitions appear in Chapter 3.

BDNF Val66Met SNP is a common single nucleotide polymorphism in which the methionine (Met) allele replaces the valine (Val) allele in the pro-BDNF sequence. This amino acid substitution is thought to result in diminished activity or trafficking of BDNF (Mandel, Ozdener, & Utermohlen, 2011).

Biobehavioral symptoms are those that involve the “interrelationship among psychosocial, behavioral and biological processes” (*American Heritage Medical Dictionary*, 2007). In the model of the pathophysiology of cancer-related symptoms that appears earlier in this chapter, fatigue, depression, pain, anxiety, sleep disturbance, and cognitive function difficulty are given as examples of biobehavioral symptoms.

Biomarkers are “biological parameters associated with the presence and severity of specific disease states” (U. S. Department of Health and Human Services, 2011). The BDNF Val66Met SNP is a type of biomarker.

A **breast cancer survivor**, as defined by the National Cancer Institute (2006), is an individual diagnosed with breast cancer from the day of diagnosis until the end of life. For the

purpose of this study, breast cancer survivors will be women who have completed initial treatment for breast cancer previous to participation and would likely not be having acute symptoms related to treatment modalities or other co-morbid conditions. More specific exclusion criteria will be covered in Chapter 3.

Cancer-related symptoms are abnormal sensations or conditions that individuals experience as a result of cancer or its treatment.

Cancer therapy regimen is the plan of treatment that may include surgery, radiation, and chemotherapy (American Cancer Society, 2007).

Chemotherapy is the use of drugs to destroy cancer cells. A person on chemotherapy may take one drug or a combination of drugs. Most often these drugs are given by intravenous infusion (IV), but some may be taken by mouth or given as a shot (American Cancer Society, 2007). Oral chemotherapy drugs commonly taken by breast cancer survivors include hormonal therapy such as Tamoxifen, Anastrozole, or Letrozole.

Daily activities include those tasks that need to be completed in order to manage daily life. This term was used in the rehabilitation literature as early as 1949. It encompasses basic responsibilities, such as personal hygiene and feeding, up to more complex tasks, such as managing housework, finances, and community involvement (Frick, 2011).

Genetic marker/indicator is a genetic sequence with a known location on a chromosome that may vary among individuals and can be used to identify characteristics or conditions of individuals for a purpose (*DNA Junction*, 2012).

Genetic variant is a gene or DNA sequence that exists in different forms from one individual to another. The variant may be as simple as a single base-pair change (single

nucleotide polymorphism, SNP), or as extreme as additional or missing copies of an entire chromosome (*DNA Junction*, 2012).

Quality of life refers to the individual's ability to enjoy normal life activities. The evaluation of quality is a personal perception and is purely subjective.

Self-care activities, for the purpose of this study, are defined as methods utilized to alleviate symptoms. Some common self-care activities might include diet/nutrition/lifestyle changes, such as modifying food and eating habits, eating vegetables and fruits, using nutritional supplements, taking naps, and getting adequate rest and sleep. Another type of self-care activity, described as mind/body control, includes activities such as prayer, meditation, or listening to music (P. D. Williams et al., 2006a; 2010a, 2010b).

Symptom clusters have varying definitions. Dodd, Miaskowski, and Paul (2001) define a symptom cluster as three or more interrelated, concurrent symptoms. The concept of a symptom cluster is important to this study as it might suggest a common underlying cause. With other researchers, the symptom clusters are shown also in the subscales of standardized, calibrated instruments (Williams et al., 1997).

Summary

In summary, this cross sectional study was conducted with a convenience sample of adult female breast cancer survivors who were at least six months out of treatment. The study considered a biomarker, the BDNF Val66Met SNP, as a possible genetic indicator of occurrence and severity of symptoms. Daily activities, self-care, and health-related quality of life were examined in relationship to symptom occurrence and severity, as well as in relationship to demographics and self-reported medical information (no medical records review was conducted to verify self-reported information). The Oncology Nursing Society (2008) and other entities

emphasize the need for research in symptom management that could enable nurses to provide more personalized care.

Chapter II

Literature Review

This study was intended to determine if breast cancer survivors with the BDNF Val66Met SNP are more likely to suffer from a greater number of and/or more severe cancer-related symptoms than survivors who lack this genetic variant (shown in Figure 2, in Chapter 1). Although circulating inflammatory cytokines and other substances are integral components of the chronic inflammatory model that may be implicated in the development of clusters of adverse symptoms, this study focused on the BDNF Val66Met SNP as the primary mode of detection for the more general inflammatory pathway. The BDNF Val66Met SNP that causes a lower circulating level of BDNF could be an underlying cause of symptoms.

This literature review is presented in six sections: (a) an overview of pathophysiological influences on symptoms, (b) personalized medicine, (c) the role of BDNF in breast cancer symptoms, (d) cancer-related symptoms/symptom clusters, (e) self-care, daily activities performance, and quality of life, and (f) a summary indicating the gap in the literature that may be met with this study. Figures 1 and 2 (pp. 6 and 7) in Chapter 1 illustrate the relationships among the primary study variables.

Pathophysiological Influences on Symptoms

Figure 2 (in Conceptual Framework, Chapter 1) illustrates the relationships between cancer symptoms and pathophysiological processes occurring in the human body. Proinflammatory cytokines, such as interleukin (IL)-1b, IL-6, and Tumor Necrosis Factor (TNF)- α , have been shown to induce a condition known as “sickness behavior,” which has many overlapping features of the comorbidities experienced by cancer patients, such as depression, insomnia, cognitive impairment, and persistent fatigue (Dantzer, 2001). One of the most

dramatic examples of the effects of cytokines on behavior is the neurophysiological sequelae of the cytokine-based immunotherapies, such as interferon and IL-2 (Capuron, Ravaud, & Dantzer, 2001).

The ability of proinflammatory cytokines to alter behaviors indicates that the brain is capable of monitoring peripheral cytokine levels. New research has provided evidence that cytokines are capable of not only signaling the brain via afferent nerves such as the vagal nerves (Quan, Whiteside, & Herkenham, 1998; Trakhtenberg & Goldberg, 2011) but are able to cross the blood-brain barrier at specific regions and enter the brain by volume diffusion (Banks, 2006). In addition, the brain contains immune cells, such as macrophages, dendritic cells, and microglia, that have cytokine receptors and can respond to inflammatory stimuli, producing their own proinflammatory cytokines and prostaglandins (Schlitz & Sawchenko, 2002). Although the brain circuitry by which cytokines influence behavioral alterations is not fully understood, it is believed that these signals provide the brain with an image of the innate immune response occurring in the periphery. In response to this inflammatory state, the Hypothalamic Pituitary Adrenal (HPA) axis releases cortisol, a potent anti-inflammatory hormone. Under normal conditions, cortisol, in addition to many anti-inflammatory cytokines, will regulate the inflammatory response in an attempt to regain homeostasis. However, if the inflammation becomes chronic, the HPA axis can become dysregulated (Raison & Miller, 2003).

The pathophysiological model underlying this study provides some evidence that the biobehavioral symptoms related to cancer may be caused by a cascade of events beginning with a chronic inflammation brought on by cancer, cancer treatment, and/or the stress of cancer diagnosis. This inflammatory immune response results in the dysregulation of the HPA axis. This peripheral inflammation is mirrored in the brain, and the resulting neuroinflammation

interferes with neural plasticity and survival. Damage to structures such as the hippocampus, prefrontal cortex, and the amygdala can result in the long-term biobehavioral changes that are exhibited by many cancer patients (Dantzer, 2001; Duman & Monteggia, 2006; Raison & Miller, 2003).

How one responds to the physiological and psychological stress of breast cancer and treatment also may be a function of an individual's coping strategy and resilience to extreme stress. Coping strategy has been found to be a consistent predictor of a patient's well-being during the cancer trajectory (Stanton et al., 2000). Women who engage in problem solving and positive reappraisal, for instance, are less likely to be depressed than women who instead wish for the problem to go away (Carver et al., 1993). How an individual responds to stress is influenced by her life experiences beginning in early childhood. Fagundes, Lindgren, Shapiro, and Kiecolt-Glaser (2012) report that breast cancer survivors who experienced maltreatment as children experience more cancer-related symptoms and a poorer quality of life. An individual's response to stress may also be associated with genetic factors, such as the BDNF Val66Met SNP mentioned above, thereby making her more vulnerable to persistent biobehavioral symptoms of cancer.

Personalized Medicine

Individualized medicine is a developing field in which decisions are tailored to individual patients in whatever way possible, including the use of information to select or optimize the patient's preventive and therapeutic care (Price Waterhouse, 2009). Variation in the human genome is common, with 1/1000 base pairs having a known variation, most of which are a single nucleotide polymorphism (SNP). A SNP variation is not likely to afford a straightforward relationship to disease or symptoms, as many deviations in the patient and environment need to

be taken into consideration. For example, certain genotypes have been linked to better survival in breast cancer, possibly due to better responses to chemotherapy (Ekhart, Rodenhuis, Smits, Beijnen, & Huitema, 2008). Knowledge about the BRCA1 and BRCA2 gene mutation association of certain tumors has guided treatment of breast cancer for many years. One study of breast cancer tumors identified 476 genetic variants in breast tumors that could impact prognosis (Chang, Hilsenbeck, & Fuqua, 2009). It is possible that each of these genetic variants is an opportunity to craft a tailored treatment for the individual patient. Cancer, in general, and breast cancer, in particular, seems to be the type of disease in which care could be personalized, including pharmacogenetics (Allen & Stewart, 2009).

A genetic variant is produced when one or more nucleotides on a particular gene is changed. The nucleotides provide instructions for the biochemical products, usually proteins, that are produced and activated by processes within the body. The BDNF Val66Met SNP is a common single nucleotide polymorphism in the BDNF gene in which a methionine-coding (Met) nucleotide replaces a valine-coding (Val) nucleotide at codon 66. This causes a valine amino acid to be replaced by a methionine at location 66 of the prodomain of the BDNF protein. The presence of this SNP results in the impairment of intracellular trafficking and secretion of the BDNF protein. Approximately two thirds of the population has a Val/Val homozygous genotype. One third of the population has a Val/Met combination, and about one percent has a Met replacing the Val in both chromosomes, resulting in a Met/Met combination (Alexander et al., 2010).

Increased insight into the mechanisms of action of biological determinants such as the BDNF Val66Met SNP may lead to more individualized treatments. The presence of the BDNF Val66Met SNP was found to be a suitable indicator of poor outcomes in 105 survivors of

aneurysmal subarachnoid hemorrhage (Siironeen et al., 2007). The BDNF Val66Met SNP has been shown to be a genetic modifier for severity in Rhetts syndrome in a study of 125 mutant positive patients (Zeev et al., 2009).

In 2008, a prospective study was conducted with a sample of newly diagnosed women with breast cancer ($N = 1,539$) for the purpose of creating a resource to examine behavioral and molecular factors and prognosis (Kwan et al., 2008). The participants were enrolled within two months post-diagnosis during a 3-hour in-person baseline interview. During the interview, anthropometric measurements were made, and questionnaires were administered concerning complementary and alternative medicine (CAM), physical activity, and psychosocial and quality of life measures. A medical records review was also a part of the study, as the participants were part of a large Western insurance network. Blood and saliva specimens were collected from 91% (1,398) of the 1,539 participants, creating a valuable biospecimen resource for genotyping, as well as testing for a number of circulating markers. At 6 and 24 months from the date of the intake, interview follow-up questionnaires were mailed, and health status updates were done; additional follow-ups were completed at 1 year and at 36 months. The final contact was made through a 48-month follow-up mailed questionnaire (Kwan et al., 2008). The undertaking of such a large, complex study by an insurance carrier emphasizes the importance of and need to collect information to provide personal care for each individual undergoing treatment for breast cancer.

The Role of Brain-Derived Neurotrophic Factor (BDNF) in Breast Cancer

Figure 2 (see Chapter 1, Conceptual Framework) illustrates the possible relationships between cancer symptoms and Brain-Derived Neurotrophic Factor (BDNF) in breast cancer.

The dysregulation of the HPA axis, acting in conjunction or synergistically with a chronic state

of inflammation, has been linked to reduced neurogenesis and neural plasticity in the hippocampus and prefrontal cortex. Neurotrophic factors, particularly BDNF and its tropomyosin-related kinase B receptor (TrkB), are critical regulators of neural plasticity, cell differentiation, cell survival, and neurotransmission. BDNF is the most abundant neurotrophin in the brain. The BDNF gene is located on chromosome 11p13 and controls the amount of BDNF produced. One third of individuals have a gene variant for BDNF that causes its production to be greatly reduced. Accumulating evidence suggests that low levels of BDNF play a role in the pathophysiology of a number of symptoms (Hashimoto, 2007), but the exact direction of the effect is not clear. An animal study (Krishnan et al, 2007) found that mice with the polymorphism who were subjected to social defeat seemed to be less susceptible to ongoing change of behaviors related to the previous social defeat. The polymorphism in this case seemed to provide a protective effect. In contrast, a recently reported study with three experiments involving rats provided evidence for the role of BDNF in reducing resilience to the behavioral effects of stress. In this study, both young and adult rats were subjected to maternal separation stress. The stress resulted in reduction of hippocampal BDNF in the young rats but not in the adult rats, therefore resulting in chronic elevations of corticosterone in the young rats (Taliaz et al., 2011).

In a different study, a sample of 57 genetically unrelated, healthy, paid subjects were tested for the Val66Met SNP. There were 31 Val/Val, 19 Val/Met, and seven Met/Met genotypes carried by the subjects. Two stimuli were defined for the study participants: A *go task* would be to push a button, and a *no go task* would be to refrain from pushing a button, depending on what prompt appeared on a computer screen. A series of 300 simple *go/no go* tasks were presented on a PC-monitor, and subjects needed to respond by pushing a button with

their thumbs. The results suggested a Met allele does affect response inhibition processes, with the Met/Met subjects having the best reaction times and making the fewest errors, resulting in these subjects being the most efficient at this simple task. The researchers boldly stated in their conclusion section that “our results, for the first time, reveal an evolutionary advantage justifying the conservation of the Met allele across generations” (Beste, Baune, Domschke, Faulkenstein, & Konrad, 2010, p.182).

An MRI neuroimaging study of 209 multiple sclerosis patients, consisting of 140 Val/Val, 62 Val/Met, and 7 Met/Met subjects, indicated that the Met allele was associated with lower damage (increased gray matter volume and lower lesion volume) on the images. A subsample of 108 patients was tested cognitively; a trend toward better cognitive function in the subjects with the Val66Met SNP was demonstrated (Zivadinov et al., 2007). Another study compared Vietnam veterans with traumatic brain injury ($n = 121$, 73 Val/Val, 45 Val/Met, 3 Met/Met) to nonhead-injured Vietnam veteran controls ($n = 47$, 29 Val/Val, 16 Val/Met, 2 Met/Met), who served in Vietnam during the same years. The groups were matched with respect to age, level of education, handedness, preinjury intelligence, and as many factors as possible from the extensive preinjury variables that were available in the military data set. The investigators discovered, contrary to what they originally hypothesized, that the Val66Met SNP promoted functional recovery after traumatic brain injury (Krueger et al., 2011). The Val66Met SNP has been demonstrated to have some positive benefits on cognitive processes with aging in a study of 131 healthy volunteers ranging in age from 65-88 (mean age 70.5, $SD = 4.5$), with the sample consisting of 79 subjects with Val/Val, 47 subjects with Val/Met, and 5 subjects with Met/Met. The results of the study suggested that Val/Val carriers did not perform as well on

cognitive efficiency testing as did the Met-allele subjects (Gajewski, Hengstler, Golka, Falkenstein, & Beste, 2011).

The role of BDNF in patients suffering from major depressive disorder (MDD) has frequently been studied. Reduced BDNF levels are directly correlated to the degree of clinical impairment and hippocampal volume. This model of neurotrophic depression is supported by evidence, indicating that many antidepressants function by increasing BDNF expression, increasing the TrkB signaling, and/or normalizing BDNF serum levels (Castren, Voikar, & Rantamaki, 2007).

Recently, a SNP in the BDNF gene was described, in which a valine (Val) to methionine (Met) substitution at position 66 of the prodomain was identified (Egan et al., 2003). The SNP is found only in humans and has been shown to be related to reduced hippocampal volume and poor hippocampus-mediated memory performance (Bath & Lee, 2006; Dempster et al., 2005; Egan et al., 2003; Szeszko et al., 2005). This SNP has been utilized as a tool to determine the contributions of BDNF to the symptoms of various disorders, such as Post Traumatic Stress Disorder (PTSD; Frielingsdorf et al., 2010), diabetes (Gray et al., 2006), Parkinson's disease (Ahlskog, 2011), anxiety (Hashimoto, 2007), schizophrenia (Lu & Martiowich, 2008), bipolar disorder (Grande, Fries, Kunz, & Kapczinski, 2010), and Major Depressive Disorder (MDD; Castren et al., 2007; Mata, Thompson, & Gotlib, 2010; Terracciano et al., 2011; You et al., 2010).

A meta-analysis of adult attention-deficit hyperactivity (ADHD) patients (1,445 from four European countries with 2,247 gender-matched controls) showed no association with BDNF. The researchers listed several limitations: gender is likely a significant influence on the impact of the BDNF Val66Met SNP, and the ADHD population is predominantly male

(Sanchez-Mora et al., 2009). The impact of BDNF levels has also been studied in additional care settings, specifically, in delirium patients in an intensive care unit (Grandi et al., 2011) and in the mental health of hemodialysis patients (Nishichi, Higashi, Washio, Todo, & Kumagai, 2011). The findings indicated that the presence of the BDNF SNP resulted in a negative effect on the outcomes measured with these patients.

Few studies have examined how healthy Val66Met individuals cope with acute or chronic stress. Alexander et al. (2010) reported an attenuated HPA axis response in carriers of the Met allele compared to subjects with the Val/Val genotype. In addition, Shalev et. al. (2009) reported a gender-dependent effect for the Met allele, with male subjects exhibiting a reduced cortisol response to a psychological stressor. Further study to determine if there is a relationship to stress in females was recommended.

A study conducted in Spain with 40 tissue samples of both mammary tumors and normal breast tissue implicated lowered BDNF as one of the important substances in differentiating the malignant tissues (Blasco-Gutiérrez, José-Crespo, Zozaya-Alvarez, Ramos-Sánchez, & García-Atarés, 2007). Aloe, Manni, Properzi, De Santis, and Fiore (2000) discovered lowered amounts of BDNF in the paws, bladders, and spinal cords of rats that had been given cisplatin, a chemotherapy agent that may cause neuropathy. The discussion of the study includes a statement that the findings might be clinically useful as these are the anatomical target areas for the neuropathic symptoms.

Breast cancer and prostate cancer are often aligned in the literature due to their hormonal etiologies. A study of tissue samples (16 prostate cancers and 20 benign prostatic hypertrophy growths) showed that the BDNF Val66Met SNP is expressed to a greater degree in malignant tumors (Bronzetti et al., 2008). Fundamental questions remain concerning how these *in vitro*

effects relate to the *in vivo* consequences in humans. According to Chen, Bath, McEwen, Hempstead, and Lee (2008), “It is possible that the identified genetic variant has a direct effect ... but it is also plausible that the genetic variation mediates an effect through some other downstream functional change or through the regulation of some other gene” (p. 3). The importance of understanding BDNF may help researchers discover why some individuals have severe decompensation for a certain situation and others do not, making these patients an important focus for clinical and preclinical studies (Pitinger, 2011).

Cancer Symptoms

Although advances in detection and treatment of breast cancer have increased the survival rate for women over the past several years, many of these survivors continue to suffer from physiological and psychological late effects of treatment, which can seriously affect their quality of life, as well as their morbidity and mortality (Falagas et al., 2007; Mehnert & Koch, 2008). Demographics have demonstrated an important impact on symptoms in many studies. Recently, several large, cross-sectional studies provided support for this observation, including one study of 287 patients with mixed cancer diagnoses (Karabulu, Erci, Özer, & Özdemir, 2010), and another of 703 breast cancer survivors (Ashing-Giwa & Lim, 2011). In particular, a number of demographic characteristics have been shown to have an impact on Cancer-Related Fatigue (CRF). For example, a 2010 study of Israeli women with breast cancer (Prigozin, Uziely, & Musgrave, 2010) indicated that education and age are inversely related to symptom severity and interference. Current employment status and whether or not a woman has children living in her home were considered important factors in another study (Andrykowski, Schmidt, Salsman, Beachum, & Jacobsen, 2006).

Many studies have verified that the type of treatment impacts fatigue (Jacobsen, Andrykowski, & Thors, 2004). Wu, Davis, and Natavio (2012) reported “a strong and potentially reciprocal relationship between cancer-related fatigue (CRF) and disrupted sleep-wake patterns” (p. 181) that might indicate a shared physiological basis. An important longitudinal study found that the type of therapy was one of the major significant contributors to CRF (Bower et al., 2000). The same longitudinal study found that approximately 30% of breast cancer survivors reported persistent fatigue of unknown origin. Linking fatigue to HPA axis dysregulation was accomplished in a later experimental study again led by Bower, Ganz, Dickerson, Aziz, and Fahey (2005). Salivary cortisol measures were obtained from breast cancer survivors with persistent fatigue ($n = 13$) and a control group of nonfatigued survivors ($n = 16$), which correlated with blunted cortisol in the fatigued group (Bower et al., 2005). A large ($N = 1,569$) national cross-sectional study of patients receiving chemotherapy or radiation therapy for cancer found that 80% of patients reported fatigue, followed by 48% of patients reporting pain and 48% reporting nausea (Henry et al., 2008).

