July 2018

Genetic Moderation of Pain and Fatigue Symptoms Resulting from the Mindfulness-Based Stress Reduction for Breast Cancer Program

Carissa Bea Alinat
University of South Florida, calinat@health.usf.edu

Genetic Moderation of Pain and Fatigue Symptoms Resulting from the Mindfulness-Based Stress Reduction for Breast Cancer Program

by

Carissa Bea Alinat

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
College of Nursing
University of South Florida

Major Professor: Cecile A. Lengacher, Ph.D., R.N., F.A.A.N., F.A.P.OS.
Jong Y. Park, Ph.D., M.S., M.P.H.
Kevin E. Kip, Ph.D., F.A.H.A.
Carmen S. Rodriguez, Ph.D., A.R.N.P., A.O.C.N.

Date of Approval:
June 12, 2018

Keywords: MBSR, genetics, pain, fatigue, breast cancer

Dedication

Having five children together with my husband, Guillaume, one would think this project impossible. We are not only husband and wife and best friends, but also a powerhouse for making things happen and this project is the result of the never-ending support my husband has provided me since day one. I met him when I was a single mother working at a daycare center, surviving on hopes and dreams. Guillaume provided me with absolute honesty, trust, and encouragement, and most, if not all, of my success is because he and my family have given me what I needed to thrive. My daughter, Brooke, is one of the most talented and strong young women I know. Thank you for never letting anything stop you from making your dreams happen. I thank my son, Bradley, for continuing to flourish in school and for being such a gentleman. He makes having a boy look easy. My daughter, Scarlett, is a ray of sunshine and she clears the clouds when she enters the room. To my stepchildren, Julian and Brune, for accepting me into their family and sharing their dad with me. A notable piece in the success of this project and all past endeavors are my grandparents. My grandmother, Bea, is the hardest working woman I know and her unconditional love, generous help, and limitless availability to care for the children has helped me get to where I am today. I am also grateful for my grandfather, Gil, who was my father figure growing up and was always there to make me laugh, dry my tears, stick up for me, and chase away the bad guys on his Harley Davidson. I also thank my mother, Deanna, for raising me, which was no small feat for any single mother. To my brother, Jesse, for surviving childhood with me and growing into a successful geek like myself. I owe thanks to my mother-

in-law, Chantal, for supplying an abundance of wine, cheese, and saucisson in her home in the South-of-France while I wrote part of this paper.

Acknowledgments

First and foremost, I would like to thank my major professor, Dr. Cecile Lengacher. Several years ago, she took me aside and provided the direction, encouragement, and support I needed to get through graduate school as well as a position as a research assistant. Not only did she devote a considerable portion of time and energy to my training as a research scientist, but she also graciously offered the use of her data for secondary data analysis, of which this study would not have been possible. Dr. Lengacher is my mentor and she sets the bar high. She has pushed me to succeed without knocking me down.

I also thank Dr. Jong Park for his expertise in genetic analyses. He provided one-on-one training in his laboratory as well as financial generosity, which allowed me to explore an additional gene in this project. Although he is a guru in his area of research, he offered an unintimidating environment where I could ask any question without questioning my intelligence. He has a pretty great sense of humor and I also enjoyed our culinary discussions as well.

Dr. Richard Reich deserves an accolade for his assistance in the statistical methods used in this study. Despite having a busy schedule and life of his own, he made himself available on numerous occasions and never complained about me blowing up his email inbox. He also served as Outside Chair during my dissertation defense.

Dr. Kevin Kip is a statistical Jedi Master and I am grateful for his help with analyzing the results of this study. If every graduate student took a class on statistics led by him, the world would be much better off and people could also place more trust in research findings.

I would also like to thank Dr. Carmen Rodriguez for her expertise in symptom management as well as editing recommendations. She is also an inspiration to nurse practitioners who want to continue working clinically while teaching and performing research.

Table of Contents

List of Tables

List of Figures

Abstract

Breast cancer survivors (BCS) account for the largest group of cancer survivors living in the United States and they often experience lingering physical symptoms that may affect quality of life, with fatigue and pain the most commonly reported. This genetic research study was conducted within a parent R01 study, with the purpose of exploring associations between genetic variants and fatigue and pain symptoms and the Mindfulness-Based Stress Reduction for Breast Cancer (MBSR(BC)) program. The aims of this study were to: 1) identify specific genotypes involved in fatigue and pain symptoms, and 2) explore whether single nucleotide polymorphism (SNP) rs1800795 in gene *IL6*, SNP rs16944 in gene *IL1B,* and SNP rs4680 in gene *COMT,* moderate the effects of the MBSR(BC) intervention on fatigue and/or pain symptoms.

As part of a larger R01 trial, one-hundred-fifty-eight participants were randomized to either a six-week MBSR(BC) intervention or Usual Care (UC). Data were collected at baseline, six-week, and 12-weeks on subjective measures of pain, fatigue, along with demographic and clinical history information. In addition, DNA was collected for genotyping among the 158 participants using the PCR analysis method. For Aim 1, one-way linear trend analysis of variances (ANOVAs) were implemented to explore associations between the SNPs in genes with subjective symptom measures of pain and fatigue. For Aim 2, comparison of mean scores along with linear mixed model (LMM) analyses were used to explore if the patient's SNPs moderated the effects of the MBSR(BC) intervention on fatigue and pain symptoms.

Results found the mean age of the total sample was 58.4 years and 89% were White, non-Hispanic. Although participants were randomized 1:1 to either the MBSR(BC) or UC groups, chi square analyses found that there was a significant difference for time since treatment, with the

UC group being closer to treatment end (< 1 year) than the MBSR(BC) group ($p < .05$). No other statistically significant differences between groups for baseline demographic or clinical characteristics were found. For Aim 1, one-way linear trend ANOVAs among fatigue and pain scores and the three SNPs (*COMT* rs4680, *IL1B* rs16944, *IL6* 1800795) included as part of this study, fatigue and/or pain, resulted in no statistically significant associations ($p > .05$). Linear Mixed Model (LMM) analyses, implemented to assess the between-group interactions between pain and/or fatigue symptom, time, and SNP, resulted in no statistically significant findings for SNP rs4680 in *COMT* and SNP rs16944 in *IL1B*, however significant findings were found for the interaction between assignment (MBSR(BC) versus UC) and genotype for SNP rs1800795 in *IL6*. Second, a comparison of means suggests that participants in the MBSR(BC) group who had CG genotype for SNP rs1800795 in *IL6* benefited more from the intervention than those with CC or GG genotypes for fatigue severity, fatigue interference, pain severity, and pain interference, with small to large effect sizes ranging from $d = 0.38$ to $d = 0.72$. Although this genetic study was exploratory in nature, the results suggests that the effects of the MBSR(BC) program may be moderated by SNPs in genes that are involved in cytokine production, which means that BCS with specific genotypes experience a greater improvement in symptoms than those with other genotypes. The results of this study also suggest that further research is needed, with larger sample sizes, to assess the genetic moderation of symptoms experienced by BCS.

Chapter One

Introduction

Background

Breast cancer in the United States. Breast cancer is the most prevalent form of cancer in women and in 2018 in the United States, there were over 3.1 million women with a history of breast cancer, including patients and survivors (U.S. Breast Cancer Statistics, 2018). Breast cancer is increasing in prevalence and as new discoveries of improvements for the detection and treatment of cancers rise, the number of cancer survivors continues to rise also (Siegel, Miller, & Jemal, 2018). Breast cancer is expected to account for 30% of all cancer cases in 2018 (American Cancer Society, 2017) and approximately one in eight women in the United States will develop invasive breast cancer at some point in life (U.S. Breast Cancer Statistics, 2018). Breast cancer survivors comprise the largest group of cancer survivors living in the United States, with an estimated five-year breast cancer survival rate of 91% in 2017 (American Cancer Society, 2017). Unfortunately, many BCS suffer from a multitude of adverse symptoms after treatment that can affect quality of life.

Physical symptoms and quality of life in women with breast cancer. Despite successful treatment, BCS often experience lingering physical symptoms that may affect their quality of life. Survivors of breast cancer report pain, fatigue, neuropathies such as weakness, tingling, and numbness, sexual dysfunction, bone and joint problems, lymphedema, skin changes, memory loss, and decreased immune function after cancer treatment ends. Fatigue and pain are reported to be the most commonly experienced physical symptoms and are often co-

occurring (Reich et al., 2017a; Miaskowski et al., 2007), and have been shown to be strongly associated with satisfaction with quality of life (Gavric-Kostic, 2016; Hamer et al., 2016).