Symptom Clusters

Patients who have undergone cancer treatment often have multiple lingering symptoms, such as fatigue, insomnia, and depression, which commonly occur together and have come to be called symptom clusters (Agarwal, Hamilton, Moore, & Crandell, 2010; Barsevick, 2007; P. D. Williams et al., 1997a; P. D. Williams et al., 2001). There are varying definitions for a symptom cluster. Dodd et al. (2001) define a symptom cluster as three or more interrelated, concurrent symptoms, while others accept two symptoms as sufficient for a cluster (Kim et al., 2009). With other researchers, the symptom clusters are defined by the subscales of standardized, calibrated instruments (P. D. Williams et al., 1997).

The methods used to determine the symptom clusters have varied. For example, based on 282 male and female patients with a wide variety of cancer diagnoses who were undergoing chemotherapy, radiation therapy, or both combined, the Therapy-Related Symptom Checklist (TRSC) symptom clusters were objectively derived or identified by P. D. Williams et al. (1997; 2001) and A. R. Williams et al. (2000). Principal components analysis resulted in a 25-item TRSC with 14 components or subscales, six of which were multiple items or symptom clusters. The symptom subscales or clusters were Fatigue, Eating Difficulties, Oropharynx, Nausea/Vomiting, Fever, and Respiratory-Related; the rest were single items (A. R. Williams et al., 2000). Using discriminant analysis, the principal components differentiated between radiation and chemotherapy patients; thus, there is evidence of both discriminant and construct validity of the TRSC. Skin changes, constipation, bleeding, decreased interest in sex, and oropharyngeal problems (sore throat, jaw pain) predominated in radiotherapy patients. Hair loss, fever, bruising, nausea and vomiting, numbness of fingers and toes, and fatigue (feeling sluggish, difficulty sleeping) were predominant in chemotherapy patients. Evidence of the reliability and construct validity of the tool were found (P. D. Williams et al., 1997; 2001). Cronbach's alpha of the TRSC multiple-item principal components all exceeded 0.70. The final TRSC and Oncology Treatment Toxicity Assessment Tool (OTTAT) were correlated at 0.97. The TRSC and functional status (Karnofsky) scores were significantly and inversely correlated (A. R. Williams et al., 2000; P. D. Williams et al., 1997). It is noted here that the TRSC symptom subscale (cluster) labeled as Fatigue contains the symptoms of feeling sluggish, depression, difficulty concentrating, and difficulty sleeping. Dodd et al. (2001) have reported a cluster containing similar individual symptoms.

In another study of 160 patients undergoing radiation therapy (78 females with breast cancer and 82 males with prostate cancer), Kim et al. (2009) identified symptom clusters using the 32-item Memorial Symptom Assessment Scale (MSAS) created by Portenoy et al. (1994). Three symptom clusters were identified: the mood-cognitive symptom cluster, the sickness behavior symptom cluster, and the treatment-related symptom cluster. The symptoms in the mood-cognitive symptom cluster were difficulty concentrating, difficulty sleeping, feeling sad, sweats, worrying, itching, and feeling irritable. The sickness behavior cluster included pain, lack of energy, and feeling drowsy. The treatment-related symptom cluster included two symptoms: problems with urination and changes in skin. Significant differences in all three symptom cluster severity scores were found between the females with breast cancer and the males with prostate cancer. Patients with breast cancer had higher symptom cluster severity scores than the patients with prostate cancer for all three symptom clusters.

A cross-sectional study of 400 newly diagnosed patients with inoperable lung cancer at two Swedish academic medical centers identified three slightly different symptom clusters (Hench, Ploner, & Tishelman, 2009). The study used a variety of instruments and statistical techniques. The three clusters included a physical cluster consisting of pain, nausea, bowel issues, appetite loss, and fatigue; a mood cluster consisting of mood, outlook, concentration, and insomnia; and, finally, a respiratory cluster consisting of breathing and cough (Hench et al., 2009). A cross-sectional pooled analysis of three studies of 154 patients with breast cancer resulted in a symptom cluster of fatigue, cognitive impairment, and mood issues based on a hierarchical cluster analysis of 13 symptoms using binary symptom variables within each study (Bender et al., 2008).

Patients who have multiple symptoms, such as those present in symptom clusters, perceive their symptoms to be more severe and debilitating (Gift, Jablonski, Stommel, & Given, 2004). Researchers suggest that by addressing symptom clusters instead of individual symptoms, negative patient outcomes could be minimized. Later in the course of treatment, there seems to be a cumulative negative impact with the presence and combination of some symptoms (Given, 2008).

Although there is no unifying explanation that accounts for all of these cancer-related symptoms, there is compelling evidence that chronic inflammation, involving a complex interaction between the central nervous system, the neuroendocrine system, and the immune system, may be the common etiological factor causing these biobehavioral symptoms. Chronic inflammation is believed to play a major role in many pathophysiological and psychological disorders, including diabetes, coronary artery disease, chronic fatigue, metabolic syndrome, arthritis, and major depressive disorder (Antoni et al., 2006; Dantzer, O'Conner, Freund, Johnson, & Kelley, 2008; Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008; Zunszain, Anacker, Cattaneo, Carvalho, & Pariante, 2010). The presence of the BDNF Val66Met SNP, generally associated with lowered levels of circulating BDNF, may be an important biomarker for increased susceptibility to chronic inflammation, leading to biobehavioral cancer symptoms. The primary research question of this study sought to discover if there is a significant relationship between symptom occurrence and severity and the presence or absence of the BDNF Val66Met SNP.

Self-Care, Daily Activities, and Quality of Life

The use of a standardized patient-report symptom checklist (the Therapy-Related Symptom Checklist, TRSC), combined with corresponding measures of self-care and quality of

life (QOL), is the hallmark of many studies by P. D. Williams and colleagues. The earliest study, with 91 adult oncology patients at three outpatient oncology clinics, was done in the mid-1980s by practicing certified oncology nurses with over 40 years combined clinical oncology experiences between them (Youngblood, Williams, Eyles, Waring, & Runyon, 1994). The purpose of the study was to compare the standard clinical interview responses, or “usual assessment” responses (for example, responses to the question, “How do you feel today?” that were documented in the charts and later copied and analyzed) of patients with those same patients’ self-reported responses and total scores on the newly developed Oncology Treatment Toxicity Assessment Tool (OTTAT), the precursor of the TRSC (described above in Cancer Symptoms). Also, OTTAT scores were correlated with scores on the Quality of Life Index (QLI), a tool with good psychometric properties (Padilla, Presant, & Grant, 1983). The key finding was that the number of symptoms recorded with the usual assessment (Mean = 1.5; SD = 1.6; range = 0-9) was significantly lower than the mean number of symptoms reported using the checklist (OTTAT, Mean = 11.5; SD = 8; range = 0-37; $t = 8.7$; $p = .001$). This showed significant under-reporting of symptoms with the usual assessment. Concurrent validity also was shown with a significant correlation found between the symptom checklist score and QLI ($r = -0.67$, $p = .0001$). Thus, higher symptom occurrence and severity (checklist total scores) was related to lower quality of life (total QLI scores).

The literature also revealed that several studies were recently conducted using the TRSC in the United States, as well as in Asia, Europe, and Puerto Rico. Two TRSC studies were published in 2006, including one with adults in a Midwestern state (P. D. Williams et al., 2006a), the results of which were further replicated in studies published in 2010 and 2011 and are described below. The second study was conducted with children (P. D. Williams,

Schmideskamp, Ridder, & Williams, 2006b), which formed the basis of an instrument development study on the newly calibrated instrument, the Therapy-Related Symptom Checklist-Children (TRSC-C; P. D. Williams et al., 2012b). The studies involving children are not further described here.

Self-Care and Daily Activities

The adult descriptive study (P. D. Williams et al., 2006a) was conducted with 37 adults receiving chemotherapy for leukemia, lymphoma, or breast cancer or for radiation for head and neck cancer. Study participants reported their symptoms on the TRSC and also described the symptom alleviation methods they used to control their symptoms, a qualitative precursor of the Symptom Alleviation: Self-Care Methods (SA: SCM) quantitative tool used in the current study. The reported results showed that (a) 10 symptoms were reported as mild to moderate in severity, and 40% or more of the patients reported at least 17 symptoms on the TRSC; (b) care providers prioritized interventions based on the TRSC patient-reported symptom occurrence and severity scores; and (c) the self-care strategies, grouped according to complementary medicine categories as a framework, showed that the two categories most used were diet/nutrition/lifestyle change and mind/body control. Responses also indicated the use of biological products, such as vitamins, and the use of herbal treatments and ethno-medicine, such as lime juice and garlic, green mint tea, and others, to alleviate symptoms.

The same study was replicated in cancer centers in Hong Kong and in mainland China (Xi'an), using 222 adult oncology patients. Similar methodology and instruments (with appropriate translation methods) were used, and good reliability, as well as validity, indicated by significant correlations between TRSC total scores and the Karnofsky functional status scale, were reported. The findings were similar to the results of the study based in the Midwestern

United States. Self-care strategies most often used fell in the same two categories (diet/nutrition/lifestyle change and mind/body control) and were reported as helpful by the patients. Tai-chi was mentioned by some as part of mind/body control self-care measures utilized by the Chinese patients; biological treatments were also utilized (P. D. Williams et al., 2010b).

Another replication of the study was conducted with 100 oncology patients at the national medical center in Manila, the Philippines. Findings similar to the studies conducted in China and the United States were reported. The self-care methods most often used by patients in the Philippines fell into two categories. The first type of self-care methods utilized were diet/nutrition/lifestyle changes, such as modifying food and eating habits, eating vegetables and fruits such as papaya, using nutritional supplements, taking naps, and getting adequate rest and sleep. These self-care methods were all mentioned as useful to manage the symptoms in the Eating and Fatigue subscale symptoms. The second type of self-care methods reported by patients were in the mind/body control category, such as prayer, praying the rosary, and listening to music; these self-care methods were used to relieve the symptoms in the Fatigue subscale, or cluster, as well as other symptoms (P. D. Williams et al., 2010a). The key role of family support during treatment also was described by the patients, similar to findings on Filipino-Americans reported by Harle et al. (2007). In TRSC replications with Puerto Rican patients and Mexican-American patients undergoing treatment for cancer, two other studies have reported similar quantitative findings. Moreover, qualitative findings have shown that patients focused on religious practices and utilized the support of family as part of self-care strategies (Gonzalez, Williams, Tirado, & Williams, 2011; Lantican, Williams, Bader, & Lerma, 2011), similar to practices employed by the patients in the Philippine study.

Another replication study was conducted in Thailand using the TRSC and similar methods, with a convenience sample of 202 patients receiving treatment for cancer at the National Cancer Institute, as well as at a cancer center of a provincial city in Thailand (Piamjariyakul et al., 2010). The results closely mirrored those previously reported in the studies conducted in the Midwestern United States, mainland China, and the Philippines. One of the unique self-care findings reported in Thailand was the use of the herbal treatment “purple flower” for hair loss. The use of music and religious icons were also common, including the use of tapes related to Buddhist prayers.

Recently, P. D. Williams et al. (2011b) reported the inter-correlations among the variables of symptom occurrence and severity (as measured by the TRSC), daily activities performance, self-care strategies, and health-related quality of life. This study has been replicated in Puerto Rico (Gonzalez et al. 2010) and with Mexican-Americans (Lantican et al. 2011). The current study now adds an investigation of the potential linkage between the presence or absence of the BDNF Val66Met SNP (a genetic marker) and the occurrence and severity of symptoms experienced by breast cancer survivors after their cancer treatments have ended. Thus, over several years, the work by P. D. Williams and a variety of U.S. and international colleagues has provided rich quantitative data through the use of calibrated instruments, as well as qualitative data to give insights into how self-care is related to cancer treatment-related symptoms. Gathering information about common symptoms and monitoring the success of patient self-reported strategies can guide nurses in helping patients optimally during treatments for cancer (P. D. Williams et al., 2006a).

Quality of Life

Tested for potential use in evidence-based nursing practice on a small sample of cancer patients, a study by P. D. Williams et al. (2011b) found that use of the TRSC for symptom management by advanced practice nurses resulted in a higher quality of life in the intervention group, as compared to the group receiving usual care. Patients also reported that symptom assessment using the TRSC and ensuing symptom management had enhanced patient-nurse communication. Moreover, in a sequential cohort design in a health services study on 113 patients done at a Midwestern cancer center, findings showed that (compared to usual care), the use of the TRSC resulted in significantly higher patient-reported quality of life and functional status as measured on the Karnofsky scale, and significantly more symptoms were documented and managed (P. D. Williams et al., 2011b, 2012a).

The symptoms associated with cancer and cancer treatments impact quality of life (QOL), but self-care can be a mediating factor. In a study of lung cancer patients, John (2010) focused on personal strategies to promote quality of life. The concept of self-care is represented in many ways in the literature, including the use of several synonymous terms. A recent delineation of self-care and associated concepts was published in the *Journal of Nursing Scholarship* (Montazeri, 2008). This important work was based on a review of 65 articles, book chapters, and books, representing the years 1994-2010. The review included tables of commonalities, concept relationships, and a conceptual model depicting the five terms that are often used interchangeably in the literature: self-care, self-management, self-monitoring, symptom management, and self-efficacy. The consequences of self-care, as represented in the literature, included improved quality of life and symptom management (Richard & Shea, 2011).

Quality of life (QOL) has also been the subject of at least 606 studies in breast cancer patients from 1974 to 2007 (Montazeri, 2008). From the time of diagnosis through the entire continuum of life as a survivor, there are situations that can cause psychosocial distress and impact quality of life (Lacovara & Ray, 2007). For instance, decision making about treatment can cause distress for patients, particularly for breast cancer patients. Patient preference is the guiding principle for making treatment decisions in early stage breast cancer (National Guideline Clearinghouse, 2010). Measuring satisfaction with the decisions that patients had made was the subject of a pre-post design study. A nine-item tool was administered to a convenience sample of 30 early stage breast cancer patients of one surgeon at a large university medical center in the Southwest United States. Although only 19 of the patients completed the 6-month follow-up phase of the study, there was an indication that nurses played a crucial role in advocating for the patients' ability to make surgical treatment decisions with which they were satisfied (Lacovara, Arsouman, Kim, Degan, & Horner, 2011).

In another study, nine women who were receiving chemotherapy for various types of cancer reported that the side effects, particularly nausea and vomiting, impacted daily life and decisions about future treatment (Bergkvist & Wengström, 2006). The importance of measuring QOL from the patient perspective is emphasized in one early study of 130 cancer patients receiving either chemotherapy or radiation therapy. The participants completed a 14-item visual analog quality of life measure. The purpose of the study was evaluation of the instrument using a healthy (nonpatient) comparison group. Interestingly, concurrent validity with physician rating of quality of life was very poor (Padilla et al., 1983). A more recent study illustrated the practitioner-patient dichotomy in view of QOL. Rossman (2004) stated that the onset of hair loss is the second most traumatic event after initial communication of the diagnosis of cancer, making

it an incredibly important moment in the cancer-related quality of life trajectory. Health-care providers often minimize the importance of alopecia, as it is temporary and easy to remedy. Unfortunately, the literature indicates that this opinion fails to reflect the patient view. Hair loss as a consequence of cancer treatment is a constant reminder to the patient of her disease.

Freedman (1994), in a study about hair loss and breast cancer patients, wrote:

Embodied in the symbolism of hair is a concept of the whole self, a completed person, who has the possibility of expressing individualism through the design of her hair. The loss of hair is an extremely traumatic experience precisely because it is a symbolic precursor to the loss of self. (p. 336)

An independent study of 20 patients conducted by Heinze (2010a) at an additional approved site for HSC#12048 (P. D. Williams et al., 2009) found that patients provided more care to alleviate hair loss than any other symptom. For example, they wore a wig, hat, or scarf; cut their hair short; or shaved or massaged their heads. There were individuals who wore wigs only on special occasions; conversely, one patient reported wearing it constantly, even in bed. The finding that all of the eight patients who reported hair loss as a symptom listed a corresponding self-care action emphasized the importance of this symptom to cancer patients.

Borsellino and Young (2011) sent a six-item survey electronically to 1,322 women cancer survivors as part of an e-newsletter for a group that helps women cope with the emotional upheaval of medical hair loss; the survey yielded 319 responses. The data gathered led to the conclusion that preparation for cancer-related hair loss could be a pivotal point in the quality of life for patients. Those who were well-prepared by nurses and proactively engaged in anticipatory coping for this symptom engendered a feeling of control that impacted their total symptom experience.

In another study, 206 responses to a mailed survey of multiple myeloma patients indicated that pain and mood disturbances had a significant impact on their quality of life (Poulos, Gertz, Pankratz, & Post-White, 2001). In a secondary data analysis, 263 chemotherapy patients' responses showed that insomnia, fatigue, depression, and anxiety were negatively correlated with quality of life (Redeker, Lev, & Ruggiero, 2000). A six-month longitudinal study of 291 individuals diagnosed with multiple sclerosis indicated that individuals with the lowest scores on symptoms had the highest QOL. Those participants who had the highest scores in fatigue, pain, and depression had the worst QOL (Motl & McAuley, 2010). A study conducted at a university hospital in Sao Paulo, Brazil, used four measures to explore the impact of cancer-related symptoms synergisms on QOL and performance status. The participants were outpatients not receiving active treatment for their cancer. They were divided into two groups: one group had multiple and severe symptoms and the other group had fewer symptoms with less severity. Those patients in the multiple symptom group were six times as likely to report poor role functioning, five times more likely to have poor emotional quality of life, four times more likely to have poor overall QOL, and three times more likely to have poor cognitive and social QOL. The only single symptom that had a negative impact on QOL was depression. These results were independent of gender, age, level of education, and economic condition. The researchers concluded that there is a synergistic effect among symptoms that result in reduced QOL (Ferreira et al., 2008).

Predictors of quality of life in elderly hospice patients with cancer were the focus of a study of 533 adults (Garrison, Overcash, & McMillan, 2011). Of the variables studied, number of symptoms, depression, and functional status accounted for 46% of the variance in quality of life.

Toftthagen (2010) reported on 14 cancer patients' experiences with peripheral neuropathy. The semi-structured, private interviews indicated that neuropathic symptoms interfered with many aspects of daily life, resulting in frustration and depression due to the need to give up enjoyable activities that decreased their quality of life.

The Montazeri (2008) review of the literature on health-related quality of life in breast cancer patients included a table listing 27 studies linking quality of life to common symptoms in breast cancer patients. Seven studies focused on fatigue, six on lymphedema, five on hot flashes or menopausal symptoms, three on surgery-related symptoms, two on tamoxifen-related symptoms, and one each on pain and sleep difficulties. All 27 studies illustrated symptom impact on quality of life.

Symptoms research concerning fatigue has been commonly associated with quality of life and interference with self-care. Fatigue is often described in the literature as one of the most common and distressing ongoing symptoms experienced by cancer survivors. An estimated 80% to 100% of people with cancer experience fatigue (Gonzalez et al., 2011; Lantican et al. 2011; Prue, Rankin, Allen, Gracey, & Cramp, 2006; Servaes, Verhagen, & Bleijenberg, 2002; P. D. Williams et al. 1997; 2001; 2006a; 2010a, b). Fatigue may be related directly to the cancer or its treatment and may continue for years after treatment is completed (Wang, 2008). Despite its prevalence, there is still much to learn about fatigue in breast cancer.

A literature review that culminated in a live focus group with the authors (Zee & Ancoli-Israel, 2009) sought to address effective management of sleep disorders to reduce cancer-related fatigue yielded several specific recommendations for underlying mechanisms for cancer-related fatigue (similar to those raised in this study). For example, areas of particular interest for further study and discussion included the following:

How is any apparent relationship between sleep and CRF driven by the various mechanisms they affect (e.g. inflammatory markers, circadian rhythm disturbances, depressed mood, HPA axis dysregulation)? . . . What mechanisms underlie the effects of various cytokines in sleep-related pathologies, and how are these influenced by pharmacological agents? (Zee & Ancoli-Israel, 2009, p. 39)

This study, as well as many other studies, raised the issue of exploration of biological mechanisms in conjunction with symptoms as a recommendation for future research.

Summary

The pathophysiology of cancer-related symptoms has been reviewed. Based on the available literature, the question of whether the BDNF Val66Met SNP is a possible genetic modifier of symptom occurrence and severity has not been examined in previous breast cancer studies. This study fills in the gap by exploring a possible relationship between the presence or absence of the BDNF Val66Met SNP and symptom occurrence and severity in breast cancer patients.

Targeting therapy toward the underlying symptom etiology is the crux of personalized medicine, an issue that has not been explored in nursing management of symptoms in breast cancer patients. The discovery of a relationship between cancer-related symptoms and particularly symptom clusters to the BDNF Val66Met SNP might be an important first step to personalized nursing care. The ability to relieve or decrease all symptoms in a cluster makes the research to discover common biological mechanisms an important endeavor (L. A. Williams, 2007). Investigating the relationship between the BDNF Val66Met SNP and the occurrence and severity of patient-reported symptoms, as well as the relationship between symptom-based

alleviation and self-care, has the potential to lead to a much-improved quality of life for cancer patients.

Chapter III

Methodology

Research Design

This study used a cross-sectional design with two phases: (a) Phase 1, an electronic survey collecting data on symptoms occurrence and severity, daily activities, and quality of life; and (b) Phase 2, the collection of physiological data and symptom alleviation self-care methods. Using inclusion criteria, an enriched sample was selected for Phase 2. The subsets of Phase 1 participants included in Phase 2 were the top and bottom scorers on the Therapy-Related Symptom Checklist (TRSC). The top scorers ($n = 25$) had TRSC scores ranging from 23-54; the bottom scorers ($n = 26$) had scores ranging from 0-14. This design maximized the variation between the groups on the dependent variable, the TRSC total score, as well as reduced the number of individuals for the most costly aspect of the study, the BDNF analysis.

Primary Research Question

Is there a significant relationship between symptom occurrence and severity in breast cancer survivors and the presence or absence of the BDNF Val66Met SNP?

Secondary Research Questions

1. What are the occurrence and severity of symptoms among breast cancer survivors as reported on the TRSC after the completion of their cancer therapy regimen?
2. Are there significant relationships among symptom occurrence and severity, daily activities ratings, and health-related quality of life and selected demographic and other variables (age, ethnicity, education, treatment method, and time since treatment)?
3. What self-care methods are used by survivors to alleviate symptoms, and what are the survivors' perceptions of the usefulness of these self-care methods?

Setting of the Study

The Mid-Atlantic states in which the data were collected have over one million residents, according to the 2010 census. The residents of the state from which the majority of subjects were enrolled are mainly Caucasian (69%) and Protestant (51%). Residents responding with “no religion” combined with those refusing to answer the census question regarding religious preference totaled over 20% of the responses, and 9% reported being Catholic. In the state, 21% of the residents are black, 3% are Hispanic, 3% are Asian, and 3% are two or more races. The largest employer in the state is the government, including a large number of positions in the military, followed by the fields of education, banking, chemical industry and pharmaceuticals, health care, manufacturing, and agriculture (Hartley, 2004).

Sample

The convenience sample of volunteer participants was initially recruited from the data base of a statewide breast cancer coalition of a single Mid-Atlantic state. When additional subjects were needed, recruitment was expanded to a number of hospital-based survivor groups and the local and state chapters of a national breast cancer organization in neighboring states. The study had two phases: (a) Phase 1, an electronic survey collecting data on symptom occurrence and severity, daily activities, quality of life, as well as subject characteristics, medication, treatment, and other health information (no medical records review was conducted to verify self-reported health and treatment information); and (b) Phase 2, the collection of physiological data and self-care information. In Phase 1, breast cancer survivor respondents completed the online questionnaires. Using inclusion criteria, an enriched sample was selected for Phase 2. The subset of Phase 1 participants included in Phase 2 completed a measure of self-care, as well as provided a salivary sample for the BDNF Val66Met SNP.

Inclusion and Exclusion Criteria

Since a maximum number of participants were desirable in Phase 1, the only exclusions from the original data base were (a) all males, (b) females under 18 years of age, and (c) breast cancer patients at less than six months post treatment completion. Protection of human subjects is an important primary concern in all research. The study was approved by the University of Kansas Cancer Center Protocol Review and Monitoring Committee (PRMC) and KUMC Human Subjects Committee (HSC) before recruitment began; the approval form is included in Appendix A. Breast cancer survivors were sent an electronic invitation to participate. A copy of the invitation email is included in Appendix B.

The main inclusion criterion was an adult female breast cancer survivor who completed therapy six months or more prior to the survey. The url link to the electronic survey (see Appendix C) was sent via email to all potential participants listed in the coalition data base, inviting them to involve themselves in the research. The Phase 1 survey instrument was composed of the TRSC, Daily Activities Rating Scale (DARS), Health Related Quality of Life – Linear Analogue Self Assessment (HRQOL-LASA), and the Demographic and Health Form. As shown in the Phase 1 packet, the Demographic and Health Form included questions related to any “current illnesses” and to “medicines currently taken” in order to be able to evaluate the possible impact of current illness or medication on the study variables. Tables 1 and 2 in the section Data Collection Procedures outline the specific steps followed in the study.

Instruments

The study variables were self-reported symptom occurrence and severity; self-care; daily activities performance; health-related quality of life; and the presence or absence of the genetic variant, the BDNF Val66Met SNP. Measurements are described below, along with selected

demographic and other variables (age, ethnicity, education, treatment type, and time since treatment completion).

Therapy-Related Symptom Checklist. The first instrument included as items 2-27 of the electronic survey was the Therapy-Related Symptom Checklist (TRSC). See Appendix D for the paper and pencil version of the instrument for comparison. Patient-reported occurrence and severity of symptoms were operationalized by the total score on the TRSC. The Cronbach's alpha of the total scale score for this study was 0.91. The study participants indicated the occurrence of symptoms experienced by checking whether the symptom was present and then rating the severity of each symptom on a 5-point scale, from 0 (*none*) to 4 (*very severe*). Space was provided to write in and rate other symptoms that were not listed. The 25 items were summed (*range* 0 – 100), where higher scores on the TRSC indicated greater frequency (occurrence) and severity of symptoms reported. The psychometric properties of the TRSC are reported in Chapter 2.

Symptom clusters. The TRSC has fourteen subscales developed through the use of principal components analysis (P. D. Williams et al., 1997, 2000) and subsequently used in numerous studies by P. D. Williams and colleagues. The conceptual framework and literature search for this study supported the fact that a biomarker, such as the BDNF Val66Met SNP, may display its impact through the grouping or clustering of symptoms. Eight of the subscales are single item scales (Pain, Numbness in Fingers and/or Toes, Bleeding, Hair Loss, Skin Changes, Constipation, Soreness in Vein, and Decreased Interest in Sexual Activity). The two longest subscales contain four items each. The Fatigue subscale consists of the items feeling sluggish, depression, difficulty concentrating, and difficulty sleeping. This Fatigue subscale contained the four items that are consistent with biobehavioral symptoms. These four items were not scored to

create a subscale but used individually in a subanalysis for the primary research question. The other four-item subscale, Eating, includes the TRSC items of taste changes, loss of appetite, weight loss, and difficulty swallowing. There is one three-item subscale designated as Oropharyngeal that includes sore mouth, sore throat, and jaw pain. The remaining three subscales included two items each: Nausea (nausea and vomiting), Fever (fever and bruising), and Respiratory (cough and shortness of breath). However, all of the items were considered individually and not scored as subscales for this study.

Daily Activities Rating Scale. The second instrument (items 28-32 on the electronic survey) was the Daily Activities Rating Scale (DARS). The Cronbach's alpha for this survey was 0.70. See Appendix E for the paper and pencil version for comparison. The daily activities rating total score queried about level of ease or difficulty in performing Activities of Daily Living (ADL), with higher scores reflecting more problems performing ADLs. The five items on this scale are related to respondents' levels of ease or difficulty in performing ADLs, answered on a scale of 1 (*not at all*) to 4 (*very much*). For example, Item 29 asks: "Do you have any trouble taking a long walk?" The scale ranges from one to twenty; thus, higher scores reflect more problems performing ADLs. Basch et al. (2007) reported concurrent validity of this scale with established, longer scales. Construct and discriminant validity also showed strong, positive correlations between scores on this instrument and the total scores on the TRSC (Gonzalez et al., 2011; P. D. Williams et al., 2011b).

Health-Related Quality of Life - Linear Analogue Self Assessment. The third instrument, items 33-38 of the electronic survey, was the Health-Related Quality of Life - Linear Analogue Self Assessment (HRQOL-LASA; see Appendix F for the paper and pencil version). The HRQOL-LASA is used to measure health-related quality of life. The HRQOL-LASA has

six items that use a 10-point scale, from 0 (*as bad as it can be*) to 10 (*as good as it can be*). Scale scores range from 0 to 60, with a high score on the HRQOL-LASA indicating a high quality of life. The Cronbach's alpha for this usage was 0.93. The items have been validated as general measures of global QOL dimensional constructs in numerous settings (Bretscher et al., 1999; Grunberg, Groshen, Steingass, Zaretsky, & Meyerowicz, 1996; Gudex, Dolan, Kind, & Williams, 1996; Hyland & Sodergren, 1996; Sloan et al., 2002; Sriwatanakul et al., 1983; Wewers & Lowe, 1990). The series of six LASA items were constructed and validated at Mayo Clinic for use in cancer patients (Bretscher et al., 1999). A community-based, translational research study conducted by P. D. Williams et al. (2011a, 2012) on self-reported symptoms on the TRSC as related to symptom management in the context of a oncology care delivery system was completed online by 138 oncology patients during repeated treatment clinic visits (for chemotherapy, radiation therapy, or a combination of both) and was found significant. The researchers discovered strong inverse correlations between total scores on the TRSC and HRQOL-LASA. Moreover, the HRQOL-LASA overall physical well-being item was most strongly correlated with the TRSC total score. Construct and discriminant validity also have shown strong, inverse correlations between scores on this instrument and the total scores on the TRSC (Gonzalez et al., 2011; P. D. Williams et al., 2011b).

Subject Characteristics and Health Form. Subject characteristics and health information were obtained via electronic survey items 39-47 (see Appendix B). Subject characteristics and other data collected for Phase 1 included the respondent's age and ethnicity. Other self-reported medical information (medications, co-morbid conditions, and treatment modality) were collected, as they were important in the context of the symptom literature. The last part of the electronic survey included a section (a) inviting participants to join study Phase 2,

briefly described, and (b) requesting that they provide information to enable the researcher to contact those respondents who met the inclusion criteria for Phase 2 participation. A subject characteristics form in the electronic survey included items that have been modified from those used in previous studies by P. D. Williams and colleagues (Heinze, 2010a, b; Piamjariyakul et al., 2006; P. D. Williams et al., 2006a, b; 2009; 2010a, b; 2011a, b, c). Some adaptations of the subject characteristics selected for this study were made based on the literature and the options for the selections available in the electronic format. Adaptations also were made based on the most common responses given on the 2010 census by residents of the state from which the majority of respondents were drawn. Previous use of the subject characteristics in pilot studies was helpful in refining the variables selected.

Subject characteristics were chosen as variables for the study because they have been shown to impact symptoms in breast cancer patients in previous studies. A study of Israeli women with breast cancer (Prigozin et al., 2010) indicated that education and age are inversely related to symptom occurrence and severity. Current employment status and whether or not a woman has children living in her home (Andrykowski et al., 2006) were considered important for the study, although no significant differences were found among the variables in this sample. Type of therapy and time since completion of therapy were found to be significant in a major longitudinal study (Bower et al., 2000). Marginal differences in the symptom of fatigue were demonstrated for lower income levels and marital status in the same study. In a cross-sectional study of 703 multiethnic breast cancer survivors, the main conclusion was that HRQOL is closely linked to demographic contexts and influences emotional well-being. The implication for nursing was to use the subject characteristics to inform and enhance the assessment of emotional outcomes for clinical and scientific purposes (Ashing-Giwa & Lim, 2011).

Symptom Alleviation: Self-Care Methods. The Phase 2 instrument, Symptom Alleviation: Self-Care Methods (SA: SCM; see Appendix G), was used by respondents to report self-care strategies performed to alleviate any symptoms experienced and marked on the TRSC. Frequency of use and effectiveness of the performance of self-care methods are operationalized by the SA: SCM. The instrument is directly based on the symptoms checklist of the TRSC. For each symptom reported, the patient was asked what methods were used to attempt to alleviate the symptom, and to rate how often each self-care method was done using the scale 1 (*seldom done*) to 4 (*very often done*). Scores ranged from 0 to 100. Whether or not the method helped relieve the symptom was also asked (indicated by a check in a “yes” or “no” answer column). Thus, the higher the score on the SA: SCM, the more often self-care was performed. Cronbach’s alphas above 0.70 have been reported (Gonzalez et al., 2011; P. D. Williams et al. 2011b). In addition, the construct validity of the SA: SCM was shown in a finding that higher depression scores were related to patient reports of self-care for nausea being "not helpful," as compared to patients with significantly lower depression scores, who reported that their self-care methods "helped." Similar results were found with the symptom of hair loss. The study included a large number of Mexican-Americans (Lantican et al., 2011). Moreover, on the TRSC Chinese version of the SA: SCM tool, a total of over 500 "helpful" self-care methods (SCMs) was reported as well as a few SCMs that were "not helpful." The highest number of helpful SCMs mentioned was for the most frequently reported symptom of feeling sluggish (P. D. Williams et al., 2010a).

BDNF Val66Met SNP. Single nucleotide polymorphism (SNP) is a common genetic variant in which a single nucleotide is replaced with a different one (in this case methionine replaces valine). Most SNPs have no effect on health or development while others may predict or influence an individual’s response to a medication, an environmental toxin, or his or her risk

of developing a particular disease. A common SNP found in the BDNF gene (rs6265) results in an amino acid substitution of methionine (Met) for a valine (Val) at codon 66 and is designated as Val66Met. Egan et al. (2003) reported that Met substitution leads to inefficient trafficking of BDNF to secretory granules leading to reduced BDNF in neuronal survival, differentiation, and synaptic plasticity. The Val66Met SNP has been assessed for its potential contributions to symptoms of psychiatric illness and neurodegenerative diseases. The presence of the BDNF Val66Met SNP in saliva was measured by genotyping in all Phase 2 subjects.

Protection of Human Subjects

Full information concerning the study was disclosed at the time that consent was given by participants. The consent form (see Appendix H) included background, purpose, procedures, risks, benefits, alternatives, cost/payment, right to withdraw, and confidentiality. The researcher was present to answer all questions before the subject signed the consent. The copy of the consent that each of the participants received included the researcher's contact information in the event that concerns, complaints, or additional questions should arise. To protect confidentiality, each participant was assigned a code number that was used for identification of all data. Since this study involved genetic testing, there was a special section of the form that explained the special requirements outlined by the KUMC Human Subjects Committee.

Data Collection Procedures

The data collection process was comprised of two phases (see Figure 3). The study design involved collecting quantitative data first (Phase 1) to provide the basis for a purposive subsample (Phase 2). This design maximized the variation between the groups on the variable symptom occurrence and severity, as measured by the TRSC total score, as well as reduced the

number of individuals for the most costly aspect of the study, the BDNF analysis. Figure 4 illustrates the data collection process.

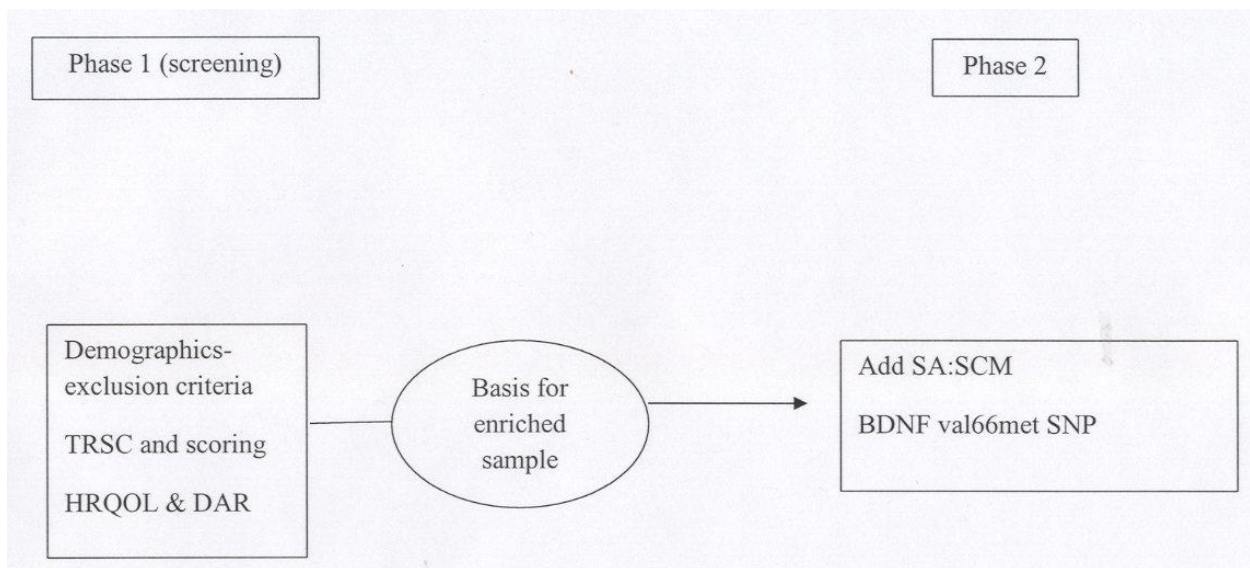


Figure 4. Study data collection procedures.

Phase 1

In Phase 1, the invitation to participate in this study (see Appendix B) was sent via email to the approximately 800 female breast cancer survivors who are included in the primary state's coalition data base, along with the url that gave them access to the electronic survey (see Appendix C). In order to prevent potential respondents from inadvertently deleting the email containing access to the survey, an announcement first appeared in the coalition's newsletter, notifying subscribers that an important survey would be coming by email. Another method used to optimize participation was a recruitment announcement on the coalition Web site and Facebook page. When additional recruitment became necessary, the coalition project director provided information for the researcher to contact leaders of other breast cancer groups in the area.

The electronic survey was formatted in Zoomerang™, a survey software package available through the hospital at which the researcher is employed. The survey was developed in cooperation with the information technology director and the Webmaster at the hospital. The coalition staff and dissertation advisor reviewed initial drafts, and corrections were made according to reviewers' recommendations. A pilot of 10 participants was then conducted. Additions were made to clarify the symptom time frame that was to be addressed by adding the word "current" to the introductory section. Pages were adjusted to include only five or six items per page so that the mandatory item prompt would appear on each screen without the need for the participant to do extensive scrolling. The questionnaire was designed with color, customized bolding, and spacing to improve the appearance, as a "fancy" questionnaire is more likely to be completed and has been shown to increase response rate by 5%; this type of motivation is important for increased response to Internet research (Im & Chee, 2003), and the cooperation with the coalition was assumed to be a good motivator. There are seasonal response rate fluctuations to Internet research (Im & Wonshik, 2004), and the winter has been found to be a much better season to launch than summer, as the potential participants would be more likely to be indoors and attending to their computers during the more inclement weather.

Collaborating with the breast cancer coalition for this study was integral to the feasibility and success of this project. The researcher has worked in partnership with the coalition on various scientific projects for nearly four years, with excellent cooperation. A data base was established to catalogue breast cancer survivors who have connected in a significant way with the coalition in terms of volunteering or having multiple, continuing contacts. Part of the mission of the organization is to promote research to benefit breast cancer survivors. The database has been used for previous studies. The return rates traditionally have been very high

and are better for email than for traditional postal mailings, as noted by the special projects manager for the coalition. The project director reported that 100% of subscribers on the email list have access to a computer at home or another accessible venue that they use routinely.

The recruitment email was sent from the coalition email address in order to avoid the possibility of the email being screened out as spam. This list of subjects was used and updated often so that the number of undeliverable emails should have been small. Once the electronic survey was launched on February 10, 2012, the returns were monitored. A number of questions were recurring in emails sent to the researcher, so the first reminder that was sent included answers to those questions. Unfortunately, one of the questions that was emailed to the researcher led to a discovery later that same day that there was a problem with the skip logic on the survey, and the first five questions were being omitted. Attempts to resolve the situation were not successful, and the original survey was closed. A supplemental survey including the missing five questions was emailed to those individuals who provided contact information for participation in Phase 2, and a new survey was launched. The timing of the reminder was based on knowledge that responses normally will come within eight days (Sheehan & McMillen, 1999). Two or more reminders were sent, but the number of additional returns was not sufficient. Additional participants were recruited until a total of 214 responses were received. The completed TRSCs were scored as they were received. The returns were reviewed to see who had given consent to participate in Phase 2. Table 2 provides an overview of the Phase 1 data collection procedures.

Table 2

Study Participant Data Collection Procedures, Phase 1

Research activity	Follow-up
Email invitation to participate sent to approximately 800 survivors on coalition distribution list.	Email reminders sent to those on the coalition list.
Zoomerang™ was used to administer the survey through a url in an email and on the coalition Web site. Eligibility criteria were listed in item 1, and individuals were screened from completing the survey if the eligibility criteria were not met. The demographic form also included exclusion criteria information to provide a double check that only results from eligible participants were included.	Email reminders were sent.
Scored TRSC	Those who completed the TRSC and provided contact information received follow-up contact.
Phone calls were made to those giving initial consent beginning with highest and lowest scores until two groups were created (Group 1 – 26 top scorers, and Group 2 – 25 bottom scorers) who satisfied the inclusion criteria.	Locations for the collection of salivary specimens and completion SA: SCM were determined. Inquiry was made about whether dry mouth would be an issue, and complete instructions about the amount and activities to avoid before salivary sample collection were reviewed, including good hydration. Each participant was contacted to confirm commitment to the date, time, and location.

Phase 2

Phase 2 began with selection of a purposive, or enriched, subsample of the original respondents. The enriched subsample contained only those respondents willing to participate in Phase 2 who had high (≥ 23) and low scores (≤ 14). To prepare for Phase 2, the locations for sample specimen collections were established based on the participants' addresses and were coordinated with the assistance of the coalition special project manager. Once the willing respondents from Phase 1 were screened, 51 individuals were selected for two groups based on their TRSC scores. The first group consisted of the 26 individuals who had the highest total

TRSC scores (ranging from 23 to 54), indicating a high occurrence and severity of symptoms, and the second group of 25 was composed of the participants who had the lowest total scores on the TRSC (0 to 14), indicating minimal occurrence and/or severity of symptoms. This procedure was followed in order to maximize the variability. Dates for sample collection were scheduled, and each participant was contacted to confirm her commitment to the date, time, and location. Packets were prepared for each individual, including the SA: SCM and saliva sampling packets.