Fatigue in BCS. Fatigue is a very common symptom that plagues BCS and the National Cancer Institute (2015) has included cancer-related fatigue as one of the "first tier high-priority areas for research." In a study by Lengacher et al. (2012), 85% of BCS suffered from fatigue, making it one of the top two most common adverse effects of cancer treatment. Women with breast cancer report fatigue to be one of the most distressing symptoms related to cancer treatment, which has been shown to be strongly associated with satisfaction with quality of life (Bower, 2014; Gupta, Lis, & Grutsch, 2007). Cancer patients can experience fatigue long after treatment ends, and chronic fatigue has been defined as fatigue lasting for a period of at least six consecutive months (Wessely, Hotopf, & Sharpe, 1998). Approximately one-third of extensively treated disease-free BCS experience chronic fatigue up to ten years after breast cancer diagnosis (Bower, 2014; Bower et al., 2006; Reinertsen et al., 2010; Servaes, Gielissen, Verhagen, & Bleijenberg, 2006). It is unknown how cancer treatments cause fatigue, but common cancer treatments contributing to cancer-related fatigue include chemotherapy, radiation therapy, biologic therapy, and surgery (National Cancer Institute, 2014).

Pain in BCS. Pain is highly prevalent among BCS. Breast cancer survivors comprise the greatest percentage of cancer survivors reporting problems related to pain or discomfort (Jefford et al., 2017). In a study by Lengacher et al. (2012), 60% of BCS suffered from pain, and a study on a specific category of pain such as persistent pain found that approximately 25-60% of women experience persistent pain after mastectomy (Gartner et al., 2009), making pain one of the top two most common adverse effects of cancer treatment. Pain is also highly deleterious, with an approximate rate of 5-10% of cancer survivors experiencing chronic pain so severe that

it interferes with functioning (Glare et al., 2014). Pain may plague BCS for years after treatment ends.

The physical symptom experience and genetics. Cancer survivors have their own unique symptom experiences, with some suffering more or less from post-treatment symptoms (Avis, Levine, Marshall, & Ip, 2017). The variance in frequency and intensity of symptoms experienced by BCS may be partly explained by individual genetic factors (Doong et al., 2015; Shi et al., 2015). Genetic factors predicting patient outcomes from adverse symptoms such as pain and fatigue may lead to better quality of life for BCS utilizing personalized therapies based on individual needs. Genetics and genomics in cancer screening, diagnosis, treatment, and particularly for symptom management after behavioral interventions, are increasingly in the forefront of cutting edge research. Aside from screening purposes, focus on genetics may prove to be an important piece in predicting symptom outcomes experienced by BCS. The assessment of common genetic variations can be beneficial for outcomes in patients with cancer, and with the revolutionary advances in molecular technology, associations between genetic variations and symptoms experienced by cancer patients are of great importance. There is a need to individualize treatment for fatigue and pain in women with breast cancer, particularly BCS, and genetic studies can contribute to the field of precision medicine, to tailor complementary and alternative medicine therapies to best suit patients' needs (Grady & Gough, 2015).

Interventions to improve fatigue and pain in BCS. According to the Department of Health, Macmillan Cancer Support, and NHS Improvement's National Cancer Survivorship Initiative Vision (2010), as the growth of cancer survivors increases, future survivorship care should be tailored to meet the needs of individual cancer survivors and support for self-management care needs to be expanded. The American Cancer Society and American Society of

Clinical Oncology developed and released a Breast Cancer Survivorship Care Guideline in 2015, which details recommendations for managing side effects. Current survivorship care for post-treatment symptoms in BCS include pharmacological and non-pharmacological therapies. However, as many pharmacological treatments cause other unwanted side effects, evidence supports the use of non-pharmacological treatments, which appear to be a safer alternative (Blaes, Kreitzer, Torkelson, & Haddad, 2011). Multiple non-pharmacological interventions have been used for the management of post-treatment side effects after breast cancer. Non-pharmacological strategies include psychological and behavioral interventions, exercise interventions, and complementary and alternative medicine techniques (Palesh et al., 2017).

Currently, non-pharmacological level one recommendations for treatment of fatigue in cancer survivors are exercise and cognitive behavioral therapy (Runowicz et al., 2016). Unfortunately, an estimated up to 70% of BCS do not discuss exercise with their oncology providers or exercise according to public health guidelines set forth by the American College of Sports Medicine (Palesh et al., 2017). In addition, age, physical limitations, and other comorbidities may pose a problem for cancer survivors when participating in an exercise program. Fortunately, other interventions are promising and have been found to improve the quality of life in BCS by reducing adverse side effects that sometimes remain after cancer treatment ends, including stress-reducing techniques (Carlson et al., 2013) such as Mindfulness-Based Stress Reduction (Lengacher et al., 2016) and acupressure (Rosenberg, 2016; Yeh et al., 2016), acupuncture (Tao et al., 2016) and massage (Kinkead et al., 2018).

Non-pharmacological level one recommendations for the management of pain in BCS include physical activity and acupuncture (Runowicz et al., 2016). Acupuncture has been found to be an effective treatment for pain in cancer patients (Tao et al., 2016), as well as exercise

interventions (Galiano-Castillo et al., 2016). Unfortunately, many BCS who were treated with aromatase inhibitors experience musculoskeletal symptoms (aromatase inhibitor-induced arthralgia) resulting from the medication, and although exercise is recommended to treat this side effect, BCS experiencing aromatase inhibitor-induced arthralgia report exercising less than those who were not treated with aromatase inhibitors, possibly as a result of impaired lower extremity function and joint pain (Brown et al., 2014).

Mindfulness-based stress reduction. Mindfulness-Based Stress Reduction for Breast Cancer (MBSR(BC)) is a stress-reducing technique that has been proven effective in improving symptoms experienced by women with breast cancer after treatment (Lengacher et al., 2012). The MBSR(BC) program is a six-week complementary alternative medicine program adapted and tested by Lengacher et al. (2009) from Dr. Jon Kabat-Zinn's original eight-week program aimed at reducing stress through self-regulation of symptoms to improve the quality of life in BCS (Lengacher et al., 2009). Positive effects have been found through its utilization towards treating anxiety, cognitive impairment, depression, fatigue, fear of recurrence, and sleep disturbances in BCS (Lengacher et al., 2009, 2015, 2016, 2017).

Precision medicine in cancer survivorship. Precision medicine is a medical model that suggests that healthcare be personalized to each individual patient, including its selection of treatments and services, and takes into account each individual's genetic makeup, or, "genotype." The basis for this medical model is that there is no "one size fits all" solution to the problem; Every patient is unique in the way that they respond to certain therapies. Individual biological responses may vary and often are due in part to the genes within their DNA, which encode amino acid sequences, which shape the way bodies function. A treatment that works for one patient may not be as effective for another (Ziegelstein, 2017). Although the concept of

precision medicine has existed for some time, in 2015 during his State of the Union address, United States President Barack Obama declared the launch of the Precision Medicine Initiative, investing $215 million in 2016 towards biomedical advances that will supply healthcare providers with new knowledge and tools to personalize treatments for the best outcomes.

Statement of the Problem

The American Cancer Society and the American Society of Clinical Oncology (2016) developed breast cancer survivorship care guidelines for assessing and managing physical, psychological, and social long-term effects that recommended that interventions be tailored to the needs and abilities of the individual breast cancer survivor (Runowicz et al., 2016).

Statement of the Purpose

The purpose of this study was to explore potential genetic variations that may or may not moderate pain and fatigue symptoms among women with BC who participated in a MBSR(BC) program. This study was conducted in part as a secondary data analysis within the *RO1 MBSR Symptom Cluster Trial for Breast Cancer Survivors/1R01CA131080.*

Research Aims and Hypotheses

The overall objective of this research study was to explore whether individual genetic variants moderate improvement of fatigue and pain symptoms resulting from the MBSR(BC) program. It was hypothesized that specific single nucleotide polymorphisms (SNPs) of genes are associated with fatigue and pain in BCS, and may moderate improvement from MBSR(BC).

The primary study aims of this research are as follows:

Aim 1: To identify the specific genotypes related to symptoms of fatigue and pain among BCS.

Hypothesis 1: It is hypothesized that specific genotypes in SNPs *COMT* rs4680, *IL1B* rs16944, and *IL6* rs1800795 are associated with higher or lower levels of pain and fatigue among BCS.

Aim 2: To explore whether the single nucleotide polymorphism (SNP) rs1800795 in gene *IL6*, SNP rs16944 in gene *IL1B,* and SNP rs4680 in gene *COMT,* moderate the effects of the MBSR(BC) intervention on fatigue and/or pain symptoms.

Hypothesis 2: It is hypothesized that the SNPs *IL6* rs1800795*, IL1B* rs16944, and *COMT* rs4680, will positively moderate symptoms of fatigue and pain among BCS participating in the MBSR(BC) intervention compared to the UC group.

Definitions of Relevant Terms

The definitions of relevant terms that were used in this study are as follows:

1. *Gene:* The basic unit of heredity, made up of DNA, which act as instructions to make proteins and determines characteristics (Genetics Home Reference, 2018a).
2. *Genotype:* The two alleles inherited for a particular gene; An individual's collection of genes (National Human Genome Research Institute, 2018).
3. *Fatigue:* The subjective phenomenon of a sense of persistent tiredness or exhaustion that is commonly distressing, measured by the Fatigue Symptom Inventory (Donovan & Jacobsen, 2011).
4. *Fatigue* Severity: A subscale of the Fatigue Symptom Inventory that assesses the level of fatigue in the past week as well as current fatigue (Radiation Therapy Oncology Group, 2010).

5. *Fatigue Interference:* A subscale of the Fatigue Symptom Inventory that assesses the degree to which fatigue in the past week hindered on daily activities and mood (Radiation Therapy Oncology Group, 2010).
6. *Mindfulness-Based Stress Reduction for Breast Cancer (MBSR(BC)):* A 6-week clinical program designed to assist BCS in self-managing stress and symptoms through meditative activities (Lengacher et al., 2009; Reich et al., 2017a).
7. *Pain:* An unpleasant feeling experienced physically or emotionally, often associated with previous tissue damage, measured by the Brief Pain Inventory (Cleeland, 2009; IASP Task Force on Taxonomy, 2017).
8. *Pain Severity:* A subscale of the Brief Pain Inventory that assesses the degree of pain intensity (Cleeland, 2009).
9. *Pain Interference:* A subscale of the Brief Pain Inventory that assesses the impact of pain on functioning in daily activities (Cleeland, 2009).
10. *Single Nucleotide Polymorphism:* A variation in a gene that represents a difference in a single DNA base (Genetics Home Reference, 2018b).
11. *Usual Care:* Participation by the control group in standard treatments after cancer treatment ends. Participants were asked not to participate in a mindfulness program until the study ended (Lengacher et al., 2009; Reich et al., 2017a).

Delimitations

The sample included:

1. Women at least 21 years of age or older
2. Diagnosed with early stage breast cancer (Stage 0-III)
3. Surgically treated (lumpectomy and/or mastectomy)

4. Are at least two weeks out from or a maximum of two years out from completion of adjuvant radiation and/or chemotherapy

Exclusion criteria consisted of the following:

1. Diagnosed with advanced stage breast cancer (Stage IV)
2. Self-reported a severe current psychiatric diagnosis
3. Received treatment for recurrent breast cancer

Limitations

This study is the first step in exploring the potential genetic moderation of pain and fatigue symptoms in BCS participating in a MBSR(BC) program. Study limitations include:

1. This study included only Hispanic and non-Hispanic white women; generalizations to women of other races and men are limited.
2. The sample size was small for a genetic study. Sufficient statistical power is critical for the detection of genetic association and moderation studies.
3. This study explores the presence or absence of SNPs and their association with symptoms experienced by BCS, however, it does not address gene expression, which leaves an open gap between the presence of SNPs and their effects on protein synthesis.
4. Although genotype was identified for genes involved in inflammatory and anti-inflammatory pathways, there were no direct measures of systemic levels of circulating *IL6* and *IL1B*, which would have provided supplementary information on the latent mechanisms for pain and fatigue severity.
5. There was no assessment of fatigue or pain prior to a breast cancer diagnosis, so it is impossible to determine if there were pre-existing symptoms prior to cancer treatment.

6. As there was no healthy control group, inferences cannot be made about the relationship between these genetic variations and fatigue and pain in the general population or in people with other types of cancer (prostate, lung, etc).

Significance of the Study

There is limited empirical knowledge and data regarding the relationships between fatigue and pain-associated single nucleotide polymorphisms (SNPs), and mind-body therapies such as the MBSR(BC) program. This study will contribute to symptom science and precision medicine by exploring these associations and disseminating findings to target optimal therapies for BCS based on their genetic profiles, which may help improve quality of life. Although this study is exploratory in nature and lacks the larger sample size needed for the precision of genetic association research, it is anticipated that this study will warrant future research involving larger clinical trials on the genetic moderation of symptoms experienced by BCS as well as the use of MBSR(BC) to treat such symptoms.

Chapter Two

Literature Review

Introduction

Chapter two introduces the theoretical framework, the hypothesized research model, and a review literature on the study variables in this dissertation. First, a review of empirical research will be presented on pain and fatigue symptoms experienced by BCS. This review is followed by a review of empirical literature on genetic variants (single nucleotide polymorphisms) associated with pain and fatigue. Concluding this review is a review of complementary and alternative medicine therapies used to treat pain and fatigue, particularly the Mindfulness-Based Stress Reduction for Breast Cancer Program, which is the intervention implemented in this study.

Theoretical Framework and Hypothesized Research Model

This research was guided by a hypothesized research model, which was adapted from a logic model based upon the Psychosocial Nursing Research Model (Evans (1992). The hypothesized research model postulates that:

- Outcomes resulting from the Mindfulness-Based Stress Reduction for Breast Cancer (MBSR(BC)) program are moderated by genetic variations such as single nucleotide polymorphisms (SNPs).
- Changes in physical symptoms (fatigue and pain) resulting from MBSR(BC) are expected to improve from baseline to 6 and 12-week assessments to a greater or lesser degree based on genetic profile.

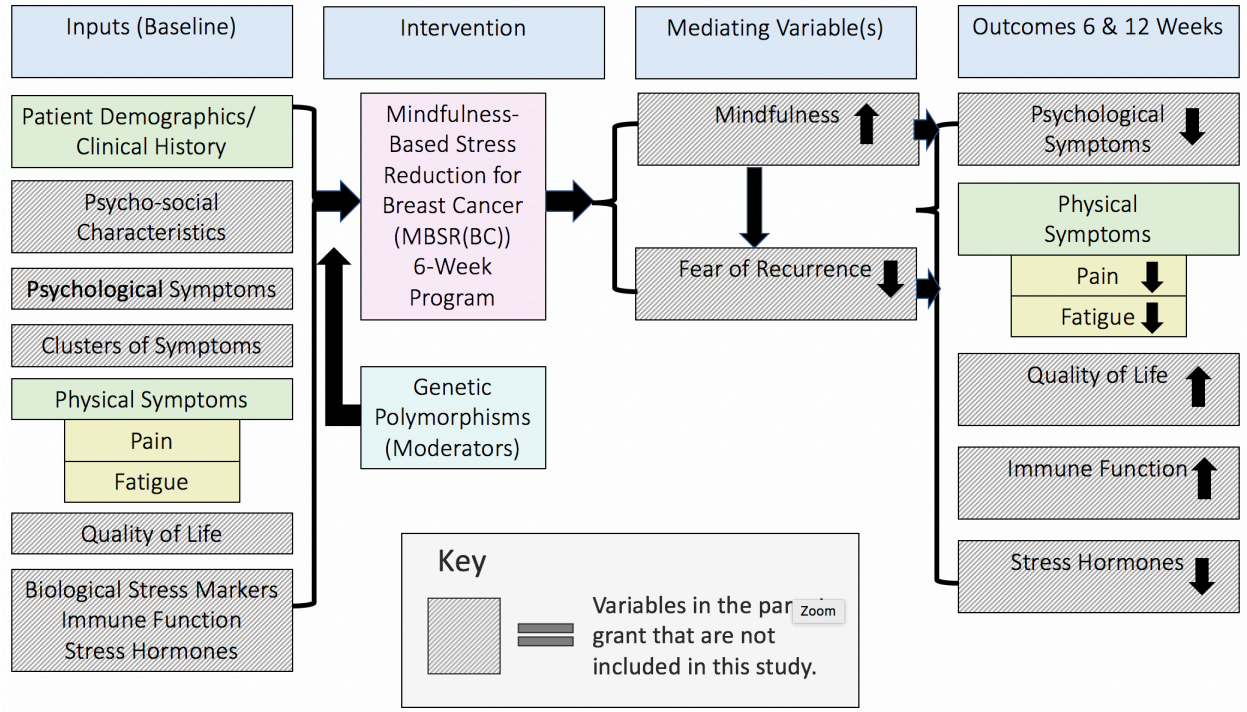


Figure 1. Hypothesized Research Model

Review of Empirical Literature

This review of empirical literature examined the variables within this study. First, a review of research on physical symptoms experienced by BCS, with a particular focus on fatigue and pain as they are the main symptom outcomes of this study, are presented. Next, genetic polymorphisms that have been found to be associated in fatigue and pain symptom pathways are reviewed, followed by mind-body interventions such as MBSR(BC), which was used to treat fatigue and pain symptoms by this study's participants in the intervention group.