All arrangements were made by the researcher to procure and prepare the site(s) before participants arrived. Participants received individual reminders the day before the in-person data collection. If any of the individuals were unable to keep the appointment, an effort was made to schedule an alternate appointment. Table 3 describes the step-by-step method implemented in Phase 2 of the study for saliva sample collection. Presence of the Val66Met SNP was determined by genotyping a single saliva sample collected from consenting subjects. A transcript of the instruction video was available upon request. The OG-500 data collection system was selected for use as this collection device has the proper design and components to promote ease of collection and protection of the integrity of the specimen. The tube was a standard size, facilitating use in most laboratory equipment. Most of the studies that require the collection of saliva samples have used the OG-500 because the instructions were clearly written and the device was easy to use. If there was any difficulty obtaining the saliva sample, the subject was permitted to take a break or reschedule at another time.

Table 3

Consent, Saliva Sample, and Instrument Collection Procedures, Phase 2

Research activity
Participants were welcomed and completed informed consent (see Appendix H).
The SA: SCM was completed with the researcher.
<p>Researcher screened participants to ensure that they</p> <ul style="list-style-type: none"> • did not have a cold or sinus infection, • had not consumed alcohol for 24 hours, • had not brushed their teeth, or had anything to eat or drink for two hours, • had not chewed gum or smoked for 30 minutes before collecting sample (Mandel, Ozdener, & Utermohlen, 2009, 2011). <p>On arrival at the study site, the researcher gave the participants (a) the written instructions for saliva collection (see Appendix I), as well as answered any questions.</p> <p>Collection of salivary sample was directly observed and assisted by one researcher. The steps were for the participant were as follows:</p> <ul style="list-style-type: none"> • Relax and rub cheeks for 30 seconds. • Allow the saliva to pool in their mouth, and imagine they are eating their favorite food. • Take all the time needed to deposit 2 ml of saliva (excluding foam) indicated by a fill line marking. The time needed was generally no more than 2-5 minutes. Several collections did take over 30 minutes, but the sample integrity was not compromised as the company certified that the sample remains stable for hours if collection is protracted. • The collection device was sealed as indicated by a loud click, releasing the buffer and raising the level of fluid in the tube. • While holding the tube upright, the funnel top was unscrewed and replaced with the cap provided. • Once the cap was in place, the tube was shaken for 5 seconds. • The sample was placed immediately in the shipping container marked with only the study identifier (no personal identifiers) and biohazard labeling and was transported or shipped according to instructions (Shipping Recommendations, 2009).
Researcher administrated collection of instrument data and the departure routine, including a verbal thank you, and reviewed study material before departure.

BDNF Val66Met SNP data collection. Presence of the BDNF Val66Met SNP was determined by a genetic test. Consenting subjects were asked by the researcher to collect 2 ml of saliva using the passive drool method for saliva collection. Passive drool method means that the patient simply spits into the specialized, sealable container up to the fill marker without any

swabs employed to stimulate or absorb the saliva. Since saliva is naturally foamy, careful attention was given to assure that the liquid level was raised to the 2 ml marker or above, excluding foam or bubbles. If the subject had difficulty producing the 2 ml of saliva recommended, the presampling method to stimulate salivation, massaging the jaws, could be repeated multiple times. The laboratory where the samples were analyzed routinely reports a less than 1% problem with specimens, even though the majority of specimens are self-collected. This study included the safeguard of supervision. A copy of the manufacturer's instructions for the patient is included in Appendix I. The DNA Self-Collection Kit from DNA Genotek in Kanata, Canada, contained a DNA stabilizing buffer. This buffer ensured stability of the sample for transport to the testing site without any specialized procedures. The samples were transported to the Institute of Genomic Medicine (IGM) at the University of Medicine and Dentistry of New Jersey (UMDNJ). The IGM is an academic contract research organization that provides evaluation of biomarkers. The center for Medicare and Medicaid Services (CMS) developed Clinical Laboratory Improvement Amendments (CLIA) beginning in 1988, which provides the basis for CLIA certification. The laboratory used was CLIA certified and College of American Pathologists (CAP) accredited. The CAP's accreditation program is an internationally recognized program. CAP assessors visit the UMDNJ laboratory every two years to perform an on-site assessment and evaluation according to CAP standards. For DNA testing laboratories, such as the IGM lab at UMDNJ, CAP evaluates the techniques that the technicians use and ensures that they are complying with or exceeding national regulations (DNA Junction, 2012). UMDNJ affiliates with hospitals and academic institutions throughout the region and maintains an ongoing association with the neuroendocrine lab at the University of Delaware.

All subject samples were labeled with a code number to protect the identity of participants. Samples received at the IGM laboratory were prepared for analysis using a strict protocol of incubation and ethanol rinses. Samples were quantified for DNA content and then diluted to appropriate concentration for analysis. UMDNJ laboratory personnel had specific probes and primers already available to amplify the region surrounding the Val66Met SNP. The genotyping was completed using a Taqman probe assay for the presence or absence of the Val66Met polymorphism. All testing was run in triplicate, and any variations in results for one subject's sample prompted a quality check with samples run at varying dilutions for that subject. Three of the subjects' samples needed to be repeated for the current study. All cost associated with testing and materials were underwritten by the University of Delaware. After the analysis, all saliva samples were destroyed.

Plan for Data Analysis

The methods of data analysis were selected due to their robustness in view of the sample size, possible deviations from normal distribution, and variance issues. Data analysis was limited to simple techniques that could be completed using Statistical Package for the Social Sciences (SPSS) version 20. A theoretical approach was taken to assure that variables were conceptually intact when it was necessary to collapse categories or dichotomize for analysis.

The primary research question for this study was as follows: Is there a significant relationship between symptom occurrence and severity in breast cancer survivors and the presence or absence of the BDNF Val66Met SNP? This question was first analyzed using a Fisher's exact test followed by logistic regression analysis.

The first secondary research question was as follows: What are the occurrence and severity of symptoms among breast cancer survivors as reported on the TRSC after the

completion of their cancer therapy regimen? Frequencies and descriptive statistics were used to address this question. The standard descriptive statistics profile was used (including mean, median, and standard deviation; standard error of the mean; and minimum and maximum; Leech, Barrett, & Morgan, 2008).

The second secondary research question was as follows: Are there significant relationships among symptom occurrence and severity, daily activities ratings, and health-related quality of life and selected demographic and other variables (age, ethnicity, education, treatment method, and time since treatment)? This question was addressed using Fisher's exact test and linear regression.

The third secondary research question was as follows: What self-care methods are used by survivors to alleviate symptoms, and what are the survivors' perceptions of the usefulness of these self-care methods? This question was addressed by descriptive statistics and content analysis according to standard guidelines for organizing according to themes and concepts.

Overview of Robustness of Data for Analysis

Several possible selection biases were explored to examine the robustness of the data. As previously discussed, missing data in Phase 1 was an issue. Fortunately, there were no statistically significant TRSC score differences between the subjects with at least one item missing on the TRSC and the 135 subjects with no missing data (Levene's test for equality of variances $p = 0.010$, t -test for equality of means $p = 0.002$). There were no missing data for Phase 2 subjects. Standard checking procedures for data entry were used to avoid missing data in processing. Polit and Beck (2008) provided a framework for designing a quantitative analysis strategy from data collection through interpretation.

Another possible bias was whether or not the subject was interested in participating in Phase 2 of the study. It is possible that there could be something unique about those subjects. However, there were no differences in age or ethnicity between the Phase 1-only subjects and those who were willing to continue to Phase 2, if selected. One finding was that a larger percentage (56%) of the initial deployment respondents ($n = 82$) agreed to participate in Phase 2, while only 37% of the subsequent deployment respondents agreed to participate in Phase 2. The simple explanation seems to be that the initial group was engaged and ready to participate fully, showing enthusiasm by replying within a week of the deployment. In contrast, the remainder of the respondents came through some concerted recruitment efforts over a period of more than two months and may have been less enthusiastic about participation. The methods of analysis were selected due to their robustness in view of possible deviations from normal distribution and variance.

Missing data were a concern for this study that needed to be carefully considered when approaching analysis. Technical problems with the initial survey deployment resulted in the first 82 of the 214 respondents not being offered the first five questions on the survey due to an error in skip logic. A problem with the way the electronic administration prompted for responses to questions left blank may have added to the number of individuals not responding to the complete survey. Item one of the on-line surveys was the eligibility screening question, and items 2-26 were the TRSC. One hundred and ninety-five individuals provided answers to at least 15 of the first 25 items (the entire TRSC). Employment of a mean scale score enabled the use of the responses from all 195 subjects for the TRSC. The decision to use a mean scale score was verified by Levene's test and a t -test, both of which demonstrated no significant differences between the scores of those who had missing data and those respondents who had no missing

data. One-hundred and seventy-five subjects provided sufficient data for the DARS and HRQOL-LASA, as well as for the Subject Characteristics and Health Form. Subject characteristics and health information were the most often missed items, perhaps due to the sensitive nature of the questions and the fact that they came at the end of the survey. There were 40 participants who had nearly complete data and 135 individuals who had complete data, for a total of 175 providing sufficient subject characteristics and health information for analysis for the final three portions (DARS, HRQOL-LASA, Subject Characteristics and Health Form) of the on-line survey.

Originally, the survey instrument was designed by the researcher as one continuous document with a button at the end following item 50 that allowed the study participant to submit results. The Webmaster consultant advised that it would be frustrating to the subjects to need to return scroll through multiple screens to fill in missing items. The on-line survey was adapted in such a manner that page breaks were determined based on what was visible on a single screen. After participants finished each survey page, any item(s) left blank were marked with an asterisk as mandatory, and respondents were prompted to complete the items marked by the asterisk before moving from the page. This was designed for ease of review, but also apparently contributed to a tendency for the respondents to quit the entire survey at the end of a page rather than respond to the prompts to fill in items left blank.

Chapter IV

Results

The purpose of this study was to explore how breast cancer survivors described their treatment experience and how their symptom management was impacted through the presence or absence of the BDNF Val66Met SNP. The results obtained were significant in several areas, from both Phase 1 and Phase 2. This chapter presents the results of the study, including the subject characteristics and the findings for each research question.

The primary aim of the study was to examine the relationship between self-reported symptom occurrence and severity, as measured by the Therapy-Related Symptom Checklist (TRSC) total scores, and the presence or absence of the BDNF Val66Met SNP in breast cancer survivors. The primary research question (RQ) was as follows: Is there a significant relationship between symptom occurrence and severity in breast cancer survivors and the presence or absence of the BDNF Val66Met SNP? Secondary RQs included the following: (a) What are the occurrence and severity of symptoms among breast cancer survivors as reported on the TRSC after the completion of their cancer therapy regimen? (b) Are there significant relationships among symptom occurrence and severity, daily activities ratings, and health-related quality of life and selected demographic and other variables (age, ethnicity, education, type of treatment, and time since completion of treatment)? and (c) What self-care methods are used by survivors to alleviate symptoms, and what are the survivors' perceptions of the usefulness of these self-care methods?

Sample – Phase 1

The sample size for Phase 1 analysis varied for several reasons, as described in Chapter 3. The overall sample for Phase 1 originally consisted of 214 individuals who completed at least some of the 50 items of the on-line survey. Of these 214 respondents, 195 completed sufficient

responses (15 out of 25) to compute a mean scale score for the TRSC, and 175 of these also provided subject characteristics and health information.

Sample Demographics

Sample demographics for the Phase 1 subjects are provided in Table 4.

Table 4

Sample Characteristics – Phase 1 and Phase 2

Variables	Categories	Phase 1 subjects (N = 175) ^a (f ^b , %)	Phase 2 subjects	
			High TRSC (n = 26)	Low TRSC (n = 25)
Age groups	≤50 years	48 (27.4)	9 (36.4)	4 (16.0)
	51-60 years	68 (38.9)	10(38.5)	12 (48.0)
	≥61 years	59 (33.7)	7 (26.9)	9 (36.0)
Ethnic background	White	162 (92.6)	25 (96.2)	25 (100.0)
	African American/Black	6 (3.4)	1 (3.8)	0 (0.0)
	Asian	2 (1.1)	0 (0.0)	0 (0.0)
	Hispanic	3 (1.7)	0 (0.0)	0 (0.0)
	Other	2 (1.1)	0 (0.0)	0 (0.0)
Years of education	High school	42 (24.0)	9 (34.6)	2 (8.0)
	Vocational/Associate's degree	30 (17.1)	6 (23.1)	2 (8.0)
	Bachelor's degree	49 (28.0)	7 (26.9)	11 (44.0)
	Master's/Graduate degree	54 (30.9)	4 (15.4)	10 (40.0)
Treatment	Surgery only	24 (13.7)	0 (0.0)	5 (20.0)
	Radiation only	5 (2.9)	0 (0.0)	1 (4.0)
	Surgery/chemotherapy	38 (21.7)	7 (26.9)	7 (28.0)
	Surgery/radiation	27 (15.4)	1 (3.8)	8 (32.0)
	Surgery/chemo/radiation	81 (46.3)	18 (69.2)	4 (16.0)
Completed treatment	≤ 2 years	42 (26.9)	6 (23.1)	6 (24.0)
	3-4 years	59 (33.7)	10 (38.5)	8 (32.0)
	≥5 years	69 (39.4)	9 (34.6)	11 (44.0)
	Missing	0 (0.0)	1 (3.8)	0 (0.0)

(continued)

Variables	Categories	Phase 1 subjects	Phase 2 subjects	
		(N = 175) ^a (f ^b , %)	High TRSC (n = 26)	Low TRSC (n = 25)
Primary caregiver				
	Self	71 (40.6)	10 (38.5)	12 (48.0)
	Spouse	36 (20.6)	9 (34.6)	4 (16.0)
	Other	4 (2.3)	0 (0.0)	1 (4.0)
	Self/spouse	40 (22.9)	2 (7.7)	4 (16.0)
	Self/other	9 (5.1)	2 (7.7)	3 (12.0)
	Spouse/other	4 (2.3)	1 (3.8)	1 (4.0)
	Self/spouse/other	11 (6.3)	2 (7.7)	0 (0.0)
Children living at home				
	No children	120 (69.4)	18 (69.2)	20 (80.0)
	<6 years	6 (3.5)	1 (3.8)	2 (8.0)
	7-17 years	20 (11.6)	1 (3.8)	2 (8.0)
	18-26 years	15 (8.7)	2 (7.7)	1 (4.0)
	>26 years	4 (2.3)	1 (3.8)	0 (0.0)
	<6 and 7-17 years	3 (1.7)	2 (7.7)	0 (0.0)
	7-17 and 18-26 years	3 (1.7)	1 (3.8)	0 (0.0)
	7-17 and >26 years	1 (0.6)	0 (0.0)	0 (0.0)
	18-26 and >26 years	1 (0.6)	0 (0.0)	0 (0.0)
Other conditions				
	If yes, please specify	0 (0.0)	0 (0.0)	8 (32.0)
	Yes	68 (39.1)	6 (23.1)	0 (0.0)
	No	106 (60.9)	20 (76.9)	17 (68.0)
Taking medications (OTC, herbals, prescriptions, etc.)				
	If yes, please specify	0 (0.0)	21 (80.8)	19 (76.0)
	Yes	147 (84.5)	2 (7.7)	1 (4.0)
	No	27 (15.5)	2 (7.7)	5 (20.0)

^aTwenty of the individuals who responded to the TRSC did not provide demographic information.

^bThe symbol f stands for frequency.

The overwhelming majority of the 175 participants who provided demographic and health information were Caucasian (92.6 %), as compared to the population of the state in which the preponderance of the study participants resided, which was 69% Caucasian, according to the U.S. census data (U.S. Census Bureau, 2010). Nearly all of the study participants had surgery as part of their treatment (92.1%). Almost three fourths of the Phase 1 subjects (72.6%) were over

50 years old. The respondents were highly educated; 58.9% held a bachelor's degree or higher, and an additional 17.1% had vocational training or an associate's degree. A great number of the subjects (73.1%) were three or more years post-treatment and had no other conditions that they felt contributed to symptoms (60.9%). Eighty-four percent of subjects reported taking some type of medication; the survey did not include a question about the frequency of the medication.

Sample - Phase 2

A purposive subsample of 51 Phase 1 participants was chosen for Phase 2 of the study. The subsample of Phase 2 subjects did not reflect any selection biases regarding age, ethnicity, or education. The descriptive statistics profile did not vary from the Phase 1 sample (see Table 1).

Reliability and Validity Assessment

Internal consistency reliability was investigated based on the data from all self-report instruments. The instruments in this study demonstrated internal consistency reliability as evidenced by acceptable Cronbach's alpha levels: the TRSC at 0.91, the DARS at 0.70, the HRQOL-LASA at 0.93, and the SA: SCM at 0.89. Information substantiating validity was included in Chapters 2 and 3.

Primary Research Question

The primary research question for this study was as follows: Is there a significant relationship between symptom occurrence and severity in breast cancer survivors and the presence or absence of the BDNF Val66Met SNP?

Association Between BDNF and TRSC Scores (Phase 2 Data)

Initially, no potential confounders were controlled for in the analysis. In the Phase 2 (enriched) sample, 36% (9 out of 25) of the subjects with a low TRSC score had the Val66Met

SNP, which would be expected in a healthy control sample. In contrast, only 7.7% (2 out of 26) of the subjects with high TRSC scores had the Val66Met SNP. Eight or nine subjects with the Met variant would have been expected to align with the one third that is common in healthy controls. In this sample, before adjusting for potential confounders, the presence of the BDNF Val66 Met SNP variant was significantly associated with low TRSC scores (odds ratio, $OR = 0.148$; 95% confidence interval ($CI [0.028, 0.78]$); Fisher's $p = 0.019$). This means the odds that a subject with the variant has a high TRSC score was 85% lower than the odds for a subject without the variant, ($[0.148-1] \times 100 = -85\%$). The association (lower TRSC scores were related to the presence of the BDNF Val66Met SNP or variant, and higher scores were related to the absence of the variant) was in the opposite direction of what was originally expected based on the literature reviewed.

A possible explanation for these unexpected results was explored. The BDNF literature has suggested that certain biobehavioral symptoms may be more sensitive to the presence or absence of the BDNF variant. The four biobehavioral symptoms included in the TRSC (feeling sluggish, difficulty concentrating, depression, and difficulty sleeping) were considered in a subanalysis to explore further possible relationships between the BDNF variant and TRSC symptom ratings. There were some problems in this approach as the purposive sample design was predicated on the complete TRSC score and not the subscale, but the exploration proceeded with the realization that the violation of the design would need to be taken into consideration. However, there was no relationship demonstrated between the score from four symptoms listed above and the presence or absence of the variant. Consequently, further research is needed to replicate and explain these findings. The frequencies for the sum of the scores for question 14 (feeling sluggish), question 15 (depression), question 16 (difficulty concentrating), and question

23 (difficulty sleeping) were examined. A cutoff score of 7 (a score of 0-7 indicated a low score, while 8-14 indicated a high score) was chosen for the purpose of analysis. The results were not significant: There is no relationship demonstrated between the score from these four symptoms and the presence or absence of the variant.

Adjustment for Possible Confounders

Logistic regression was conducted to investigate the association between the BDNF Val66Met SNP variant and TRSC scores. To control for potential confounders, the Phase 2 (enriched) sample of high-scoring (> 23 , $n = 26$) and low-scoring (< 14 , $n = 25$) subjects was used. A stepwise selection procedure was used to build a logistic regression model of high TRSC scores. The variable BDNF was forced to remain in the model during the selection procedure regardless of its degree of statistical significance. Information concerning the final model is in Table 5. The potential independent variables investigated were age, education, type of treatment, and time since treatment completion. Ethnicity was not included as there was only one nonwhite subject (1 out of 51). Only two variables were significantly associated with high TRSC scores: treatment type (defined as chemotherapy versus no chemotherapy) and education (defined as high level, bachelor's degree or higher, versus low level, less than a bachelor's degree). After adjusting for treatment type and education, the BDNF genotype did not have a significant effect on high TRSC scores ($OR = 0.27$; $95\% CI$, [0.036, 1.98]; $p = 0.196$). Thus, after adjusting for confounders, the odds that a subject with the variant has high TRSC score was 73% lower than the odds for a subject without the variant, ($[0.27-1] \times 100 = -73\%$); however, this reduction in the odds was not statistically significant. With the small sample, power was an issue.

Table 5

Final Logistic Regression Model of High TRSC Scores in Phase 2 (Enriched) Breast Cancer Survivor Sample That Included Only Subjects with High Scores (≥ 23 , $n = 26$) and Subjects with Low Scores (≤ 14 , $n = 25$)

Variable	Odds ratios	95% CI lower	95% CI upper	p value
Val66Met SNP present	0.27	0.036	1.981	0.196
Chemotherapy included as part of treatment	29.29	2.812	305.096	0.005
High level of education (bachelor's degree and higher)	0.14	0.025	0.798	0.027

Note. The Hosmer and Lemeshow Goodness of Fit Test results (Chi-square = 2.4, $p = .662$) provided evidence that the model fit well.

Table 5 also shows the sizes of the effects (odds ratios) of treatment type and education on the odds of having a high TRSC score. After adjusting for education and BDNF genotype, the odds of having a high TRSC score were significantly and substantially increased (almost by 3000%) if the type of treatment included chemotherapy ($OR = 29.29$, $p = 0.005$). After adjusting for treatment type and BDNF genotype, the odds of having a high TRSC score were 86% lower in subjects with a high education level ($OR = 0.14$, $p = 0.027$).

Secondary Research Questions

Three secondary research questions were addressed by this study. Each question will be discussed in a separate section, but tables and information presented in one section may have a bearing on the other questions.