Post-treatment physical symptoms in BCS. Breast cancer survivors commonly suffer from treatment-related symptoms that may linger for years after treatment ends, which are often distressing (Syrowatka et al., 2017) and decrease quality of life (Gavric-Vukovic-Kostic, 2016; Koch et al., 2013). In a systematic review of 243 studies by Zomkowksi et al. (2018) on physical

symptoms and their interference with the ability to perform work tasks in BCS, the investigators found that the most commonly reported symptoms included pain, fatigue, lymphedema, arm and/or breast paresthesia, decreased range of motion and weakness in the upper limbs. Evidence shows that fatigue and pain are two of the most commonly experienced symptoms in BCS (Doong et al., 2015; Lengacher et al., 2012). Research also suggests that the patients' symptoms vary among individuals, suggesting a need for individualized treatments for symptom management (Miaskowski et al., 2015).

Pain. The symptom of pain is one of the main subjective variables in this analysis. In this section, a review of the definition of pain is presented, followed by its prevalence among BCS. The effects of pain on quality of life in BCS and its interference with the ability to complete daily activities are also reviewed. Finally, the etiology of pain and its risk factors among BCS are examined and presented.

Pain is often viewed as the fifth vital sign (Lynch, 2001) and is a complex process that varies among patients and may be easily misunderstood as it is often defined subjectively and may seem disproportional to physical signs observed by clinicians. Pain is a subjective experience and its definition varies. The International Association for the Study of Pain (2017) is a collaboration of scientists, clinicians, health-care providers, and policymakers who are dedicated to studying pain and translating research findings into pain relief for patients worldwide. They have defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Pain, International Association for the Study of Pain, 2017). Among breast cancer patients, a study by Hickey et al. (2011) involving persistent breast pain after mastectomy with reconstruction

described pain as “itching”, “burning”, “tightness”, “ache”, “piercing”, “annoying”, “exhausting”, and “miserable”.

Pain is highly prevalent among BCS. In a cross-sectional study of 410 BCS by Hamood, Hamood, Merhasin, and Keinan-Boker (2017) on the prevalence and risk factors associated with chronic pain and other symptoms related to breast cancer and its treatment, the investigators found that 74% of BCS reported chronic pain, of which 84% reported the pain to be moderate. The median since diagnosis was 7.4 years. Pain was assessed using a numeric pain rating scale from 0 (no pain) to 10 (worst pain imaginable) and higher ratings were found to be significantly associated with decreased quality of life ($p < 0.001$), which was assessed using the 36-item short-form health survey (SF-36). Breast cancer survivors were found to have a positive association with chronic pain if they received mastectomy vs. breast conserving surgery ($p = 0.005$), radiotherapy vs. non-radio therapy ($p = 0.003$), regional breast cancer vs. localized at time of diagnosis ($p < 0.001$), younger vs. older age ($p = 0.002$), and time since diagnosis ($p < 0.001$).

The pain that BCS experience may often affect quality of life. A study by Gavric & Vukovic-Kostic (2017) involving BCS found that pain negatively influenced quality of life. The authors assessed quality of life using a self-report questionnaire (QLQ-C30- The Core Quality of Life Questionnaire of The European Organization for Research and Treatment of Cancer, version 3.0) among 100 women. The questionnaire consisted of five functional scales: Physical functioning; Role functioning; Emotional functioning Cognitive and Social functioning; and three scales of symptoms: pain, nausea/vomiting, Dyspnea, Insomnia, Appetite loss, Constipation and Diarrhea. Although there were statistically significant differences in emotional, role, and social functions, one of the most influential was the symptom of pain. In another study, Rim et al. (2017) investigated the quality of life of BCS during the first three years after breast

cancer treatment including radiotherapy. Their large sample of 1156 participants were drawn from 17 hospitals and the patients were separated into three groups (first, second, and third year from the end of radiotherapy). Participants were asked to complete two self-administered quality of life questionnaires: The breast cancer-specific module of the EORTC Quality of Life Questionnaire and the 5-dimensional questionnaire by the EuroQol group (EQ-5D). It was found through the 3-grade Likert scale of the EQ-5D that the worst grades for problems related to health status (2 = some/moderate problem; 3 = extreme problem) were in the pain/discomfort category among the total participants ($p < 0.001$). Results also showed that pain/discomfort was significantly associated with less satisfaction with quality of life but improved with each time period (i.e. year one to year two, year two to year three) ($p < 0.001$).

Pain can be debilitating after breast cancer treatment and can interfere with the ability to carry on with daily activities. In a cross-sectional study by De Groef et al. (2017) on pain characteristics and their contribution to upper limb dysfunction in 274 BCS the investigators found that pain quality ($p = 0.003$), pain intensity ($p = 0.005$), pain catastrophizing ($p < 0.001$), and signs of central sensitization ($p < 0.001$) contributed to limb dysfunction. Risk factors including treatment-related variables, patient-related variables, and impairment-related variables were analyzed by bivariable and multivariable analyses. Upper limb function was assessed using the Disability of Arm, Shoulder, and Hand (DASH) questionnaire. The mean time after surgery was 1.5 years, which reveals that pain resulting from breast cancer treatment can affect long-term functioning (i.e. more than one year after surgery).

A variety of risk factors has been found to contribute to the pain experience in BCS. A systematic review of literature and meta-analysis by Leysen et al. (2017) was performed on risk factors of chronic pain in BCS. The authors included 17 eligible studies and 17 risk factors for

the development of chronic pain in their meta-analysis. They found that eight (obesity/Body Mass Index >30, education <12-13 years, lymphedema, non- or ex-smoker, axillary lymph node dissection, chemotherapy, hormone therapy, and radiotherapy) out of 17 risk factors were significantly associated ($p < 0.05$) with increased risk of chronic pain development in breast cancer survivorship. Lymphedema was found to be the strongest risk factor (OR: 2.58, 95% CI 1.93-3.46, $p < 0.00001$).

The etiology of pain is not fully understood. Pain is considered a neurotoxic symptom resulting from breast cancer and its treatment. In a study by Lacourt and Heijnen (2017) on the mechanisms of neurotoxic symptoms resulting from breast cancer and its treatment, the authors found that neuro-inflammation related to stress, cancer treatment, or cancer-related stress is a predictor of neurotoxic symptoms such as pain both during and after breast cancer treatment. Since stress is commonly experienced by BCS and is often prolonged over a long period of time, the stress response is altered and thus stress hormones have a diminished capacity to regulate the inflammatory response, leading to neuro-inflammation. The authors also suggested that mitochondrial dysfunction results from breast cancer and its treatment, which may potentiate neurotoxic symptoms such as pain. It is also suggested that changes in levels of pro- and anti-inflammatory cytokines and genes associated with their pathways are associated with pain in cancer patients. Miaskowski and Aouizerat (2012) found that among cancer patients, pro- and anti-inflammatory cytokines and their genes, including *IL1B, IL2, IL4, IL6, IL8,* and *TNF-*α are potential biomarkers for pain.

Additional biomarkers that have been found in the literature to contribute to the etiology of pain include neurotransmitter (catechols: dopamine, adrenaline, and noradrenaline) and opioid receptor dysregulation. Miaskowski and Aouizerat (2012) found that among cancer patients,

opioid receptors and neurotransmitters such as COMT and five hydroxtryptamine (5-HT) and genes (*COMT, 5-HTT, OPMR1*) involved in their production pathways, are potential biomarkers for pain.

In summary, pain is a subjective experience that has multiple definitions. It is highly prevalent in BCS, distressing, and often affects their quality of life and the ability to carry on everyday activities. Its etiology is often misunderstood, however, it is suggested that circulating pro- and anti-inflammatory cytokines and genes involved in their pathways, as well as other biomarkers including neurotransmitters and opioid receptors, all play a part in the pain experience.

Fatigue. The symptom of fatigue is another main variable in this study. In this section, a review of fatigue will be presented, including its definition found in the literature, as well as its prevalence among BCS. The etiology of fatigue will also be reviewed.

Fatigue is a subjective experience and its definition varies in the literature. The Farlex Partner Medical Dictionary (2012) defines fatigue as "physical and/or mental exhaustion that can be triggered by stress, medication overwork, or mental and physical illness or disease." A cross-sectional study by Bower et al. (2000) described fatigue as a subjective feeling of tiredness, weakness, and lack of energy, in their article on the occurrence of fatigue and its correlates and impact on quality of life in their sample of 1,957 BCS. Additionally, Cleveland Clinic (2017) describes fatigue as "a daily lack of energy; an unusual or excessive whole-body tiredness, not relieved by sleep." It is also worth mentioning that cancer-related fatigue has been differentiated from fatigue caused by daily life, as cancer-related fatigue is often worse, lasts longer, is unpredictable, and increases distress, according to the American Cancer Society (American Cancer Society, Cancer Related Fatigue, 2016). Cancer-related fatigue has also been

differentiated from healthy fatigue as healthy fatigue, which is more acute and is experienced by healthy people in their everyday lives, is relieved by sleep and rest and cancer-related fatigue is not (Berger et al., 2010).