First Secondary Research Question

The first secondary research question was as follows: What is the occurrence and severity of symptoms among breast cancer survivors as reported on the TRSC after the completion of their cancer therapy regimen? Table 6 shows the symptom occurrence and severity as measured

by the TRSC for the Phase 1 sample. Note that Table 6 and several other tables reflect the fourteen subscales of the TRSC.

Table 6

TRSC Scores of Phase 1 Subjects - Percent Distributions on Symptom Severity and on Symptom Occurrence (N =195)

TRSC symptom items by subscales/clusters	Degree of Severity ^c					Mean Severity	Percent Occurrence	Total N
	0	1	2	3	4			
1. Fatigue^a								
Feeling sluggish	41 (21.0)	63 (32.3)	62 (31.8)	21(10.8)	8 (4.1)	1.45	79.0	195
Depression	74 (37.9)	71(36.4)	38 (19.5)	11 (5.6)	1 (0.5)	0.94	62.1	195
Difficulty concentrating	56 (28.7)	69 (35.4)	56 (28.7)	11 (5.6)	3 (1.5)	1.16	71.3	195
Difficulty sleeping	55 (30.1)	41 (22.4)	63 (34.4)	19 (10.4)	5 (2.7)	1.33	69.9	183
2. Eating^a								
Taste change	73 (52.1)	25 (17.9)	31 (22.1)	9 (6.4)	2 (1.4)	0.87	47.9	140
Loss of appetite	85 (60.7)	25 (17.9)	26 (18.6)	4 (2.9)	0 (0.0)	0.64	39.3	140
Weight loss	106 (75.7)	20 (14.3)	14 (10.0)	0 (0.0)	0 (0.0)	0.34	24.3	140
Difficulty swallowing	161 (82.6)	25 (12.8)	8 (4.1)	1 (0.5)	0 (0.0)	0.23	17.4	195
3. Oropharyngeal^a								
Sore mouth	143 (73.3)	24 (12.3)	23 (11.8)	4 (2.1)	1 (0.5)	0.44	26.7	195
Sore throat	169 (86.7)	22 (11.3)	3 (1.5)	1 (0.5)	0 (0.0)	0.16	13.3	195
Jaw pain	179 (91.8)	10 (5.1)	6 (3.1)	0 (0.0)	0 (0.0)	0.11	8.2	195
4. Nausea^a								
Nausea	81 (57.9)	35 (25.0)	18 (12.9)	5 (3.6)	1 (0.7)	0.64	42.1	140
Vomiting	113 (80.7)	17 (12.1)	7 (5.0)	2 (1.4)	1 (0.7)	0.29	19.3	140
5. Fever^a								
Fever	161 (84.3)	25 (13.1)	4 (2.1)	1 (0.5)	0 (0.0)	0.19	15.7	191
Bruising	133 (69.6)	40 (20.9)	16 (8.4)	2 (1.0)	0 (0.0)	0.41	30.4	191
6. Respiratory^a								
Cough	162 (83.1)	27 (13.8)	6 (3.1)	0 (0.0)	0 (0.0)	0.20	16.9	195
Shortness of breath	132 (67.7)	48 (24.6)	14 (7.2)	0 (0.0)	1 (0.5)	0.41	32.3	195
7. Pain^b								
Pain ^b	79 (43.2)	47 (25.7)	44 (24.0)	8 (4.4)	5 (2.7)	0.98	56.8	183
8. Numbness in fingers and/or toes^b								
Numbness in fingers and/or toes ^b	100 (51.3)	43 (22.1)	36 (18.5)	15 (7.7)	1 (0.5)	0.84	48.7	195
9. Bleeding^b								
Bleeding ^b	167 (87.4)	18 (9.4)	5 (2.6)	1 (0.5)	0 (0.0)	0.16	12.6	191
10. Hair loss^b								
Hair loss ^b	83 (43.5)	24 (12.6)	8 (4.2)	28 (14.7)	48 (25.1)	1.65	56.5	191
11. Skin changes^b								
Skin changes ^b	72 (37.7)	58 (30.4)	55 (28.8)	3 (1.6)	3 (1.6)	0.99	62.3	191
12. Constipation^b								
Constipation ^b	90 (49.2)	34 (18.6)	42 (23.0)	13 (7.1)	4 (2.2)	0.95	50.8	183
13. Soreness in vein^b								
Soreness in vein ^b	144 (78.7)	28 (15.3)	7 (3.8)	4 (2.2)	0 (0.0)	0.30	21.3	183
14. Decreased interest in sexual activity^b								
Decreased interest in sexual activity ^b	50 (27.3)	43 (23.5)	40 (21.9)	34 (18.6)	16 (8.7)	1.58	72.7	183

^aTRSC multiple item subscales/clusters.

^bTRSC single item subscale.

^cTRSC rating: 0 = None/No Symptom; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very Severe.

Feeling sluggish was the most commonly occurring symptom, with 79% of Phase 1 subjects indicating that they had a problem with this symptom. The other three symptoms in the

Fatigue symptom cluster were rated in the top six in terms of occurrence (difficulty concentrating, 71%, difficulty sleeping, 70%, depression, 62%). It is noted that 40% or more (*range* 42.1% to 79%) reported the occurrence of 11 TRSC symptoms on the 25-item checklist. The least frequently reported symptoms was jaw pain at 8%, and it also had the lowest mean severity score at 0.11. Hair loss had the highest mean severity score (1.65). Table 7 shows the occurrence and percent distribution by severity of TRSC scores for Phase 2 participants based on their whether the Val66Met SNP was present or absent.

Table 7

Phase 2 TRSC Scores - Present Versus Absent BDNF SNP and Percent Distributions on Symptom Severity^c and on Symptom Occurrence (n = 51)

TRSC total score and items by symptoms/subscales	Val/Val (BDNF SNP absent) (n = 40)								Val/Met or Met/Met present (n = 11)									
	0	1	2	3	4	Mean ^d	%	Severity	Occur	0	1	2	3	4	Mean ^d	%	Severity	Occur
1. Fatigue^a																		
Feeling sluggish	15.0	27.5	35.0	15.0	7.5	1.73	85.0	36.4	45.5	0.0	18.2	0.0	1.00	63.6				
Depression	27.5	35.0	30.0	5.0	2.5	1.20	72.5	45.5	36.4	18.2	0.0	0.0	0.73	54.5				
Difficulty concentrating	12.5	42.5	32.5	10.0	2.5	1.47	87.5	36.4	36.4	27.3	0.0	0.0	0.91	63.6				
Difficulty sleeping	30.0	15.0	40.0	7.5	7.5	1.48	70.0	36.4	18.2	36.4	9.1	0.0	1.18	63.6				
2. Eating^a																		
Taste change	43.2	18.9	24.3	8.1	5.4	1.14	56.8	80.0	0.0	10.0	10.0	0.0	0.50	20.0				
Loss of appetite	45.9	27.0	24.3	2.7	0.0	0.84	54.1	80.0	0.0	10.0	10.0	0.0	0.50	20.0				
Weight loss	70.3	18.9	10.8	0.0	0.0	0.41	29.7	70.0	30.0	0.0	0.0	0.0	0.30	30.0				
Difficulty swallowing	80.0	12.5	5.0	2.5	0.0	0.30	20.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0				
3. Oropharyngeal^a																		
Sore mouth	72.5	12.5	12.5	2.5	0.0	0.45	27.5	81.8	18.2	0.0	0.0	0.0	0.18	18.2				
Sore throat	87.5	10.0	0.0	2.5	0.0	0.18	12.5	81.8	18.2	0.0	0.0	0.0	0.18	18.2				
Jaw pain	87.5	10.0	2.5	0.0	0.0	0.15	12.5	90.9	0.0	9.1	0.0	0.0	0.18	9.1				
4. Nausea^a																		
Nausea	43.2	27.0	21.6	8.1	0.0	0.95	56.8	80.0	10.0	10.0	0.0	0.0	0.30	20.0				
Vomiting	73.0	13.5	10.8	2.7	0.0	0.43	27.0	80.0	10.0	10.0	0.0	0.0	0.30	20.0				
5. Fever^a																		
Fever	80.0	17.5	2.5	0.0	0.0	0.23	20.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0				
Bruising	60.0	27.5	12.5	0.0	0.0	0.53	40.0	90.9	0.0	9.1	0.0	0.0	0.18	9.1				
6. Respiratory^a																		
Cough	82.5	17.5	0.0	0.0	0.0	0.18	17.5	90.9	9.1	0.0	0.0	0.0	0.09	9.1				
Shortness of breath	62.5	30.0	7.5	0.0	0.0	0.45	37.5	72.7	27.3	0.0	0.0	0.0	0.27	27.3				
7. Pain^b	37.5	20.0	40.0	2.5	0.0	1.07	62.5	36.4	36.4	18.2	9.1	0.0	1.00	63.6				
8. Numbness in fingers and/or toes^b	50.0	17.5	22.5	10.0	0.0	0.93	50.0	54.5	18.2	9.1	9.1	9.1	1.00	45.5				
9. Bleeding^b	85.0	15.0	0.0	0.0	0.0	0.15	15.0	90.9	9.1	0.0	0.0	0.0	0.09	9.1				
10. Hair loss^b	27.5	20.0	2.5	17.5	32.5	2.07	72.5	81.8	0.0	0.0	0.0	18.2	0.73	18.2				
11. Skin Changes^b	30.0	37.5	30.0	0.0	2.5	1.08	70.0	72.7	18.2	9.1	0.0	0.0	0.36	27.3				
12. Constipation^b	47.5	17.5	22.5	10.0	2.5	1.02	52.5	63.6	18.2	18.2	0.0	0.0	0.55	36.4				
13. Soreness in vein^b	72.5	20.0	2.5	5.0	0.0	0.40	27.5	90.9	0.0	9.1	0.0	0.0	0.18	9.1				
14. Decreased interest in sexual activity^b	17.5	25.0	22.5	25.0	10.0	1.85	82.5	45.5	18.2	18.2	9.1	9.1	1.18	54.5				

^aTRSC multiple item subscales/clusters.

^bTRSC single item subscale.

^cTRSC rating: 0 = None/No Symptom; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very Severe

^dMeans were calculated in a restricted or “enriched” sample.

In Table 7, a pattern emerged that (compared to the “present” group, which reported low occurrence) the “absent” BDNF SNP group showed that 50% or more of the subjects (range 51.3% to 87.2%) reported the occurrence of 12 TRSC symptoms on the 25-item checklist (four symptoms were on the Fatigue subscale; two on the Eating subscale; one on the Nausea subscale;

and one each on the single-item subscales of Pain, Numbness, Hair Loss, Skin changes, Decreased Interest in Sexual Activity, and Constipation). Moreover, in the absent group, higher mean severity (*range* 2.10 to 1.00) on those symptoms was reported. It is important to note that this mean value included those with 0 values (*no symptoms*). Thus, if the mean severity calculations included only those who experienced the symptom, the mean severity for that symptom would be one point higher, reflecting moderate to severe mean severity on the TRSC. Power is an issue due to the low number of survivors who had the Met allele.

To further explore the results in Table 7, two significant variables (chemotherapy use and education) were considered along with the gene variant. Table 8 illustrates the relationship in the Phase 2 subjects regarding chemotherapy use, BDNF presence or absence, and TRSC scores. This descriptive analysis was based on the purposive sample of 51 Phase 2 subjects, as described in Methods. In the present exploratory analysis, TRSC scores greater than 23 were high scores; scores less than 23 were low scores.

Table 8

Frequency and Percentage of Phase 2 Subjects Having a High TRSC Score (> 23) Based on Treatment Type and Presence or Absence of BDNF Val66Met SNP (n = 51)

	BDNF Val66Met SNP present	BDNF Val66Met SNP absent
Chemotherapy as part of treatment	2/5 (40%)	23/31 (74%)
No chemotherapy as part of treatment	0/6 (0%)	1/9 (11%)

Each cell illustrates the proportion of high TRSC scores as designated by the column and row headings. For example, cell 1.1 displays the results for the number of survivors who would simultaneously have the variant, had chemotherapy as part of their treatment, and earned a high TRSC score. Thus, referring to Table 7 for all the specific symptoms, Table 8 shows that 74% of

subjects with high symptom occurrence and severity on the TRSC were on chemotherapy and had an absent BDNF Val66Met SNP.

Table 9 shows Phase 2 subjects and the relationships among education, BDNF presence or absence, and high TRSC scores.

Table 9

Frequency and Percentage of Phase 2 Subjects Having a High TRSC Score (> 23) Based on Education Level and Presence or Absence of BDNF Val66Met SNP (n = 51)

	BDNF Val66Met SNP present	BDNF Val66Met SNP absent
High level of education	1/9 (11%)	10/23 (43%)
Low level of education	1/2 (50%)	14/17 (85%)

The highest proportion of survivors as illustrated in the table is in cell 2.2. The values include the survivors who would simultaneously not have the variant, held less than a bachelor’s degree, and earned a high TRSC score. Again, referring to Table 7, Table 9 shows that 85% of subjects with high symptom occurrence and severity on the TRSC had low education levels and absent BDNF Val66Met SNP.

Second Secondary Research Question

The second secondary research question was as follows: Are there significant relationships among symptom occurrence and severity, daily activities ratings, and health-related quality of life and selected demographic and other variables (age, ethnicity, education, treatment method, and time since treatment)? This question was addressed using correlation and regression.

Relationships between the instruments. Since the DARS and the HRQOL-LASA are moderately correlated (Pearson’s $r = -0.42$; $p < 0.001$), they were not included together in linear

regression models due to potential colinearity problems. Linear regression was conducted to assess whether the DARS or HRQOL-LASA were associated with TRSC score.

Health-related quality of life. Only HRQOL-LASA ($p < 0.001$) and chemotherapy ($p < 0.001$) have a significant relationship with TRSC. Table 10 displays the final model.

Table 10

Regression Coefficients of Final Linear Model of TRSC Scores –Not Including DARS (N = 175)

Variable	Regression coefficient ^a	95% CI lower	95% CI upper	p value
HRQOL-LASA ^b	-0.114	-0.154	-0.075	<0.001
Chemotherapy included as part of treatment	0.393	0.261	0.526	<0.001

Note. The model was built using a backward selection procedure that did not include the DARS in the initial set of investigated independent variables.

^aRegression coefficients are unstandardized *B*.

^bHealth-Related Quality of Life – Linear Analog Self-Assessment (HRQOL-LASA).

Health-related quality of life-linear analogue scale assessment (HR-QOL). Table 10 shows that, after adjusting for chemotherapy, a one unit increase in the quality of life score was significantly associated with a reduction of 0.114 in the TRSC score, 95% *CI* [-0.154, -0.075]. After adjusting for quality of life, the mean TRSC score for the group of subjects who reported receiving chemotherapy was increased by 0.393, compared to the group who did not receive chemotherapy as a part of their treatment regimen. After adjusting for both quality of life and chemotherapy, the variables of age, education, and time since treatment were not significantly associated with TRSC scores, and they were eliminated from the final model. Additional analyses showed that conclusions were essentially the same when all categories of age, education, and time were included in the regression model in place of the dichotomized variables.

Daily activities. Only the DARS ($p < 0.001$), chemotherapy ($p < 0.001$), and age ($p = 0.007$) were significantly associated with the TRSC. Table 11 displays the model coefficients.

Table 11

Regression Coefficients of Final Linear Model of TRSC Scores – Not Including HRQOL-LASA (N = 175)

Variable	Regression ^a coefficient	95% CI lower	95% CI upper	p value
DARS ^b	0.102	0.069	0.134	<0.001
Chemotherapy included as part of treatment	0.382	0.252	0.512	<0.001
Age ^c	-0.106	-0.183	-0.029	0.007

Note. The model was built using backward selection procedure that did not include the HRQOL-LASA in the initial set of investigated independent variables ($N = 175$).

^aRegression coefficients are unstandardized B.

^bDaily Activities Rating Scale (DARS).

^cAge was a dichotomized variable with individuals above and below 50 years old.

After adjusting for chemotherapy treatment and age, a 1-unit increase in the Daily Activities Rating Scale (DARS) score was significantly associated with an increase of 0.102 in TRSC score, 95% CI [0.069, 0.34]. See Table 11 for details. After adjusting for daily activities and age, the mean TRSC score for the group of subjects who reported receiving chemotherapy increased by 0.382, compared to the group who did not receive chemotherapy as a part of their treatment regimen, 95% CI [0.252, 0.512]. Furthermore, after adjusting for chemotherapy and daily activities, older subjects had a reduction of their TRSC score of 0.106 as compared to the younger subjects (see Table 11). The results obtained after adjusting for daily activities, age, and chemotherapy revealed that education and time since treatment were not significantly associated with TRSC scores, and they were dropped from the final model (see Table 11).

Third Secondary Research Question

The third secondary research question was as follows: What self-care methods are used by survivors to alleviate symptoms, and what are the survivors' perceptions of the usefulness of these self-care methods? This question was addressed by descriptive statistics and content analysis according to standard guidelines for organizing according to themes and concepts (Krippendorff, 2004; P. D. Williams et al., 2009; 2010 a, b). The categories of self-care established in the studies of P. D. Williams et al. (2006; 2010 a, b) were used: (a) diet/nutrition/lifestyle, (b) mind/body control, (c) herbs vitamins/complementary therapies, (d) medication, (e) other, and (f) doing nothing. The diet/nutrition/lifestyle categories included such self-care actions as reading to alleviate difficulty sleeping, eating fiber for constipation, and playing tennis to cope with depression. The mind/body control category included "working through it" to alleviate depression, "pretend I was interested" for the symptom of decreased interest in sexual activity, and "listening to music" that one participant listed as the alleviation method for each of the symptoms she rated. Herbs/vitamins/complementary therapies included such methods as acupuncture (one subject) and sesame oil. The medication category included both prescription and over-the-counter drugs. The "other" category seemed to collect very symptom-specific interventions, such as the use of lotions for skin changes or going to a physician specialist that related to the particular symptom. "Doing nothing" was the most frequent response for six of the symptoms. Table 12 lists the frequency of use of the six categories of self-care methods that were utilized by survivors to alleviate symptoms as grouped in the subscales.

Table 12

Frequencies of Symptom Alleviation: Self-care Methods (SA: SCM) by Categories (n = 51)

TRSC items by symptomsubscales/clusters	Self-care categories ^a						Rank of most often reported self-care for symptoms
	A	B	C	D	E	F	
1. Fatigue^d							
Feeling sluggish	30 ^f	4	2	4	0	7	1
Depression	7	14	0	11	4	6	
Difficulty concentrating	14	8	0	3	2	18 ^k	4 ^b
Difficulty sleeping	8	4	1	15	0	10	
2. Eating^d							
Taste change	17 ^f	0	0	2	0	5	5 ^c
Loss of appetite	10	0	0	1	0	10	
Weight loss	4	0	0	0	0	9	
Difficulty swallowing	1	0	0	1	1	5	
3. Oropharynx^d							
Sore mouth	3	0	0	4	3	3	
Sore throat	3	0	0	2	0	3	
Jaw pain	2	0	0	0	1	3	
4. Nausea^d							
Nausea	8	0	1	18 ^g	2	1	4 ^b
Vomiting	1	1	0	6	1	2	
5. Fever^d							
Fever	0	0	0	5	0	3	
Bruising	3	0	1	1	0	12	
6. Respiratory^d							
Cough	3	0	0	1	1	3	
Shortness of breath	6	4	0	1	0	8	
7. Pain^e	6	0	2	25 ^g	2	3	2
8. Numbness in fingers and/or toes^c	6	0	2	5	3	10	
9. Bleeding^c	1	0	0	0	1	5	
10. Hair loss^e	14	1	0	1	2	15	
11. Skin changes^e	3	0	2	5	17 ^h	8	5 ^c
12. Constipation^c	7	0	0	12	1	3	
13. Soreness in vein^e	0	0	0	1	3	7	
14. Decreased interest in sexual activity^e	1	7	0	4	2	24 ^k	3

^a Self-care categories: A. Diet/nutrition/lifestyle; B. Mind/body control; C. Herbs/vitamins/complementary therapy ; D. Medications; E. Other, and F. Do nothing.

^{b,c}These items were tied in the ranking.

^dTRSC multiple item subscales/clusters.

^eTRSC single item subscale.

^f “Diet/nutrition/lifestyle” was most frequently used for *Feeling Sluggish* and *Taste Change*

^g “Medications” were most frequently used for *Nausea* and *Pain*

^h “Other” self-care alleviation methods (usually lotion) were most often used for *Skin changes*

^k “Do nothing” was the most common response for *Difficulty concentrating* and *Decreased interest in sexual activity*

The subjects could identify more than one symptom alleviation method per symptom.

The top-ranked symptom alleviation method category used was diet/nutrition/lifestyle for the

symptom of depression (30 subjects out of 47 used self-care for this symptom). Second-ranked

was the medications category for pain (25 out of 38). In third place was “do nothing” (24 out of 38) for decreased interest in sexual activity. Tied for the fourth most common alleviation method, with 18 responses each, was “do nothing” for difficulty concentrating (18 out of 45) and medications for nausea (18 out of 30). Seventeen responses each earned a tied ranking for fifth place for the diet/nutrition/lifestyle category for the taste change symptom (17 responses out of 24) and “other” (most often some version of applying lotion or moisturizer) for skin changes (17 responses out of 35).

“Medication” was the leading alleviation method for difficulty sleeping (39% of the responses). Herbs/vitamins/complementary therapy was the least often used category of any alleviation method with only one or two subjects indicating that they used that alleviation method for each of seven symptoms (two subjects listed feeling sluggish, 4%; two listed pain, 5%; two listed numbness in fingers and toes, 8%; two listed skin changes, 6%; one listed difficulty sleeping, 3%; one listed nausea, 3%; and one listed bruising, 6%).

Biobehavioral Symptom Cluster. The biobehavioral TRSC symptom cluster of Fatigue includes four symptoms (feeling sluggish, depression, difficulty concentrating, difficulty sleeping). The most common and highest rated alleviation methods for feeling sluggish were in the diet/nutrition/lifestyle category, with “rest” and “exercise” listed as frequent responses. This also was the symptom for which the greatest number of responses for alleviation methods was reported. For depression, mind/body control techniques, such as “remaining positive” or “prayer,” were the most common, with “medications” as a close second. For difficulty concentrating, the most common response was “do nothing” (40% of the responses), with lifestyle changes, such as “making a list,” the next most frequent at 31% of the responses for that symptom. As mentioned, “medication” was often used for difficulty sleeping.

Table 13 displays the frequency of survivors' use of self-care methods in four categories, from the lowest frequency category (*seldom done*) to the highest frequency category (*very often done*). For each symptom, the table illustrates survivors' perceptions of the usefulness of whatever self-care method(s) they chose, as indicated by a positive response to the survey question, "Did it help?"

Table 13

Frequencies of Symptom Alleviation Occurrence and Usefulness (n = 51)

	Alleviation occurrence ^a				Helped alleviate
	1	2	3	4	
1. Fatigue^b					
Feeling sluggish	0	5	18	8	27 (87.1%)
Depression	0	4	11	12	25 (92.6%)
Difficulty concentrating	0	4	10	7	19 (90.5%)
Difficulty sleeping	0	4	5	12	20 (95.2%)
2. Eating^b					
Taste change	1	1	7	10	18 (94.7%)
Loss of appetite	1	1	5	3	8 (88.9%)
Weight loss	0	1	1	2	2 (50.0%)
Difficulty swallowing	0	1	0	2	2 (100.0%)
3. Oropharynx^b					
Sore mouth	1	2	2	4	9 (100.0%)
Sore throat	0	2	1	2	4 (100.0%)
Jaw pain	0	0	1	1	3 (100.0%)
4. Nausea^b					
Nausea	0	10	7	7	21 (91.3%)
Vomiting	0	5	2	2	8 (100.0%)
5. Fever^b					
Fever	1	2	1	1	5 (100.0%)
Bruising	1	1	1	1	3 (75.0%)
6. Respiratory^b					
Cough	1	2	1	0	4 (100.0%)
Shortness of breath	1	2	5	0	9 (100.0%)
7. Pain^c	4	2	11	6	22 (95.7%)
8. Numbness in fingers and/or toes^c	2	3	2	5	11 (84.6%)
9. Bleeding^c	0	1	0	0	1 (100.0%)
10. Hair loss^c	2	1	2	8	14 (93.3%)
11. Skin changes^c	0	1	9	14	18 (81.8%)
12. Constipation^c	3	5	4	7	19 (95.0%)
13. Soreness in vein^c	0	2	2	0	1 (25.0%)
14. Decreased interest in sexual activity^c	2	6	3	1	9 (81.8%)

^aAlleviation occurrence: 1. Seldom done; 2. Done occasionally; 3. Often done; 4. Very often done.

^bTRSC multiple item subscales/clusters.

^cTRSC single item subscale.

There were nine symptoms that were alleviated 100% of the time, regardless of the method of self-care or the frequency with which it was performed (difficulty swallowing, sore

mouth, sore throat, jaw pain, vomiting, fever, cough, shortness of breath, and bleeding). The lowest effectiveness percentage was 25% for soreness in vein. While this table gives a snapshot of the effectiveness of the self-care methods used for symptom alleviation, a constructed case using a qualitative approach is described below.

A Constructed Case Example

A woman who might be expected to have a high TRSC score is represented in this constructed case. The woman would have a high school education and be fairly recently out of treatment, between 6 months to a year. She would have had combination therapy that included chemotherapy. The woman with high scores on the TRSC likely would have included additional symptoms, beyond the 25 items listed on the TRSC. Dry mouth and lymphedema were commonly added symptoms. The typical subject with high scores would likely report that the alleviation method was used “very often,” and most self-care methods helped relieve the symptom. However, relief measures that were “seldom done” were still effective.

Summary

Data analyses included logistic and linear regression analyses, Fisher’s exact test, and descriptive and content analyses.

The primary research question examined the relationship between self-reported symptom occurrence and severity as measured by the Therapy-Related Symptom Checklist (TRSC) total scores and the presence or absence of the BDNF Val66Met SNP in breast cancer survivors. Findings showed that lower TRSC scores were significantly associated with the presence of the BDNF Val66Met SNP. However, this relationship did not persist when controlling for the confounders of education and treatment type to the logistic regression model.

Secondary research questions 1-3 were investigated using three additional self-report measures: Daily Activities Rating Scale (DARS), Health-Related Quality of Life - Linear Analogue Self Assessment (HRQOL-LASA), and the Symptom Alleviation: Self-Care Methods (SA: SCM) scale.

With secondary research question 1, a pattern emerged that showed that compared to the present BDNF SNP group, the absent BDNF SNP group showed a greater symptom burden. No conclusions could be made due to lack of power.

With secondary research question 2, logistic regression used five predictors (age, education, type of treatment, time since treatment completed, and BDNF variant). The results showed significant odds ratios for education and for treatment type, suggesting that the odds of having a low TRSC score are increasingly greater as education increases and are diminished if the type of treatment included chemotherapy.

With secondary research question 3, content analysis showed that the most often used self-care symptom alleviation method category was diet/nutrition/lifestyle and the least was herbs/vitamins therapy. The effectiveness of the methods ranged from 25% to 100%, with most responses indicating a high percentage of effectiveness regardless of how often the self-care alleviation method was done. The results of the study are discussed in Chapter 5, along with the conclusions, implications, and recommendations for further study.

Chapter V

Discussion

The primary aim of this study was to examine the relationship between self-reported symptom occurrence and severity as measured by the Therapy-Related Symptom Checklist (TRSC) total scores and the presence or absence of the BDNF Val66Met SNP in breast cancer survivors. Prior to this study, the 25-item TRSC had not been used in conjunction with BDNF genotyping. While the expected result was that higher symptom occurrence and severity scores would align with the presence of the variant, the data analysis revealed that those subjects with the variant absent had higher scores. However, the effect size was small.

With the Secondary Aims, findings revealed that high symptom occurrence and severity on the TRSC was related to problems with activities of daily living (i.e., high scores on the DARS), as well as to low quality of life (i.e., low scores on the HRQOL-LASA). The higher the daily activities rating score, the higher the TRSC score and the lower the quality of life. The results of the analyses suggested that the odds of having a low TRSC score are increasingly greater as the subject's level of education increased and were diminished if the type of treatment included chemotherapy.

The most common self-care method used was diet/nutrition/lifestyle and the least common was herb/vitamins/complementary therapy. The *other* category for alleviation methods yielded mostly symptom-specific measures. A constructed case study representative of the most symptomatic subjects showed a range of self-care methods used. Results indicated that symptom alleviation methods, even those "*seldom done*", were perceived as effective.

Primary Research Question

Prior to the initiation of this study, the researcher made certain assumptions based on the literature review and experience about how the Val66Met SNP was related to ongoing symptoms in breast cancer survivors. Previous employment in oncology and previous research in the course of this degree program led the investigator to believe that the presence of the Val66Met SNP would contribute to a higher symptom score; however, the findings revealed the opposite, with marginal statistical support. A possible explanation for these unexpected results was explored using a subanalysis of the Fatigue subscale. However, there was no relationship demonstrated between the score from the Fatigue subscale and the presence or absence of the variant.

On further review of the BDNF literature, the frequent use of the word *modification*, previously interpreted in favor of the variant being linked to higher symptom scores, now can be understood in its literal sense, meaning simply *a change* (McEwen 2010, 2011). McEwen (2010, 2011) also aptly noted that the ever-changing brain is impacted in ways that make it very difficult to predict what predisposes or influences processes. A literature review of symptom-reporting measures, including the TRSC, noted that “human biology and behavior are complex under normal health states. These complexities are intensified in the context of health risks or adverse health conditions” (Berry, 2011, p. 207). Feder, Nestler, and Charney (2009) reported that the BDNF Val66Met SNP significantly impairs BDNF’s intracellular trafficking, yet other studies have shown that the variant enhances resiliency to chronic stress (Gajewski et al., 2011; Kennedy, Rodriguez, Land, & Raz, 2009; Krishnan et al., 2007; Noble, Billington, Kotz, & Wang, 2011; Qin, Kim, Ratan, Lee, & Cho, 2011; Zivadinov et al., 2007).

According to Feder et al. (2009), the conflicting data underscore the possible multifaceted effects of BDNF in the context of a myriad of other factors that impact resilience. A study by Krishnan et al. (2007) was able to identify distinct variability among murine susceptibility to social defeat. Further investigation provided some evidence that mice with the BDNF polymorphism were more resilient to social defeat and had more interaction time subsequent to the social defeat than the mice with the Val/Val genotype. The investigators encouraged future studies with human subjects based on their findings. A more recent study with rats (Taliaz et al., 2011) that seemed to point to the BDNF Val66Met SNP as contributing to symptoms led this investigator to discount the conclusions of the older study (Krishnan et al., 2007).

There is some evidence in the literature in favor of some type of protective effect for the Met gene variant. In the approximately 700 subjects, studies of healthy individuals (Beste et al., 2009; Gajewski et al., 2011), patients with multiple sclerosis (Zivadinov et al., 2007), and Vietnam veterans (Krueger et al., 2011) found a positive effect of the Met variant. In comparison, there is the preponderance of evidence involving thousands of subjects in studies covering various disease states where the Met variant was linked to a negative effect. The topics of study included Post Traumatic Stress Disorder (PTSD; Frielingsdorf et al., 2010), diabetes (Gray et al., 2006), Parkinson's disease (Ahlskog, 2011), anxiety (Hashimoto, 2007), schizophrenia (Lu & Martiowich, 2008), bipolar disorder (Grande, Fries, Kunz, & Kapczinski, 2010), and major depressive disorder (MDD; Castren et al., 2007; Mata, Thompson & Gotlib, 2010; Terracciano et al., 2011; You et al., 2010). A meta-analysis of adult attention-deficit hyperactivity (ADHD) including almost 1,500 patients and twice that number of controls showed no association with BDNF (Sanchez-Mora et al., 2009).

Consequently, the evidence is mixed about the relationship between symptoms following breast cancer diagnosis and treatment with the presence or absence of the BDNF Val66Met SNP in survivors. More research is needed to examine if the findings of this study could be replicated and to determine the implications.

First Secondary Research Question

Another surprising result was the finding that time since treatment completed had no relationship to the symptom scores. Typically, not much consideration is given to the longer-term survivorship phase for older breast cancer survivors (Crane-Okada et al., 2012). Of high importance is the finding that symptoms are reported even after the end of active treatment in these breast cancer survivors. This finding emphasizes the need for continued symptom assessment and management post-treatment among breast cancer survivors. With timely education and counseling regarding symptom alleviation and self-care strategies specific to symptoms reported on a checklist like the TRSC, suffering may be lessened among breast cancer survivors. In an evidence-based study using the Stetler model, P. D. Williams et al. (2011d) reported a significant impact on quality of life by providing education and support as an intervention in a sample of cancer patients during active treatment. P. D. Williams and co-investigators also tested a pilot intervention comprised of a simple one-hour art-making session with oncology patients. They reported that on two TRSC symptoms, feeling sluggish and difficulty concentrating, the intervention group had significantly lower TRSC scores and salivary cortisol levels than the control group (Mische-Lawson et al., 2012).

A recent study (Kim, Barsevick, Beck, & Dudley, 2012) also identified a psychoneurologic symptom cluster in women receiving treatment for breast cancer. The secondary analysis, using cluster analysis of data on 282 women undergoing chemotherapy or

radiation therapy, identified a symptom cluster of depressed mood, cognitive disturbance, fatigue, insomnia, pain, and decreased functional performance. Moreover, a qualitative study with 18 breast cancer survivors regarding their experience with chemotherapy-related cognitive impairment provided a framework for understanding the patient experience (Myers, 2012). The study raised the issue of how this impairment may impact important decisions, including giving informed consent. In the current study, it is noted that “difficulty concentrating” is the symptom on the TRSC that would be indicative of cognitive problems.

The current study also revealed a high frequency and severity of decreased interest in sexual activity. This merits discussion in view of several recent international qualitative studies focused on issues related to sexuality and breast cancer. A study by Chung and Hwang (2012) conducted in Korea with seven couples where the wife had breast cancer highlighted problems which originated with both partners. One wife felt sorry for her husband, but she did not have any desire because of pain and fear. Her husband sometimes felt annoyed but could not express that to his wife and redirected his sexual energy to playing the saxophone rather than working through the relationship with his wife. This couple reported five years of celibacy. Another study of 18 Iranian men (Nasiri, Taleghani, & Irajpour, 2012) who had wives with breast cancer shared their sexual issues. The men felt they were not informed of what to anticipate, and they were not supported in their efforts to cope with their sexual problems. The participants in that study suffered from sexual frustration, but remained faithful to their ill wives by sexual restraint. Some did not have sexual desire when they saw their wives’ scars and felt pity instead of passion. One man reported that he and his wife had been able to work through their issues and their sexual relationship was much better than before his wife’s treatment for breast cancer. A separate study of Iranian women found that the loss of one or both breasts may lead to altered

body image and decreased feelings of sexual attractiveness and function (Tirgari, Iranmanesh, Fazel, & Kalantarri, 2012). Women with gynecological cancer in a Brazilian study reported significantly worse sex lives and lower frequency of sexual relations, but felt uncomfortable and did not discuss their symptoms with their oncologists (da Silva Lara, de Andrade, Consolo, & Romão, 2012).

Second Secondary Research Question

High symptom occurrence and severity on the TRSC was related to problems with activities of daily living (i.e., high scores on the DARS), as well as to low quality of life (i.e., low scores on the HRQOL-LASA). The analyses suggested that the odds of having a low TRSC score are increasingly greater as education increases and are diminished if the type of treatment included chemotherapy.

As mentioned, P. D. Williams et al. (2011b) reported significant intercorrelations among the variables of symptom occurrence and severity (as measured by the TRSC), daily activities performance (as reported on the DARS), self-care strategies (as reported on the SA: SCM), and health-related quality of life (as measured by the HRQOL-LASA) in a sample of U.S. cancer survivors of varied diagnoses and ethnicities. Similar findings also were reported in a sample population in Puerto Rico (Gonzalez et al., 2011).

Many studies also have reported the high impact of chemotherapy on symptoms, including a recent Norwegian study that found that chemotherapy doubled the number of symptoms reported by the subjects (Hofso, Miaskowski, Bjordal, Cooper, & Rustoen, 2012). The impact of symptoms goes beyond the obvious discomfort, as symptoms may cause uncertainties about prognosis, resulting in additional anxiety and distress that decrease quality of life (Cahill, LoBiondo-Wood, Bergstrom, & Armstrong, 2012). Difficulty sleeping is a common

and disturbing symptom (Erickson & Berger, 2011) that affects various physiological pathways (Wu et al., 2012).

Parallels with Alzheimer's Disease (AD) and impact of education on symptoms. One of the most unexpected findings in the current study was the impact of education. A great deal of literature exists on the effect of level of education attained by subjects on the symptoms of AD. There are a number of parallels between the current study and what has been previously discussed in the AD literature. A concept called cognitive reserve may have some applicability as to why educated subjects in the current study were inclined to less frequently identify symptoms, and tended to perceive the symptoms that they did identify as less severe. A number of studies have explored this model (Koepsell et al., 2008; Paradise, Cooper, & Livingston, 2009; Roe, Xiong, Miller, & Morris, 2007; Roselli et al., 2009).

The importance of understanding the underlying physiology of AD would be of considerable value to society (Brayne et al., 2010). Five primary physiological areas, or biomarkers, have been studied in relationship to symptoms in AD and the relationship to education: cortical thickness (Seo et al., 2011), regional cerebral blood flow (Chiu, Lee, Hsiao, & Pai, 2004), dendritic plaques or tangles (Bennett et al., 2003), amyloid load (Roe et al., 2008; Vemuri et al., 2011), and genetic influence. Of particular interest for this discussion is the genetic influence.

The genetic variant most often studied in relationship to AD symptoms is apolipoprotein. To estimate the effect of education on the risk of AD symptoms, a Norwegian study enrolled 373 patients diagnosed with AD and 559 healthy control individuals (without first degree relatives with known dementia) in a case-control study that was conducted over three years between 2003 and 2006. All individuals were genotyped for apolipoprotein (APOE) alleles. The odds ratio for

developing AD was calculated using binary logistic regression. The number of apolipoprotein epsilon 4 (APOE e4) alleles and educational level were entered as covariates. It was found that carriers of one APOE e4 allele had an odds ratio of 4.2, and carriers of two APOE e4 alleles had an odds ratio of 12.4 for developing AD. Thus, these studies indicated that education has a protective effect on the risk of developing clinical AD in a dose-dependent manner (Baek et al., 2011; Sando et al., 2008; Shadlen et al., 2005). Applicability to this study included the fact that a genetic influence may be potentiated by a variable such as education.

A 10-year longitudinal French study began in 1988 and involved nearly 3,000 subjects. A subsample of 600 participants was examined for the APOE e4 allele that has been shown to be a risk factor for dementia. The decrease in the Mini-Mental Status Examination score (MMSE) that was initially associated with the presence of the APOE e4 allele disappeared when adjusted for education (Winnock et al., 2002).

The AD literature also explores the social or coping support aspect of education that has been the focus of a number of large studies. A 3-year study conducted in a biracial community sample of older adults ($N = 3,097$) found that education and literacy may be protective factors against cognitive dysfunction and attenuated the effect of race (Sachs-Ericsson & Blazer, 2005). Individuals with higher education attainment may maintain better health and hygiene and be exposed to richer environments, in turn delaying the onset of symptoms or being better able to cope with symptoms (DenBesten, 2009). A cross sectional study of aging individuals (ages 71 - 87 with 74% female) free from dementia ($N = 951$) suggested that education was one of the most-robust proxy measures of cognitive reserve (Jefferson et al., 2011). In a community south of Chicago, over 10,000 older community members were enrolled and baseline data were collected. The data included four tests of cognitive function, U.S. census questions about race,

occupation, and income levels, as well as presence of five health conditions (myocardial infarction, hypertension, stroke, diabetes, and cancer). The mean age of the participants was 72, 61% were female, and 67% were black. The first follow-up in three years had slightly fewer than 7,000 respondents although the mean time for observation was 6.5 years with some participants providing data up to 14 years after the initial home interview. The mean educational level was 12 years and was still found to be a robust protector against cognitive decline with aging (Wilson et al., 2009). The research in the AD literature is extensive, and the impact of the physiological and genetic influences in AD have parallels to the current study, particularly linking the influence of education to symptoms as addressed by the secondary research question.

Older age of sample. Patterson, Millar, Desille, and McDonald (2012) described the impact of cancer on emerging adults. Although the sample was largely older, 19 subjects (9.7% of the sample) for this dissertation study were 18-26 years old. The higher scores on the TRSC in younger subjects might be related to the tasks of the emerging adults. Patterson et al. (2012) discussed the issue that having cancer in addition to the developmental stressors of emerging adults could help to explain why younger age was related to higher TRSC scores. In this young adult age group, stressors would include family tasks such as raising young children. Age may be an important contextual factor when making decisions and managing cancer therapies, as revealed in a literature review by Tarriman (2011).

Data reliability. Due to the subjective nature of self-reported data, there could be questions about the reliability of the data. Also, despite specific instructions to report currently experienced symptoms, several subjects were confused about whether to report symptoms currently being experienced or symptoms as they were experienced at the time of treatment.

Subjectivity impact on self-report. Meeting with the Phase 2 participants provided some opportunity to verify the accuracy of Phase 1 data. One Phase 2 participant had a full head of hair, but she rated her hair loss as a 4 (*very severe*) as her hair was not as thick, still came out, and she had lost her eyebrows permanently. In contrast, a subject whose TRSC score was zero had difficulty producing the saliva sample due to dry mouth. She verbally reported that dry mouth contributed to taste changes and loss of appetite, and the generalized dryness caused other skin issues. She had not rated any items on the TRSC as she did not consider them "problems" but just changes. The symptom occurrence and severity rating for this study was impacted by the perceptions of the individuals.

Time frame confusion. There was some confusion about the time period that was to be evaluated for a few participants, *current* versus *during treatment*. Although specific instructions were given to report *current* symptoms in the online survey, in a one-week follow-up email, and in response to any phone or email questions by participants, it was discovered in the Phase 2 personal interviews that several respondents were confused about the time period. There is no way of detecting if confusion about the time period was an issue for other on-line respondents. When meeting with the Phase 2 subjects, all except two high-scoring Phase 2 participants were clear that their ratings were to be based on current symptom experiences rather than symptoms experienced during treatment. These two scores would have been lower if they had been rating current symptoms. Conversely, a number of respondents wanted to raise their scores based on current exacerbations of symptoms. No adjustments were made to the scores that were originally entered by the subjects.

Third Secondary Research Question

The third secondary research question addressed the use and effectiveness of self-care methods. A review by Shulman-Green et al. (2012) of 101 studies in a meta-analysis revealed that self-management plans vary in importance to patients over time. Communication about the self-management plan is of critical importance to both patient and caregivers (Shulman-Green et al., 2012). The importance of continued menopausal symptom assessment and management supports the importance of continuing nursing care for breast cancer survivors who are already using hot flash treatment, and suggests that nursing interventions aimed at improving perceived control over hot flashes may be more helpful for survivors than for midlife women (Carpenter, Wu, Burns, & Yu, 2012). Hot flashes were one of the symptoms that was added when the subjects in this study were given the opportunity to list additional symptoms on the TRSC. Although women who have not experienced cancer may have hot flashes, this symptom may be more troublesome for the breast cancer survivors.