Fatigue is highly prevalent among BCS. According to the National Cancer Institute (2017), up to 82% of BCS report cancer-related fatigue after treatment ends. In a meta-analysis of 27 studies including 12,327 BCS by Abrahams et al. (2016), it was found that fatigue prevalence was 26.9% (95% CI 23.2-31). Breast cancer survivors at a higher risk for severe fatigue following breast cancer treatment include those with stage II or III cancer, and those treated with chemotherapy (RR 1.18, 95% CI 1.08-1.28), versus those with stage 0 or I cancer and not treated with chemotherapy (RR 1.12, 95% CI 1.06-1.19). In addition, chemotherapy puts BCS at a higher risk for severe fatigue. Abrahams et al. (2016) found that BCS who received a combination of surgery and radiotherapy had a decreased risk of severe fatigue than those who also received additional treatments such as chemotherapy (RR 0.83, 95% CI, 0.70-0.98; RR 0.87, 95% CI 0.78-0.96).

Fatigue is suggested to be the result of cancer treatments such as chemotherapy, radiation, and aromatase inhibitors (Lacourt & Heijnen, 2017; Schmidt et al., 2015; Vichaya et al., 2015). Although the etiology of fatigue is not fully understood, a hypothesis exists that the pro-inflammatory cytokine network induces fatigue (DeSanctis et al., 2014; Wang, 2008; Wang & Woodruff, 2015), which may be activated by cancer itself, its treatment, and psychosocial stress resulting from the cancer experience. Research suggests pro-inflammatory cytokines transmit signals to the brain, which in turn facilitate sickness behaviors including fatigue (Lee et al., 2004; Wang, 2008; Wang & Woodruff, 2015).

Breast cancer survivors have been reported to have increased pro-inflammatory cytokine levels, especially more so in those who are also suffering from fatigue. In a cross-sectional study by Zick et al. (2014) on differences in inflammatory markers between fatigued and non-fatigued BCS, the investigators performed blood analyses on 29 women (16 fatigued and 13 non-fatigued). Pro-inflammatory cytokine IL-6 was found to be significantly higher ($p = 0.03$) in BCS who were experiencing persistent fatigue versus those who were not. This evidence suggests that on a biological level, patients who produce higher levels of IL-6 are more prone to experience persistent fatigue after cancer treatment.

In summary, fatigue is a subjective experience commonly reported by BCS. The diagnosis of cancer and its treatment puts BCS at a higher risk of suffering from fatigue. It is suggested that increased circulating levels of pro-inflammatory cytokines in the blood induce fatigue.

Genetic polymorphisms associated with pain and fatigue in cancer survivors. Genetic polymorphisms are natural variations in DNA sequences that may result in different types of characteristics and account for varying perceptions and expressions of pain prevalence and/or intensity. Often, what is less painful for one patient may be more painful for another. In the following sections, a review of each gene under investigation in this study will be presented, including genes *COMT, IL6,* and *IL1B*, and their relationships to pain and/or fatigue symptoms that have been previously found in other research studies.

Catechol-O-methyltransferase (COMT). The *COMT* gene provides instructions for producing for catechol-O-methyltransferase enzyme, which is responsible for metabolizing catechol neurotransmitters (dopamine, adrenaline, and noradrenaline) in the brain's prefrontal cortex. Within the *COMT* gene, SNP rs4680 is located on chromosome 22, codon 158, with

forward orientation and has been well-studied in its role for the "Warrior vs. Worrier" behavioral phenotype and has been associated with pain.

In the public database available through the National Center for Biotechnology Information (NCBI, 2014), the wild-type allele for SNP rs4680 is a (G) and codes for valine amino acid, which results in more *COMT* enzyme available to metabolize catechol neurotransmitters and thus less extracellular dopamine in the pre-fontal cortex, and may be result in a higher pain threshold and resilience to stress, supporting the "Warrior" behavioral phenotype (Stein, Newman, Savitz, & Ramesar, 2006). Adversely, the polymorphic (A) substitution alters the amino acid to a methionine. The result of this substitution is 25% of the enzymatic activity that a wild-type allele produces, which means less *COMT* enzyme available to metabolize catechol neurotransmitters in the brain and more extracellular dopamine in the prefrontal cortex, which may be responsible for lower pain threshold, increased vulnerability to stress, supporting the "Worrier" behavioral phenotype (Stein, Newman, Savitz, & Ramesar, 2006).

Abnormalities in the COMT enzyme activity have been found to contribute to pain. In a systematic review and meta-analysis of *COMT* gene polymorphism and chronic human pain by Tammimaki and Mannisto (2012), the authors explored the association between *COMT* genotype and three chronic pain conditions: migraine headaches, fibromyalgia, or chronic widespread pain and chronic musculoskeletal pain. The results of their meta-analysis including eight studies showed that rs4680 is associated with chronic widespread pain and that the Met allele is a risk factor (OR = 1.28, 95% CI 1.06-1.55, $p = 0.01$, $n = 3811$).

In a study by Knisely et al. (2018) on associations between catecholaminergic genes and persistent breast pain phenotypes in women following breast cancer surgery, the authors found

that each additional copy of C allele for SNP rs4680 in *COMT* was associated with a 3.34-fold increase in the odds of belonging to the Severe Pain Class ($p = .028$).

Research by Wang et al. (2015) on the association of SNP rs4680 and pain perception in 285 cancer patients, participants' pain level was assessed using the Brief Pain Inventory and genotyping using Polymerase Chain Reaction (PCR) analysis was performed. It was found through pairwise comparison that *COMT* wild-type (G) (V108/158M) carriers had higher pain scores than heterozygous carriers (CG) ($p = .013$) and homozygous and variant carriers (CC) ($p = .003$).

Finally, in a non-cancer population, the major G allele of rs4680 in *COMT* has been found to be associated with an increased severity of chronic postsurgical pain ($p = .018$) (Rut et al., 2014). Participants were asked to rate their pain on a six-point Likert scale in the Oswestry Disability Index 12 months after lumbar discectomy. The study reported that the presence of major (G) alleles increased pain severity in their sample.

Other SNPs in gene *COMT* have been found to be associated with pain as well. A study by Lee et al. (2011) found that in their patients undergoing third molar extraction, specific genotypes for SNPs rs4818 and rs6269 were associated with postoperative pain. Specifically, those with GG genotype reported sufficient postoperative analgesia versus those with AA or AG genotype ($p < .0001$).

In summary, COMT is an enzyme responsible for neurotransmitter production, and variations in SNPs within the gene have been found to affect pain experiences in patients. Specific genotypes for SNP rs4680 as well as other SNPs in *COMT* have been found to result in higher or lower pain thresholds in both cancer and non-cancer populations, with mixed results for associations between +/- pain severity and (A) and (G) alleles.

Interleukin 1 beta (IL1B). The interleukin 1 beta gene provides instructions for producing pro-inflammatory *IL1B* cytokine protein that is an important facilitator for inflammation as well as cellular processes including cell proliferation, cell differentiation, and cell apoptosis. *IL1B* has been found to be involved in pain and inflammation (Ren & Torres, 2009). Within the ILB1 gene, SNP rs16944, also known as "-511," is located on chromosome 2 with forward orientation. In the public database available through the National Center for Biotechnology Information (NCBI, 2014), the wild-type allele for SNP rs16944 is a (G) while the polymorphic allele is an (A).

In a study by Kober et al. (2016) on the association between SNP rs16944 and fatigue levels, the authors evaluated fatigue levels using the Lee Fatigue Scale in (n = 398) and performed genotyping in BCS following breast cancer surgery. Results showed that those possessing the polymorphic (A) allele of SNP rs16944 in *IL1B* gene were likely to experience higher levels of fatigue than those possessing the wild-type (G). However, in a regression analysis, those possessing a GG or AG genotype were found to have a 2.98-fold higher odds of scoring higher on the Lee Fatigue Scale those possessing the AA genotype.

A study of 53 prostate cancer patients by Jim et al. (2012) examined the relationship between fatigue and SNP rs16944 in gene *IL1B*. Fatigue was assessed using the Fatigue Symptom Inventory at two time points following androgen deprivation therapy for treatment of prostate cancer and genotyping was performed via PCR analysis method. The results were non-significant for genotype by time interaction for fatigue and SNP rs16944 (p's > 0.46)

The results of a study by Collado-Hidalgo et al. (2008) suggest that a variant in SNP rs16944 in *IL1B* predicted fatigue (95% CI = 0.91–16.6, p = .007) in their sample of 47 BCS. Fatigue was assessed using the Multidimensional Fatigue Symptom Inventory (MFSI) and DNA

were genotyped using PCR analysis. An association was found between possessing at least one cytosine and fatigue (95% CI = 0.91–16.6, p = .007).

Interleukin 6 (IL6). The interleukin 6 gene provides instructions for producing *IL6* cytokine protein that plays a role in the inflammation response and maturation of B cells. Within the *IL6* gene, SNP rs1800795, located on chromosome 7 with forward orientation, is also known as the "-174 polymorphism." In the public database available through the National Center for Biotechnology Information (NCBI, 2014), the wild type allele for SNP rs1800795 is a (G). Research has found that a polymorphic (C) substitution results in less *IL6* production in humans than those possessing the wild-type allele (G) (Fishman et al., 1998). Pro-inflammatory cytokines associated with fatigue have been found to be elevated over a long period of time in cancer survivors (Bower, 2014; Bower, Ganz, Aziz, & Fahey, 2002; Collado-Hidalgo et al., 2006), which suggests that polymorphic (C) individuals may experience less fatigue than those with wild-type (G).

A study by Collado-Hidalgo et al. (2006) assessed the relationship between *ex vivo* pro-inflammatory cytokine production and fatigue status among early state BCS. Fatigue status was determined using the vitality scale of the SF-36 (score range 0-100, with higher scores indicating well-being) and participants were deemed persistently fatigued if their scores were 50 or less over two to three time points. Participants with scores greater than 70 were deemed non-fatigued and included in the control group. The investigators found that persistently fatigued (N = 32) BCS had increased *ex vivo* monocyte production of IL6 in versus non-fatigued (N = 19) following exposure to lipopolysaccharide stimulation (p = .049).

A more recent study by Collado-Hidalgo et al. (2008) studied single nucleotide polymorphisms in the promoter regions of genes associated with pro-inflammatory cytokines IL-

6 and *IL1B* and their expressions, to assess their relationships with fatigue status in BCS. Participants were screened for fatigue using the SF-36 vitality scale (score range 0-100, with higher scores indicating well-being) and women with scores of 50 or less were deemed fatigued and placed in the experimental group (N = 33) while women with scores of 70 or higher were placed in the non-fatigued control group (N = 14). The Multidimensional Fatigue Symptom Inventory was then used to confirm fatigue symptoms. The investigators extracted genomic DNA from peripheral blood leukocytes and amplified by polymerase chain reaction technique and genotypes were analyzed using chi-square and multivariate logistic regression analyses. Results showed that homozygosity for either GG or CC variant of the *IL6* −174 genotype (p = .027) predicted fatigue.

A study by Bower et al. (2013) on variations in genes responsible for cytokine production and fatigue among 171 BCS found statistically significant associations between genetic risk scores involving SNP rs1800795 in *IL6* gene and fatigue severity. Fatigue was measured using the Multidimensional Fatigue Symptom Inventory (Short Form). The authors hypothesized that polymorphisms in pro-inflammatory cytokine genes regulate expression and therefore predict fatigue severity in BCS after the completion of cancer treatment. They found that genetic risk score was significantly associated with fatigue (p = .002) with a small to medium effect size (r = 0.22). Subjects possessing the GG genotype reported higher levels of fatigue than those possessing the GC or CC genotype.

A study by Jim et al. (2012) on genetic predictors of fatigue in 53 prostate cancer patients, it was found that those possessing the GC or CC genotype of SNP rs1800795 of *IL6* gene reported increased fatigue intrusiveness, frequency, and duration than those possessing the

GG genotype ($p < .05$). In their study, fatigue was assessed using the Fatigue Symptom Inventory and DNA were genotyped via PCR analysis.

In a prospective, cross-sectional study by Shi et al. (2014) on the association between SNP rs1800795 in *IL6* and risk of persistent symptom burden in multiple myeloma patients, patients rated the severity of 13 cancer-related symptoms from the MD Anderson Symptom Inventory (MDASI) and their DNA were genotyped using PCR analysis. Of the 344 patients included in the analysis, the two most commonly reported physical symptoms included fatigue (47%) and pain (42%). For non-Hispanic whites, which comprised most of the sample (n = 222), GG genotype predicted less severe fatigue (OR, 0.53; 95% CI, 0.29-0.88; $p = .013$) and in other ethnicities, GG genotype predicted more severe pain (OR, 3.36; 95% CI, 1.23-13.64; $p = .010$).

In summary, alterations in *COMT* activity as well as circulating levels of *IL1B* and *IL6* have been previously found in the literature to affect pain and fatigue symptoms in cancer survivors. Variations in genotypes among genes associated with *COMT*, *IL1B*, and *IL6* production have also been found to influence pain and fatigue reported by cancer survivors. The findings have been mixed, which warrants further investigation of specific genotypes that may moderate symptoms in these populations.

Mind-body interventions and their impact on pain and fatigue in BCS. Multiple mind-body interventions exist in the literature for management of pain and fatigue symptoms that BCS experience after curative treatment. In 2017, the American Cancer Society updated clinical practice guidelines set forth by The Society for Integrative Oncology in 2014, for integrative treatments during and after breast cancer treatment (Greenlee et al., 2017), and the recommended mind-body therapies for the post-treatment management of fatigue and pain are as follows:

1. Acupuncture and yoga can be considered for improving post-treatment fatigue (Grade C Recommendation).
2. Acupuncture, healing touch, hypnosis, and music therapy can be considered for the management of pain (Grade C Recommendation).

Additional mind-body therapies that have been found effective for reducing fatigue in cancer include Mindfulness-Based Stress Reduction (MBSR) (Carlson & Garland, 2005), the Mindfulness-Based Stress Reduction for Breast Cancer program (MBSR(BC)) (Lengacher et al., 2009, 2011, 2015a,b,c, 2016; Reich et al., 2017a), meditation (Dobos et al., 2015), yoga (Bower et al., 2011), tai chi (Galantino et al., 2003; Larkey, Huberty, Pedersen, & Weihs, 2016; Rausch, Robins, Walter, & McCain, 2006; Mustian et al., 2004), acupressure (Rosenberg, 2016), and acupuncture (Dean-Clower et al., 2010).

Mind-body therapies that have been found effective for reducing pain in cancer include acupressure (Yeh et al., 2017), acupuncture (Tao et al., 2016; Yang et al., 2017), hypnosis (Montgomery et al., 2007, 2002), yoga and tai chi (Yang et al., 2017), healing touch (Post-White et al., 2003; FitzHenry et al., 2014), music therapy (Binns-Turner, Wilson, Pryor, Boyd, & Prickett, 2011; Li, Zhou, Yan, Wang, & Zhang, 2012), meditation (Dobos et al., 2015), Mindfulness-Based Stress Reduction (Johns et al., 2016), and Mindfulness-Based Stress Reduction for Breast Cancer (Kvillemo & Branstrom, 2011).

Mindfulness-based stress reduction (MBSR). Since its development at the University of Massachusetts Medical Center by Dr. Jon Kabat-Zinn in the 1970's, MBSR has become an increasingly popular therapy to assist patients with a wide variety of conditions (Kabat-Zinn, 1985, 1994). The goal of MBSR is to "maintain awareness moment by moment, disengaging

oneself from strong attachment to beliefs, thoughts, or emotions and thereby developing a greater sense of emotional balance and well-being" (Ludwig & Kabat-Zinn, 2008, p. 1350).

Studies have proven mindfulness-based stress reduction as an effective therapy for BCS experiencing adverse symptoms after cancer treatment ends. A study by Lengacher et al. (2016) found that a 6-week Mindfulness-Based Stress Reduction for Breast Cancer program improved a broad variety of symptoms in their randomized controlled trial of 322 BCS. Compared to UC, those who received the intervention demonstrated improvement in both psychological symptoms of anxiety and fear of recurrence, and physical symptoms including fatigue severity and fatigue interference ($p < .01$). It was also found that the largest effect sizes included those for fear of recurrence ($d = 0.35$) and fatigue severity ($d = 0.27$).

Lengacher et al.'s (2014) randomized controlled trial of 82 BCS who were randomly assigned 1:1 to either a six-week MBSR(BC) program (N = 40) or control group (N =42) reported that participants who received the intervention experienced favorable changes in the symptoms they experienced after breast cancer treatment. Improvements were found among five potential mediators: (1) the change in fear of recurrence mediated the effect of MBSR(BC) on the six-week change in perceived stress ($z = 2.12$, $p = 0.03$) and state anxiety ($z = 2.03$, $p = 0.04$); and (2) the change in physical functioning mediated the effect of MBSR(BC) on the six-week change in perceived stress ($z = 2.27$, $p = 0.02$) and trait anxiety ($z = 1.98$, $p = 0.05$).

In a randomized controlled pilot study by Johns et al. (2014) on MBSR for persistently fatigued cancer survivors, 37 participants were randomly assigned in a 1:1 ratio to either a seven-week MBSR program or a waitlisted control group and were followed for six months post-intervention. Cancer survivors who received the MBSR intervention reported greater reductions

in fatigue interference (d = -1.43, $p < 0.001$) and fatigue severity (d = -1.55, $p < 0.001$) than the control group, which were assessed at baseline, post-intervention, one-month follow-up, and six-month follow-up using the Fatigue Symptom Inventory.