The literature also revealed that several studies focused on self-care have been conducted using the TRSC in the United States, as well as in Asia, Europe, and Puerto Rico. Findings similar to the present study have been reported. A descriptive study (P. D. Williams et al., 2006a) was conducted with 37 adults living in the Midwestern United States who were receiving chemotherapy for leukemia, lymphoma, or breast cancer or radiation for head and neck cancer. Study participants reported their symptoms on the TRSC and also described the symptom alleviation methods they used to help control their symptoms. The reported results showed that (a) 10 symptoms were reported as mild to moderate in severity, and 40% or more of the patients reported at least 17 symptoms on the TRSC; (b) care providers prioritized interventions based on the TRSC patient-reported symptom occurrence and severity scores; and (c) the self-care

strategies, grouped according to complementary medicine categories as a framework, showed that the two categories most used were diet/nutrition/lifestyle change and mind/body control. Responses also indicated the use of biological products, such as vitamins, and the use of herbal treatments and ethno-medicine, such as lime juice and garlic, green mint tea, and others, to alleviate symptoms.

The above study was replicated in cancer centers in Hong Kong and in mainland China (Xi'an) using 222 adult oncology patients. The findings were similar to the findings of the study done in the Midwestern United States. Self-care strategies most often used fell in the same two categories (diet/nutrition/lifestyle change and mind/body control) and were reported as helpful by the patients. Tai-chi was mentioned by some as part of mind/body control self-care measures utilized by the Chinese patients; biological treatments were also utilized (P. D. Williams et al., 2010b).

Another replication of the study was conducted with 100 oncology patients at the national medical center in the Philippines, located in the city of Manila. Findings similar to the studies conducted in China and the United States were reported. The self-care methods most often used by patients in the Philippines fell into two categories. The first types of self-care methods utilized were diet/nutrition/lifestyle changes, such as modifying food and eating habits, eating vegetables and fruits such as papaya, using nutritional supplements, taking naps, and getting adequate rest and sleep. These self-care methods were all mentioned as useful to manage the Eating and Fatigue subscale symptoms. The second types of self-care methods reported by patients were in the mind/body control category, such as prayer, praying the rosary, and listening to music; these self-care methods were used to relieve the symptoms in the Fatigue subscale/cluster, as well as other symptoms (P. D. Williams et al., 2010a). The key role of

family support during treatment also was described by the patients, similar to findings on Filipino-Americans reported by Harle et al. (2007). In TRSC replications with Puerto Rican patients and Mexican-American patients undergoing treatment for cancer, two other studies have reported similar quantitative findings. Moreover, qualitative findings have shown that patients focus on religious practices and utilize the support of family as part of self-care strategies (Gonzalez et al., 2010; Lantican et al., 2011), similar to practices employed by the patients in the Philippine study.

Another replication study was conducted in Thailand using the TRSC and similar methods, with a convenience sample of 202 patients receiving treatment for cancer at the National Cancer Institute, as well as at a cancer center of a provincial city in Thailand (Piamjariyakul et al., 2010). The results closely mirrored those previously reported in the studies conducted in the Midwestern United States, mainland China, and the Philippines. One of the unique self-care findings reported in Thailand was the use of the herbal treatment “purple flower” for hair loss. The use of music and religious icons were also common, including the use of tapes related to Buddhist prayers. The TRSC, DARS, HRQOL, and SA: SCM measures have been used extensively in studies by P. D. Williams and colleagues, and further analysis of data from these studies may provide additional relevance to the data from this study.

The literature clearly indicates self-care methods are widely used. An understanding of what methods have been successfully utilized could be used to optimize care. Further study may provide more robust support for specific recommendations for patient teaching in preparation for the expected long trajectory of symptom management.

Theoretical Relevance

The physiological model (Figure 2 in Chapter 1) was used to design this study. Data collected did not provide clear evidence to support the model. Additional literature reviewed did provide some context for the interpretation of the finding that varied from the original expectation. The original expectation was that the homozygous high-activity Val allele would be linked to less symptoms as there would be greater neuroplasticity and repair mechanisms available (Kennedy et al., 2009). It was believed that the less active Met gene variant would exacerbate symptoms rather than provide the protective effect that was demonstrated. A better understanding of how these genetic influences, such as the BDNF Val66Met SNP, affect various physiological processes is needed (Noble et al., 2011).

Expanding on Table 1 (found in Chapter 1), Table 14 below shows a related conceptual framework, the study results, and some recommendations for further research.

Table 14

Concepts and Empirical Indicators for Future Research

Concepts	Daily activities	Quality of Life	Symptoms	Sample characteristics
Empirical indicators (operationalization)	Daily Activities Rating Scales (DARS) 5-item scale	Health Related Quality of Life (HRQOL)-Linear Analog Self Assessment (LASA) 6-item scale	Therapy Related Symptom Checklist (TRSC) 25-item scale	Five self-reported: age, ethnicity, education, treatment type, and time since treatment completion
Level of measurement	Ordinal	Ordinal	Ordinal	Nominal/ordinal
Analytic strategy	Linear regression	Linear regression	Linear regression	Linear regression
Results	DARS related to HRQOL-LASA	HRQOL-LASA related to DARS	TRSC related to DARS TRSC related to HRQOL-LASA	No relationships with time since completion of treatment or ethnicity
Recommendations for further studies	More subjects who are not Caucasian, with lower education, rural and urban residents	More subjects who are not Caucasian, with lower education, rural and urban residents	More subjects who are not Caucasian, with lower education, rural and urban residents	More subjects who are not Caucasian, with lower education, rural and urban residents

Clinical Implications

The findings of this study support the need for sustained symptom assessment and management post-treatment among breast cancer survivors. Continuing self-care is the key to symptom alleviation in the years when survivors will still be experiencing symptoms but have limited contact with providers. Nurses are pivotal to monitoring and intervening in the management of symptoms and maximizing of quality of life (Thomas, Crisp, & Campbell, 2012). According to the evidence hierarchy defined by Polit and Beck (2008), this current study provides Level IV evidence for practice; it is a single correlational (multiple regression) biobehavioral, physiologic study, with a mixed method (qualitative) component. The evidence for practice gained from this study includes the fact that breast cancer survivors have significant ongoing symptoms long after treatment is completed. These symptoms require continuing assessment and guided self-care to alleviate symptoms among these cancer survivors. Using a multiple symptoms assessment tool, such as the TRSC, to guide symptom management optimizes the care provided to patients.

P. D. Williams et al. (2011d), in an evidence-based study using the Stetler model, reported significant outcomes of education and support on quality of life in a sample of cancer patients during active treatment. Resources, such as the Oncology Nursing Society (ONS, 2010) and Yarbro, Frogge, and Goodman (2004), helped guide the interventions used in the Williams study. Moreover, Mische-Lawson et al. (2012) also reported that on two TRSC symptoms (feeling sluggish and difficulty concentrating), the “art-making” intervention group had significantly lower TRSC scores and salivary cortisol levels than the control group. These interventions could be extended to include long-term breast cancer survivors; combining these evidences can positively impact patient experience. Techniques such as Pilates that can be

advocated by nurses may be helpful for breast cancer patients to reduce symptoms and increase quality of life, and these interventions can be used on an ongoing basis without the risk of or need for continued medical care (Stan et al., 2012). Also, a literature review of 22 articles highlighting the benefits of social support and physical activity in cancer survivors (Barber, 2012) found that less than 20% of adult cancer survivors participate in physical activity and, as a result, are at greater risk for problems due to the inactivity. Lack of social support was implicated as having a significant negative relationship with physical activity engagement in 50% of the studies reviewed. Nursing interventions centered on social support and physical activities have the potential to make an impact as self-care to improve symptoms, such as fatigue, depression, and other symptoms, and could contribute to improved quality of life. Another recent study showed that use of the TRSC improves symptom documentation and management, as well as HRQOL (P. D. Williams et al., 2012a).

A study of 318 patients indicated that motivational interviewing by nurses can assist with symptom management (Thomas, Elliot, et al., 2012). Chemotherapy, not surprisingly, seems to contribute the most to the symptom burden, and this evidence has been previously demonstrated in a number of studies by P. D. Williams et al. (2001; 2010a, b); Piamjariyakul et al. (2010); and Vath & Williams (2012). Nurses may have a large impact on self-care by supporting individuals' care for symptoms such as depression (Qian & Yuan, 2012). The clinical implication of targeted nursing interventions, in conjunction with a simple assessment to gather age and education information, may be as important as a specialized genetic test.

Decreased interest in sexual activity, noted by 82.1% of respondents, had the third highest symptom occurrence after difficulty concentrating (87.2%) and feeling sluggish (84.6%) in this study. As previously discussed, decreased interest in sexual activity may cause a great

deal of suffering for survivors; the mean severity was 1.85, second only to hair loss (2.10). The standard of practice for nurses is to address sexuality issues. One evidence-based tool to support nursing practice is the BETTER Model (Mick, Hughes, & Chen, 2004) that could be used to assist oncology nurses to conduct sexuality assessments more effectively. The evidence provided by the present study about the occurrence and severity of this problem as an ongoing symptom for breast cancer survivors is a challenge to professional nurses to use the available tools to support their practice.

The long trajectory of symptoms associated with breast cancer has important implications for undergraduate nursing education. Nurses entering practice need to be better able to assist women in managing their self-care, even years after the survivors complete their treatment regimens. Additionally, this type of information needs to be conveyed in graduate nursing programs, specifically to those nursing students specializing in oncology. Research in this critical area of inquiry should move forward, and graduate nursing research will be one of the most powerful mechanisms to drive the research. Further research could pave the way for use of the BDNF Val66Met SNP genetic indicator as a screening tool. Identifying at-risk individuals so that protective nursing measures could be applied more aggressively to the personalized survivorship care plan could be important if the SNP that seems to provide a protective effect is absent.

Study Strengths and Limitations

One strength of the study was that it did provide preliminary information about a previously unstudied relationship between the BDNF Val66Met SNP and cancer symptoms. However, the sample size was very small, and although definitive evidence for a particular

relationship has not been established through this study, this research provides information for a future, larger, and better-controlled study.

The scientific approach aids in being better able to explain the human condition, yet all nursing research is inherently limited. In applying the scientific method, limitations for this study included the fact that the small convenience sample consisted of volunteers with one type of cancer. These volunteer participants were all located in a limited geographical region. These sampling deficiencies were taken into account when data were analyzed and results were reported in this preliminary study. One inherent disadvantage of the electronic survey is that there could be multiple and mischievous responses (Duffy, 2002). The design attempted to enrich the sample for Phase 2 of the study, which addresses the primary research question.

Additionally, there may have been many important confounding variables that cannot be explained with the data collected. One example is that type of treatment, stage of disease, and many other factors have been demonstrated to impact symptoms. All medical information was self-reported; no medical information verification has been included as part of the study. The complexities of the issues involved could only be properly addressed by a carefully controlled study. To the extent possible in this study, statistical control of selected variables was done with logistic and multiple regression analyses.

Finally, measurement problems were an issue with this study. The self-report instruments used in this study have had limited usage electronically (P. D. Williams et al., 2011b). However, others have electronically administered self-report instruments in their research (Basch et al., 2007). Factors that may have impacted data collection include problems with access to the electronic survey and length of the survey. The length of the survey might have contributed to partial rather than complete responses, as evidenced in the pattern of missing

items, which seemed to be related to page breaks in the survey. Difficulties with scheduling or traveling to the sites for Phase 2 were a definite limitation that eliminated at least 10 potential subjects. In order to counter this problem, the researcher offered five routine locations and utilized alternate locations, such as libraries and restaurants, and made home visits as needed. Even though the invitation to participate in Phase 2 included information that a saliva sample would be collected, when phone contact was made to schedule appointments, three potential subjects declined, specifically citing their unwillingness to give a saliva sample. The integrity of the saliva samples also may have been problematic. Although guidelines about collecting a good saliva sample were reviewed with the potential subjects during the scheduling call, there was no control over their activities previous to the face-to-face meeting. The researcher did need to remind at least five participants that it would not be appropriate to drink prior to the saliva collection during the Phase 2 visit.

In this study a homogeneous convenience sample was a limitation. The type of demographic data and the manner in which the data were gathered were also problematic. Use of continuous variables such as age, rather than age categories, would have made some aspects of data analysis more powerful. The methodological problems that contributed to missing data were a limitation. There may also have been some confusion in some participants regarding the time period considered in the rating of symptoms. The online data collection method did not allow subjects to ask any questions for clarification although the opportunity to email or call did provide some assistance for subjects. In retrospect, the researcher should have used the opportunity to gather more specific demographic information during the Phase 2 face-to-face meetings with participants.

Recommendations for Future Research

Future research needs to be conducted to further explore links between breast cancer symptoms and possible biological markers such as the BDNF Val66Met SNP. Exploring this relationship with other cancer diagnoses, including colorectal cancer, lung cancer, and prostate cancer, is suggested. As in many studies, a larger sample would enable a more robust examination of the relationships among variables. Further research with a more diverse sample, with particular regard to ethnicity, would be recommended to gain a better understanding of this phenomenon. Level of education as related to residential location (rural, urban) would provide important information for health care delivery. Table 14 shows specific recommendations for further research as related to the study variables. A better controlled study would be an important scientific improvement. In future studies, the collection of continuous data whenever possible is recommended. The use of online data collection is a special problem with the format and length of questions asked, in addition to HIPAA considerations. Methodology that would include medical records review would allow verification of participants' self-reported health information. Continued use of methods to ensure the reliability of the information is emphasized. In this study, for example, the researcher directly administered the SA: SCM instrument to Phase 2 participants; this increased the reliability of data gathered.

Conclusions

The study conclusions will be addressed by listing conclusions stemming from each research question. Relative to the primary research question, findings showed that lower TRSC scores were significantly associated with the presence of the BDNF Val66Met SNP. However, this relationship did not persist with the addition of education and treatment type to the logistic regression model. More research is needed to explore the effect of the BDNF Val66Met SNP,

particularly as it relates to the possibility of using the genetic marker as an indicator of vulnerability.

The conclusions corresponding to the secondary research questions include foremost the fact that the occurrence and severity of symptoms among breast cancer survivors are ongoing issues, beyond the end of formal oncology treatments. Thus, most of the symptom burden falls on the individual survivor outside of the time when they had frequently interacted with medical professionals. This makes the issue of self-care among survivors imperative for successful symptom alleviation. The clinical implications for the most frequently occurring symptom, difficulty concentrating, might include primarily teaching survivors that this is likely to be a long term issue. Notably, “difficulty concentrating” is a TRSC symptom indicator for cognitive problems among patients. Thus, the term “cognitive problems,” commonly used when PubMed, Medline, and CINAHL are used for literature searches, would miss many studies unless the indicator symptom “difficulty concentrating” is added also as a search term. A researcher had recently discovered this issue.

Participants in this study reported as useful various self-care symptom alleviation strategies (such as consciously focusing, taking notes, and using lists and reminders). Difficulty concentrating is one of four symptoms in the TRSC Fatigue subscale, or symptom cluster. Therefore, additional survivorship planning should be done to *also* assess the incidence of depression, feeling sluggish, and difficulty sleeping. Possible interventions for one symptom may influence the other symptoms in the cluster. For example, suggestions for interventions on how to improve sleep may prove more valuable to improving difficulty concentrating than making a list, or both strategies may actually be helpful.

The importance of good nursing assessment is highlighted by this study. In 1994, the study by Youngblood et al. had reported the significant under-reporting of symptoms of cancer patients – that was almost 20 years ago. A recent study with the Mayo Health System by P. D. Williams et al. (2012a) reported that, compared with nonuse of a checklist, use of the TRSC checklist in health care delivery at a cancer center resulted in more symptoms managed and in patients' reports of (a) higher quality of life and (b) higher functional status. Replication of this study is much needed.

Another implication of the study is that less-educated individuals might be more vulnerable to suffering from symptoms. Less-educated patients in rural, remote areas may be part of this vulnerable group. Vath and Williams (2012) recently reported that, at a rural oncology setting in the Midwestern United States, type of treatment was associated with symptoms manifested. That is, similar to the present study findings, more symptoms were observed in patients on chemotherapy, as compared to those on radiation therapy. However, Williams et al. (2001) also had reported this finding at a Midwestern urban medical center. The finding that ethnicity has no impact on symptoms in this study is mainly because all but one of the participants were Caucasian; thus, further research with a more diverse sample is needed. Moreover, in this study, the fact that many breast cancer survivors listed decreased interest in sexual activity as a problem, and yet most of them did nothing to relieve the symptom, should cause nurses to reflect about assessment and interventions that are survivor-centered. Problems with sexuality demand a self-care based approach. Perhaps failure to promote self-care is more startlingly evident with this symptom, as well as with the TRSC symptom of depression. Therefore, the question is asked again: During clinical care, do nurses fail to properly assess a

full range of symptoms in an evidence-based manner with the use of a checklist such as the TRSC? Further research is important to answer this and other questions.

Relative to the third secondary research question, the most frequent self-care symptom alleviation category was diet/nutrition/lifestyle and the least was herbs/vitamins/complementary therapy. Symptom alleviation methods used in the U. S. (Lantican et al., 2011; P. D. Williams et al., 2006a, 2006b) and in other cultures (Gonzalez et al., 2011; Piamjariyakul et al., 2012; P. D. Williams et al., 2010a, 2010b) described earlier in Chapter 2 show many similarities in the use of self-care and complementary care methods to those self-care methods used in the current study. In this study, the effectiveness of the methods ranged from 25% to 100%, with most being highly effective. The implication is that self-care is helpful, and patients should be encouraged to try some of the methods suggested by the cancer survivors in this study.

Summary

This study provided beginning evidence (Polit & Beck, 2008) that there is an association with the BDNF Val66Met SNP presence and lower TRSC scores. The SNP, as well as education, may have a protective effect against symptom occurrence and severity. Self-care methods used are generally effective. Implications of the study are important for nurses who practice clinically in oncology as well as educators. Assessment, intervention, and self-care promotion are essential; this study found that symptom burden impacted cancer survivors even beyond the cessation of their treatments for cancer. This study provides the basis for further research.

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Appendix A

IRB Approval

The University of Kansas Medical Center

Human Research Protection Program

January 17, 2012

Project Number: 13078
Project Title: Relationships Among Symptoms, Brain-Derived Neurotrophic Factor (BDNF), Daily Activities, Self-Care, and Quality of Life in Breast Cancer Survivors
Sponsor: None
Protocol Number: N/A
Primary Investigator: Phoebe Williams, Ph.D.
Department: Administration - School of Nursing
Meeting Date: 02/07/2012
HSC Approval Date: 02/08/2012
HSC Expiration Date: 02/07/2013
Type of Approval: Expedited f (3)(7)

Dear Investigator:

This is to certify that your research proposal involving human subject participants has been reviewed and approved by the KUMC Human Subjects Committee (HSC). This approval is based upon the assurance that you will protect the rights and welfare of the research participants, employ approved methods of securing informed consent from these individuals, and not involve undue risk to the human subjects in light of potential benefits that can be derived from participation.

Approval of this research is contingent upon your agreement to:

- (1) Adhere to all KUMC Policies and Procedures Relating to Human Subjects, as written in accordance with the Code of Federal Regulations (45 CFR 46).
- (2) Maintain copies of all pertinent information related to the research study including, but not limited to, video and audio tapes, instruments, copies of written informed consent agreements, and any other supportive documents in accordance with the KUMC Research Records Retention Policy.
- (3) Report unanticipated problems to the HSC by completing the Internal or External HSC Unanticipated Problem/Adverse Event reporting form, as applicable.
- (4) Submit deviations from previously approved research activities which were necessary to eliminate apparent and immediate dangers to the subjects by using the KUMC Protocol Deviation Report.
- (5) Submit Amendments to the HSC for any proposed changes from the previously approved project using the Request for Amendment form. Changes may not be initiated without prior HSC review and approval, unless a delay in implementation would place subjects at risk.
- (6) Submit Continuing Review Form (CR Form) to the KUMC HSC before the expiration date. Federal regulations and HSC policies require continuing review of research at intervals appropriate to the degree of risk, but not less than once per year.

If you have any questions regarding the human subject protection process, please do not hesitate to contact our office.

Very truly yours,



Daniel J. Voss, M.S., J.D.
IRB Administrator

Appendix B

Recruitment Flyer

If you are a female breast cancer survivor, 18 years of age or older, who has completed treatment at least 6 months ago, you are eligible to participate in a study that the coalition is promoting. If you would like to participate in the electronic survey, please call the coalition office or visit the coalition web site.

Kelly A. Kershaw

Administrative Assistant
Delaware Breast Cancer Coalition
111 W. 11th Street, Suite 3
Wilmington, DE 19801
(302) 778-1102 x 10
www.debreastcancer.org

Taking Action to Defeat Breast Cancer Since 1991



Appendix C

Phase 1 Electronic Survey

Hello, my name is Sylvia Heinze. I would like to invite you to participate in my doctoral research survey. Your responses are important to the improved care of future breast cancer survivors.