Research has also focused on not only MBSR itself, but also how it compares to other interventions aimed at treating adverse symptoms after cancer treatment. In a study by Johns et al. (2016,a) of 71 breast and colorectal cancer survivors comparing MBSR to psychoeducational support, the authors did not find a significant improvement in cancer-related fatigue after the intervention, however, they did report a trend favoring MBSR ($p = 0.073$) at one time point. They also reported a significant effect size in vitality ($p = 0.003$) at the same time point. The group who received MBSR also reported higher satisfaction with their intervention than the psychoeducational support group (M=8.7 and M=8.4, respectively).

A meta-analysis by Huang, He, Wang, and Zhou (2016) of 964 BCS in nine articles reported that compared to control groups, those who receive mindfulness-based stress reduction have statistically significant improvements in depression, anxiety, and stress ($p's < 0.00001$) and increased quality of life ($p = 0.03$).

Mindfulness-based stress reduction has also been found to have a positive effect on sleep, as evidenced by a randomized controlled trial by Lengacher et al. (2015c) in BCS. In their study, 79 participants were randomly assigned to either the intervention group (MBSR(BC)) or UC. Using subjective sleep assessments, such as a sleep diary and the Pittsburgh Sleep Quality Index, and objective sleep assessments, such as actigraphy, it was indicated that the MBSR(BC) program had greater positive effects on objective sleep parameters involving sleep efficiency ($p = 0.04$), time spent sleeping ($p = 0.02$), and less waking periods ($p < 0.01$), than the UC group at a 12-week follow-up after the intervention.

Mindfulness-based stress reduction has also been found to be effective in treating symptom clusters, defined as multiple concurrent and related symptoms "that are not required to have a shared etiology" (Dodd, Miaskowski, & Paul, 2001, p.465). In Lengacher et al.'s (2012) study of symptom clusters in 322 BCS, results indicated that mindfulness-based stress reduction modestly improved fatigue and sleep disturbances. Further, Reich et al.'s (2017a) study of immediate and sustained effects of the Mindfulness-Based Stress Reduction for Breast Cancer program found that mindfulness-based stress reduction improved clusters of symptoms in BCS at the six-week assessments, particularly for fatigue and psychological clusters, showing immediate effects.

Mindfulness-Based Stress Reduction has been found to be a cost-effective and therapy for BCS. In a study by Lengacher et al. (2015a), the authors noted that cost for increased quality of life per year was relatively low compared to other breast cancer interventions found in the literature. Mindfulness-Based Stress Reduction has been adapted to a mobile intervention for BCS, to provide an at-home accessible solution to those who find it difficult to travel.

Mindfulness-based stress reduction has also been found to be an accessible therapy for BCS. In a pilot study by Lengacher et al. (2017), a six-week Mindfulness-Based Stress Reduction for Breast Cancer program was adapted to mobile delivery of the intervention among 15 participants. Thirteen participants completed the study and the results showed that there were significant improvements in both psychological (depression, anxiety, stress, fear of recurrence) and physical symptoms (sleep quality and fatigue) and quality of life ($p's < 0.05$).

It has been shown that Mindfulness-Based Stress Reduction may also improve immune recovery during breast cancer management, as evidenced by four studies found in the literature. A randomized controlled trial of 82 breast cancer patients was conducted by Lengacher et al.

(2013). Participants were randomized to either a mindfulness-based stress reduction or control group. Immunological biomarkers were analyzed at baseline and within two weeks post-intervention and it was found that women who received the intervention experienced a faster recovery of functional T cells.

In addition, Reich et al. (2014) also found a positive relationship between immune recovery markers and Mindfulness-Based Stress Reduction, with a regression model that found predictors of gastrointestinal improvement included B-lymphocytes and interferon-γ as the ($p <$ .01), predictors of cognitive and psychological improvements included +CD4+CD8 ($p = .02$), and predictors of fatigue symptom improvement included lymphocytes and IL-4 ($p < .01$). Another study by Reich et al. (2017b) of 322 BCS found that a Mindfulness-Based Stress Reduction for Breast Cancer program affected cytokine levels, particularly in increasing levels of TNFα and IL-6, markers of immune recovery. At baseline of the study, it was found that IL6 cytokine levels varied according to type of cancer treatment, and negative correlations were found between patients who received mastectomy (versus lumpectomy) and chemotherapy, meaning they experienced lower levels of IL6 ($p < .05$). Participants who had received radiation experienced higher levels of IL6 ($p < .01$). Compared to control group participants, patients in the MBSR(BC) intervention group experienced higher increases in plasma levels of IL6 ($p = .05$) over the 12-week period of the study, versus the control group. It was suggested that MBSR(BC) supports immune system restoration in BCS.

Lastly, another randomized controlled trial by Sarenmalm, Martensson, Andersson, Karlsson, and Bergh (2017) on the effects of Mindfulness-Based Stress Reduction on immune function in 177 BCS, it was found that natural killer cell activity ($p = 0.015$) and $CD3^{+}$T and $CD3^{+}8^{+}$T-lymphocyte activity shifted ($p = 0.027$ and $p = 0.035$, respectively), in which the

authors suggested that this biological response was consistent with study by Fang et al. (2010), showing that increased post-Mindfulness-Based Stress Reduction well-being was associated with a shift in natural killer activity.

Mindfulness-Based Stress Reduction has recently entered into the personalized medicine arena, with genetic a study by Lengacher et al. (2015b) on cognitive impairment and MBSR(BC). Their two-armed randomized controlled trial tested whether 10 SNPs in eight genes known to be associated with cognitive function were associated with cognitive impairment in their sample of 72 participants, and if the SNPs moderated the effects of the Mindfulness-Based Stress Reduction for Breast Cancer program on cognitive impairment, versus a UC group. Participants (mean age 58 years) were randomized 1:1 to either a six-week MBSR(BC) program or UC and cognitive impairment was assessed at baseline, six weeks, and 12 weeks, using the Everyday Cognition (ECog) questionnaire. The ECog is a 40-item self-report questionnaire that asks patients to compare everyday functioning on a 4-point scale at the present moment versus 10 years ago (1 = better or no change, to 4 = consistently much worse). DNA samples extracted from their blood were used to genotype using TaqMan allele discrimination polymerase chain reaction (PCR). The results showed that SNPs in four genes (*ANKK1*, *APOE*, *MTHFR*, *SLC6A4*) were associated with cognitive impairment. In addition, a single nucleotide polymorphism, rs1800497 in gene *ANKK1,* moderated the effects of the Mindfulness-Based Stress Reduction for Breast Cancer program on cognitive impairment. Specifically, participants carrying the polymorphic AA or AG genotype received more benefit than those carrying the wild-type (GG) genotype. To this date, there are currently no studies examining patient outcomes involving genetic influence on pain and fatigue symptom improvement resulting from MBSR(BC).

Research has shown MBSR(BC) as a mind-body therapy that has been proven to be effective for treating individual symptoms experienced by BCS, including anxiety, depression, stress, fatigue, and sleep, as well as symptoms that occur in clusters and cognitive impairment. It has been found in the literature that MBSR affects biomarkers including circulating cytokines, and has recently entered the realm of precision medicine with a study that found genetic moderation of cognitive impairment in BCS participating in a MBSR(BC) program.

Summary

In summary, fatigue and pain are commonly reported by BCS. Findings from the literature identify fatigue and pain as highly prevalent among BCS, which negatively affects their quality of life and the ability to function in everyday activities. Fatigue and pain symptoms have been associated with biomarkers in the body, including pro- and anti-inflammatory cytokines such as *IL1B* and *IL6*, and the enzyme *COMT*, in which genes associated in their pathways are under investigation in this study. Previous research found in this review of literature has identified associations between pain and fatigue symptoms and genetic variations in subjects experiencing such symptoms. Mind-body interventions such as MBSR(BC) have been proven effective at treating multiple symptoms experienced by BCS and has recently entered the precision medicine arena.

Chapter Three

Methods

Introduction

Chapter three explains the methods and procedures for this study. The purpose of this study was to identify specific genotypes involved in fatigue and pain symptoms and explore whether SNP rs16944 in gene *IL1B*, SNP rs4680 in gene *COMT*, and SNP rs1800795 in gene *IL6* moderate fatigue and/or pain outcomes in BCS and whether the effects of the MBSR(BC) intervention on fatigue and/or pain are moderated by these SNPs. This chapter first provides detailed information regarding the research design, setting, and sample for this genetic research, which was conducted within the R01 *MBSR Symptom Cluster Trial for Breast Cancer Survivors*. Next, the instruments used to measure each outcome variable will be detailed, followed by the procedures and data analyses used.