Let me tell you a little bit more about me and my research. I am a practicing oncology nurse, and a doctoral student at the University of Kansas. This study is part of my PhD research on nursing care for breast cancer survivors. The survey is designed for women age 18 years and older who have completed their treatment for breast cancer at least 6 months ago. If this describes you, then I would like to invite you to participate in this survey. Please answer all of the questions by choosing the answer that best describes your current experiences as a breast cancer survivor. There are no right or wrong answers. It should take less than half an hour to complete the survey. Thank you for choosing to participate. If you have any questions about the study, please feel free to contact me:

Sylvia Heinze
302-519-3068
sheinze@kumc.edu

Symptoms and Breast Cancer Survivors

Created: December 16 2011, 12:46 PM
Last Modified: January 05 2012, 5:29 PM
Design Theme: Tablet
Language: English
Button Options: Custom: Start Survey: "Start Survey!" Submit: "Submit"
Disable Browser "Back" Button: False

Symptoms and Breast Cancer Survivors

Page 1 - Question 1 - Choice - One Answer (Bullets)

[Mandatory]

I am a female breast cancer survivor who is 18 years of age or older and have completed treatment 6 months ago or longer

- yes [Skip to 3]
- no [Screen Out]

Page 2 - Heading

The first section of this survey lists 25 problems that are commonly experienced by those who have survived cancer treatments. Please select the option that best describes the severity of your personal experience with each problem listed.

Description

Page 2 - Question 2 - Choice - One Answer (Bullets)

[Mandatory]

Weight loss

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 2 - Question 3 - Choice - One Answer (Bullets)

[Mandatory]

Taste change

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 2 - Question 4 - Choice - One Answer (Bullets)

[Mandatory]

Loss of appetite

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 2 - Question 5 - Choice - One Answer (Bullets)

[Mandatory]

Nausea

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 2 - Question 6 - Choice - One Answer (Bullets)

[Mandatory]

Vomiting

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 3 - Question 7 - Choice - One Answer (Bullets)

[Mandatory]

Sore mouth

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 3 - Question 8 - Choice - One Answer (Bullets)

[Mandatory]

Cough

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 3 - Question 9 - Choice - One Answer (Bullets)

[Mandatory]

Sore throat

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 3 - Question 10 - Choice - One Answer (Bullets)

[Mandatory]

Difficulty swallowing

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 3 - Question 11 - Choice - One Answer (Bullets)

[Mandatory]

Jaw pain

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 4 - Question 12 - Choice - One Answer (Bullets)

[Mandatory]

Shortness of breath

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 4 - Question 13 - Choice - One Answer (Bullets)

[Mandatory]

Numbness in fingers and/or toes

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 4 - Question 14 - Choice - One Answer (Bullets)

[Mandatory]

Feeling sluggish

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 4 - Question 15 - Choice - One Answer (Bullets)

[Mandatory]

Depression

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 4 - Question 16 - Choice - One Answer (Bullets)

[Mandatory]

Difficulty concentrating

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 5 - Question 17 - Choice - One Answer (Bullets)

[Mandatory]

Fever

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 5 - Question 18 - Choice - One Answer (Bullets)

[Mandatory]

Bruising

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 5 - Question 19 - Choice - One Answer (Bullets)

[Mandatory]

Bleeding

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 5 - Question 20 - Choice - One Answer (Bullets)

[Mandatory]

Hair loss

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 5 - Question 21 - Choice - One Answer (Bullets)

[Mandatory]

Skin changes

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 6 - Question 22 - Choice - One Answer (Bullets)

[Mandatory]

Soreness in veins where chemotherapy was given

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 6 - Question 23 - Choice - One Answer (Bullets)

[Mandatory]

Difficulty sleeping

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 6 - Question 24 - Choice - One Answer (Bullets)

[Mandatory]

Pain

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 6 - Question 25 - Choice - One Answer (Bullets)

[Mandatory]

Decreased interest in sexual activity

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Page 6 - Question 26 - Choice - One Answer (Bullets)

[Mandatory]

Constipation

- 0 = NONE-NO PROBLEM WITH THIS SYMPTOM
- 1 = MILD
- 2 = MODERATE
- 3 = SEVERE
- 4 = VERY SEVERE

Please specify any other symptom(s) that you have difficulty with and rate on the 1-4 scale as in previous questions

.....
.....
.....

[Mandatory]

Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?

N o t a t a l l A l i t t l e Q u i t e a b i t V e r y m u c h
 1 2 3 4

[Mandatory]

Do you have any trouble taking a long walk?

N o t a t a l l A l i t t l e Q u i t e a b i t V e r y m u c h
 1 2 3 4

[Mandatory]

Do you have any trouble taking a short walk outside of the house?

N o t a t a l l A l i t t l e Q u i t e a b i t V e r y m u c h
 1 2 3 4

[Mandatory]

Do you need to stay in bed or a chair during the day?

N o t a t a l l A l i t t l e Q u i t e a b i t V e r y m u c h
 1 2 3 4

[Mandatory]

Do you need help with eating, dressing, washing yourself or using the toilet?

N o t a t a l l A l i t t l e Q u i t e a b i t V e r y m u c h
 1 2 3 4

The next 6 questions are about your quality of life

Description

[Mandatory]

How would you describe your overall Quality of Life?

As bad as it can be 1 2 3 4 5 6 7 8 9 10 As good as it can be

Page 8 - Question 34 - Rating Scale - Matrix

[Mandatory]

Your overall mental (intellectual) well-being?

As bad as it can be l a b e l l a b e l l a b e l L a b e l l a b e l l a b e l l a b e l l a b e l l a b e l l a b e l As good as it can be
 1 2 3 4 5 6 7 8 9 10

Page 8 - Question 35 - Rating Scale - Matrix

[Mandatory]

Your overall physical well being?

As bad as it can be l a b e l l a b e l l a b e l L a b e l l a b e l l a b e l l a b e l l a b e l l a b e l l a b e l As good as it can be
 1 2 3 4 5 6 7 8 9 10

Page 8 - Question 36 - Rating Scale - Matrix

[Mandatory]

Your overall emotional well-being?

As bad as it can be l a b e l l a b e l l a b e l L a b e l l a b e l l a b e l l a b e l l a b e l l a b e l l a b e l As good as it can be
 1 2 3 4 5 6 7 8 9 10

Page 8 - Question 37 - Rating Scale - Matrix

[Mandatory]

Your level of social activity?

As bad as it can be l a b e l l a b e l l a b e l L a b e l l a b e l l a b e l l a b e l l a b e l l a b e l l a b e l As good as it can be
 1 2 3 4 5 6 7 8 9 10

Page 8 - Question 38 - Rating Scale - Matrix

[Mandatory]

Your overall spiritual well-being?

As bad as it can be l a b e l l a b e l l a b e l L a b e l l a b e l l a b e l l a b e l l a b e l l a b e l l a b e l As good as it can be
 1 2 3 4 5 6 7 8 9 10

Page 9 - Heading

Providing some additional personal information as accurately as you can will help us learn more about caring for cancer patients. We appreciate you sharing and will hold the information in the strictest confidence.

Description

Page 9 - Question 39 - Choice - One Answer (Bullets)

[Mandatory]

What age range do you fall into?

- 18-30
- 31-40
- 41-50
- 51-60
- 61-70
- 71+

Page 9 - Question 40 - Choice - One Answer (Bullets)

[Mandatory]

With which of the ethnic/racial group do you principally identify?

- White
- Black

- Asian
 - Hispanic
 - Other, please specify
-

Page 9 - Question 41 - Choice - One Answer (Bullets)

[Mandatory]

What is the highest level of formal schooling you have completed?

- Grade school
- High school
- Vocational or associate degree
- Bachelor's degree
- Masters or other graduate degree

Page 9 - Question 42 - Choice - Multiple Answers (Bullets)

[Mandatory] [Up To 4 Answers]

Treatment for my breast cancer included (check all that apply)

- Surgery
 - Chemotherapy
 - Radiation therapy
 - Other, please specify
-

Page 9 - Question 43 - Choice - One Answer (Bullets)

[Mandatory]

I completed my treatment

- Within the past 6 months
- 6 months to 1 year
- 1 to 2 years
- 2 to 5 years
- 5 to 10 years
- 10+ years
- I am still receiving treatment

Page 9 - Question 44 - Choice - Multiple Answers (Bullets)

[Mandatory] [Up To 3 Answers]

Primary caregiver (check all that apply)

- Myself
 - Spouse or partner
 - Other, please specify
-

Page 10 - Question 45 - Choice - Multiple Answers (Bullets)

[Mandatory] [Up To 6 Answers]

Do you have any children living at home (check all that apply)?

- No children at home

- Under 6 years old
 - 7-17 years of age
 - 18-26 years of age
 - Older than 26 years old
 - Please specify number of children in each age range selected
-

Page 10 - Question 46 - Choice - One Answer (Bullets)

[Mandatory]

Do you have any conditions (other than being a breast cancer survivor) that could cause symptoms?

- No
 - Yes
 - If yes, please specify
-

Page 10 - Question 47 - Choice - One Answer (Bullets)

[Mandatory]

Are you currently taking any medications? (Over-the-counter, Herbals, Prescription, etc.)

- No
 - Yes
 - If yes, please specify
-

Page 10 - Question 48 - Choice - One Answer (Bullets)

[Mandatory]

In order to get better information about symptoms some individuals who complete this survey will be selected to participate in an additional aspect of the study. This will involve answering a questionnaire and providing a saliva sample. Including travel, this would take 2-3 additional hours of your time. I would like to be contacted to participate in additional aspects of this study.

- Yes (please provide contact information in the fields below)
- No

Page 10 - Question 49 - Name and Address (U.S)

If you are willing to be contacted please fill out the information below accurately and completely.

- Name
- Phone number
- Address 1
- Address 2
- City
- State
- Zip
- Email Address

Please share any other information that you feel would be important if you were to be included in further study about symptoms: (for example--location, date, time, and give your preferences for these or other items)

Thank You Page

If you have any questions about the survey or additional research that will be conducted, please feel free to contact me:
Sylvia Heinze
302-519-3068
sheinze@kumc.edu

Screen Out Page

Thank you for your interest in participation but the study requires a different profile.

Over Quota Page

Standard

Survey Closed Page

Standard

Thank you for participating in this survey!

If you have any questions about the survey or additional research that will be conducted, please feel free to contact me:

Sylvia Heinze
302-519-3068
sheinze@kumc.edu

Appendix D

Therapy-Related Symptom Checklist (TRSC)

PLEASE **CHECK** THE **PROBLEMS** YOU HAVE HAD THAT YOU BELIEVE ARE RELATED TO YOUR CANCER OR TREATMENT. PLEASE **CIRCLE** HOW SEVERE THE PROBLEM WAS ACCORDING TO THE FOLLOWING SCALE:

0 = NONE 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE

<u>CHECK</u> <input checked="" type="checkbox"/>	<u>EXAMPLE</u> Pain	<u>Degree of Severity (CIRCLE)</u>				
		0	1	2	③	4
<input type="checkbox"/>	Taste Change	0	1	2	3	4
<input type="checkbox"/>	Loss of appetite	0	1	2	3	4
<input type="checkbox"/>	Nausea	0	1	2	3	4
<input type="checkbox"/>	Vomiting	0	1	2	3	4
<input type="checkbox"/>	Weight loss	0	1	2	3	4
<input type="checkbox"/>	Sore mouth	0	1	2	3	4
<input type="checkbox"/>	Cough	0	1	2	3	4
<input type="checkbox"/>	Sore throat	0	1	2	3	4
<input type="checkbox"/>	Difficulty swallowing	0	1	2	3	4
<input type="checkbox"/>	Jaw pain	0	1	2	3	4
<input type="checkbox"/>	Shortness of breath	0	1	2	3	4
<input type="checkbox"/>	Numbness in fingers and/or toes	0	1	2	3	4
<input type="checkbox"/>	Feeling sluggish	0	1	2	3	4
<input type="checkbox"/>	Depression	0	1	2	3	4
<input type="checkbox"/>	Difficulty concentrating	0	1	2	3	4
<input type="checkbox"/>	Fever	0	1	2	3	4
<input type="checkbox"/>	Bruising	0	1	2	3	4
<input type="checkbox"/>	Bleeding	0	1	2	3	4
<input type="checkbox"/>	Hair loss	0	1	2	3	4
<input type="checkbox"/>	Skin changes	0	1	2	3	4
<input type="checkbox"/>	Soreness in vein where chemotherapy was given	0	1	2	3	4
<input type="checkbox"/>	Difficulty sleeping	0	1	2	3	4
<input type="checkbox"/>	Pain	0	1	2	3	4
<input type="checkbox"/>	Decreased interest in sexual activity	0	1	2	3	4
<input type="checkbox"/>	Constipation	0	1	2	3	4
	Other problems (please list below)					
<input type="checkbox"/>	_____	0	1	2	3	4
<input type="checkbox"/>	_____	0	1	2	3	4
<input type="checkbox"/>	_____	0	1	2	3	4
<input type="checkbox"/>	_____	0	1	2	3	4

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Appendix E

Daily Activities Rating Scale

We are interested in some things about you and your health. Please answer all of the questions yourself by choosing the number that best applies to you. There are no “right” or “wrong” answers. The information that you provide will remain strictly confidential.

	Not at all	A little	Quite a bit	Very much
Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
Do you need to stay in bed or a chair during the day?	1	2	3	4
Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

Appendix G

Symptom Alleviation: Self-Care Methods (SA: SCM) Tool

ID# _____ Date: _____

Name: _____ Data Collector: _____

	ALLEVIATION METHODS DONE OR USED (Please list below)	*How often Done? 4, Very Often Done; 3, Often Done; 2, Done Occasionally; 1, Seldom Done; 0, Not Done	Did it Help? <small>(Yes/No)</small>
Taste Change			
Loss of appetite			
Nausea			
Vomiting			
Weight loss			
Sore mouth			
Cough			
Sore throat			
Difficulty swallowing			
Jaw pain			
Shortness of breath			
Numbness in fingers and/or toes			
Feeling sluggish			
Depression			
Difficulty concentrating			
Fever			
Bruising			
Bleeding			

Hair loss			
Skin changes			
Soreness in vein where chemotherapy given			
Difficulty sleeping			
Pain			
Decreased interest in sexual activity			
Constipation			
Other problems (please list below)			

***Rate each alleviation method used—then, each reported symptom would have a *mean* alleviation rating**

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Appendix H

Informed Consent Form

You are being asked to join a research study. You are being asked to take part in this study because you are a breast cancer survivor. This study is part of project being conducted at the University of Kansas Medical Center (KUMC) as a dissertation study by Sylvia Heinze, a PhD candidate at University of Kansas. You do not have to participate in this research study. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

Research is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to stop early. Either way, you can still get medical care and services.

This consent form explains what you have to do if you are in the study. It also describes the possible risks and benefits. Please read the form carefully and ask as many questions as you need to, before deciding about this research.

You can ask questions now or anytime during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating. This research study will be overseen by Phoebe D. Williams, PhD, RN from KUMC. Sylvia Heinze, RN, MSN, AOCN, is the co-researcher. There will be approximately 60 participants in this phase of the study.

BACKGROUND

Health care providers need better ways to understand the symptoms that patients experience when they have been treated for cancer. When these symptoms are better understood, then health care providers can work together to reduce or eliminate the symptoms.

The cells in your body contain deoxyribonucleic acid or DNA for short. DNA is passed down from your parents

The study of DNA is called genetic research. Your entire genetic makeup will not be determined from this testing. Your DNA will only be used for research to understand symptoms. Researchers think there may be substances that are related to symptoms. Saliva samples may provide clues about a single genetic factor, or basic information coded to convey a message about a process, that could impact the symptom experiences of breast cancer survivors. A gene factor called brain-derived neurotrophic factor [BDNF] may affect cell function, and the occurrence and severity of symptoms.

PURPOSE

The purpose of the study is to find out whether the ratings on several surveys and testing for BDNF in saliva are related. Your responses about symptoms, quality of life,

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daily activities and other information may help to better understand and manage cancer related symptoms.

PROCEDURES

If you are eligible and decide to participate in this study, your participation will last approximately 2-3 hours. Your participation will involve making a trip to a study location within 30 minutes of your home for collection of a saliva sample for analysis and answering one questionnaire. The questionnaire lists the 25 symptoms included as the first part of the online survey but in addition asks you to write in any self care methods you used to make the symptom better, rate how effective the method was and how often you used the method. The study investigator will supervise the collection of the saliva sample.

RISKS

There is no risk in joining the study as it only involves answering questionnaires/ questions and collecting saliva samples. If you feel uncomfortable or do not want to answer a question or collect a specimen you may skip the question or quit participation at any time.

Genetic analysis will be done with your saliva sample. The test involves the presence or absence of a single gene element. No additional genetic testing will be done. The test is either positive for the presence of BDNF, or negative (absent). There is no known disorder or disease associated with this gene element. Your saliva sample will be sent to a lab for analysis. The sample will be identified only with a number when sent to the lab. After analysis, the saliva sample will be promptly discarded.

There is a small risk that if people other than the researchers were given your genetic facts, they could misuse them. If genetic information was given to employers or insurers it could affect your ability to get a job or be insured. Misuse could cause problems for family members. In order to minimize these risks, your genetic information will be kept confidential.

Possibility of Unknown Risks

There may be other risks that have not yet been identified and unexpected side effects that we cannot predict.

NEW FINDINGS STATEMENT

You will be informed if any significant new findings develop during the course of the study that may affect your willingness to participate in this study.

BENEFITS

There are no direct benefits to you in joining the study. However, the information gathered may help health care professionals understand the occurrence and severity of symptoms in breast cancer patients.

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ALTERNATIVES

Participation in this study is voluntary. Deciding not to participate will have no effect on the care or services you receive.

COSTS AND PAYMENTS

There is no cost for being in the study. There is no payment to study participants. *Your genetic sample will be used for research only and will not be sold or used to make products that could be sold.*

IN THE EVENT OF INJURY

There is no risk of injury in joining the study as it only involves answering questions and collecting a saliva sample. If you have any problems during the study, you should contact Sylvia Heinze at 443-945-4710 or sheinze@kumc.edu.

INSTITUTIONAL STATEMENT

If you think you have been harmed as a result of participating in research conducted by the University of Kansas Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

CONFIDENTIALITY AND PRIVACY AUTHORIZATION

The researchers will protect your information, as required by law. Absolute confidentiality cannot be guaranteed because persons outside the study team may need to look at your study records. The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in any publication or presentation about the study.

The privacy of your health information is protected by a federal law known as the Health Insurance Portability and Accountability Act (HIPAA). If you choose to participate in this study, you will be asked to give permission for researchers to use and disclose your health information. If you choose not to sign this form, you will not be able to participate in the study.

The researchers will only use and share information that is needed for the study. To do the study, they will collect health information only from the study activities. Your information will be used at KU Medical Center by Dr. Phoebe Williams and members of the research team, the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies. Study records might be reviewed by government officials who oversee research, if a regulatory review takes place.

All study information that is sent outside KU Medical Center will have your name and other identifying characteristics removed, so that your identity will not be known. Because identifiers will be removed, your health information will not be re-disclosed by outside persons or groups and will not lose its federal privacy protection.

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Your permission to use and share your health information remains in effect until the study is complete and the results are analyzed. After that time, researchers will remove personal information from study records.

QUESTIONS

Before you sign this form, Dr. Phoebe Williams, or other members of the study team should answer all your questions. Sylvia Heinze, RN, MSN, AOCN, as co-researcher, can answer your questions, too.

You can talk to the researchers if you have any more questions, suggestions, concerns or complaints after signing this form. If you have any questions about your rights as a research subject, or if you want to talk with someone who is not involved in the study, you may call the Human Subjects Committee at (913) 588-1240. You may also write the Human Subjects Committee at Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

You may stop being in the study at any time. Your decision to stop will not prevent you from getting treatment or services. The entire study may be discontinued for any reason without your consent by the investigator conducting the study.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to Phoebe D. Williams, PhD, RN. The mailing address is School of Nursing, MS4043, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. If you cancel permission to use your health information, you will be withdrawn from the study. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your cancellation.

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CONSENT

Dr. Phoebe D. Williams or Sylvia Heinze has given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you say that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered.

You will be given a signed copy of the consent form to keep for your records.

Print Participant's Name

Signature of Participant

Time

Date

Print Name of Person Obtaining Consent

Signature of Person Obtaining Consent

Date

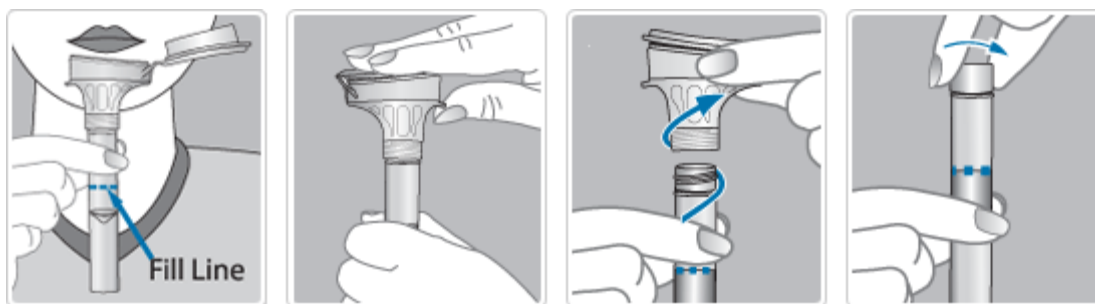
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Appendix I

Oragene DNA Self-Collection Kit User Instructions

Oragene®•DNA Self-Collection Kit User Instructions (OG-500 Tube Format)

Do not eat, drink, smoke or chew gum for 30 minutes before giving your saliva sample.



- 1.** Spit until the amount of saliva (not bubbles) reaches the fill line.
- 2.** Close lid by pushing down hard on the funnel lid.
- 3.** Unscrew the tube from the funnel.
- 4.** Close tube tightly with small cap and mix.