Research Design

This research study was partially funded by a grant awarded by Sigma Theta Tau International Honor Society of Nursing, Delta Beta-at-Large chapter and was conducted in part as a secondary data analysis within the parent study, *MBSR Symptom Cluster Trial for Breast Cancer Survivors*/ R01CA131080. This parent R01 study used a two-group randomized design, with 1:1 ratio assignment of BCS to either: (1) a six-week MBSR(BC) program, or (2) Usual Care (Figure 1). Randomization was stratified by: (1) type of breast cancer surgery (lumpectomy vs. mastectomy); (2) breast cancer treatment (chemotherapy with or without radiation vs.

radiation alone); and (3) stage of cancer at diagnosis (0-III). The current study implemented additional analyses of stored biological DNA samples and physical symptom measurement data to explore pain and fatigue outcomes resulting from the MBSR(BC) intervention and their possible genetic moderating effects.

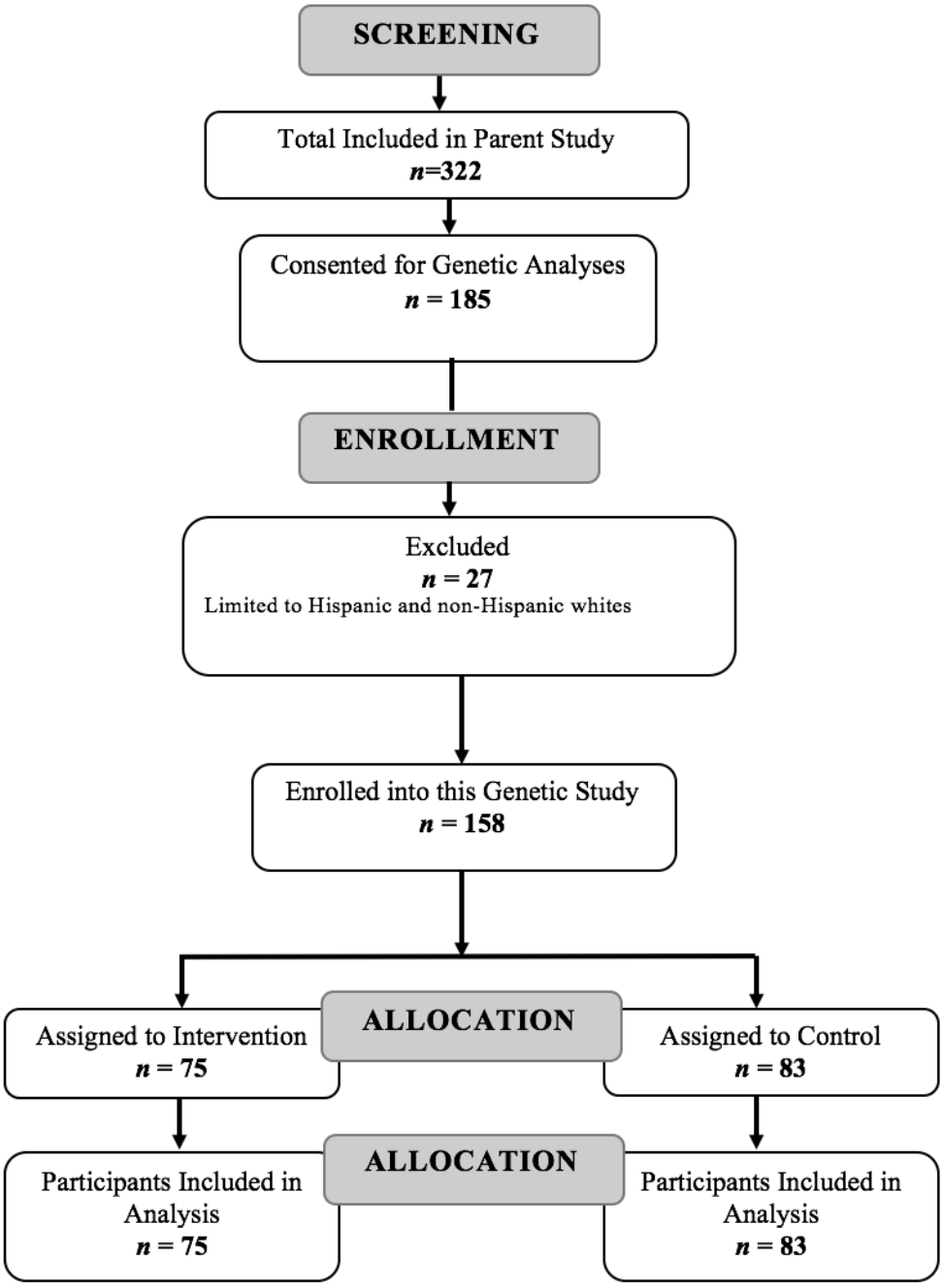


Figure 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of participant screening, enrollment and allocation from parent R01 trial to study subset.

Setting. Participants were recruited from the Carol and Frank Morsani Center for Advanced Health as well as Moffitt Cancer Center, both located in Tampa, Florida. The

assessments and delivery of the intervention took place at the Survivorship Clinic of the Moffitt Cancer Center and Research Institute. Genotyping was performed at the laboratory of Dr. Jong Park at Moffitt Cancer Center and Research Institute.

Population and Sample. The primary inclusion criteria for this study were: 1) women age 21 or older who had been diagnosed with stage 0-III BC who had undergone lumpectomy and/or mastectomy, 2) were at least two weeks but no more than two years from end of cancer treatment with adjuvant radiation and/or chemotherapy. Exclusion criteria included: 1) patients diagnosed with stage IV BC, 2) self-reported a severe current psychiatric diagnosis (e.g. bipolar disorder), or 3) recurrent BC. Out of 322 women who participated in the parent R01 *Symptom Cluster Trial for Breast Cancer Survivors* study, 158 (MBSR(BC) = 75; UC = 83) consented for genetic study with their DNA, and were included in this study.

Measurements

Demographic survey. Demographic data were collected from participants and included age, sex, gender, race, ethnicity, marital status, income status, highest level of education completed, and employment status (see Appendix A). Demographic data were gathered at baseline and updated at six and 12 weeks. A chart audit was completed through use of medical records to verify all medical and treatment information.

Clinical history survey. A Standard Clinical History form was collected at baseline and updated at six and 12 weeks to determine if there were any new problems and treatment related to problems. Data collected included types of cancer treatment, medications, stage of cancer diagnosis, date treatment ended.

Brief Pain Inventory. Pain was measured by the Brief Pain Inventory (BPI), which was developed to assess pain related to cancer and gives patients the ability to rate their pain severity

and the extent to which it interferes with dimensions of feeling and ability to function (Cleeland, 2009). The BPI (see Appendix B) contains 9-items that examine pain intensity and interference in patients (Keller et al., 2004). Items 1-6 assess pain type, pain location, and pain severity during the past week, on average and at present. Items 7-8 refer to medications and their usefulness in relieving pain. Item 9 assesses the severity of pain interference in patients' daily activities. Reliability coefficients for the BPI Severity and Interference scales were high with reliability coefficients ranging from .82 to .95.

Fatigue Symptom Inventory. Fatigue was measured by the Fatigue Symptom Inventory (FSI). The FSI (see Appendix C) is a 14-item self-report measure designed to assess fatigue severity, its frequency, and its daily pattern (Hann et al., 1998; Hann, Deniston, & Baker, 2000; Stein & Jacobsen, 1998). Items include 4 indicators of fatigue experienced in the past week and are measured on separate 11-point scales (0=Not at all fatigue; 10=Extreme fatigue) as well as current fatigue. Perceived interference is a seven-item subscale that uses separate 11-point scales to assess fatigue's interference with daily activities and was found to have good internal consistency with alpha coefficients ranging from 0.93-0.95 (Radiation Therapy Oncology Group, 2010). Convergent validity was demonstrated by significant positive correlations measures between the FSI and (POMS-Fatigue Scale) and significant negative correlations between the FSI and measures of psychological functioning (e.g., SF-36 Health Survey). Reliability coefficients for the FSI were high at >.90.

Candidate gene and single nucleotide polymorphism selection. Candidate genes and SNPs were chosen to represent polymorphisms in genes involved in various pathways, including fatigue and pain function using PubMed database. Selected genes examined in these pathways include *COMT*, *IL1B*, and *IL6*. Once candidate genes were confirmed, SNPs were selected based

on their previous associations with gene transcription or protein activity related to pain via *COMT* (Barbosa et al., 2012; Fijal, Perlis, Heinloth, & Houston, 2010; Finan et al., 2011; Jacobsen et al., 2012; Kim et al., 2006; Omair et al., 2012; Martinez-Jauand et al., 2013; Nicholl et al., 2010; Rakvag et al., 2008; Smith et al., 2014; Tammimaki & Mannisto, 2012; Vargas-Alarcon et al., 2007; Wang et al., 2015; Zubieta et al., 2003) and *IL6* (Branford, Droney, & Ross, 2012; Kovacs et al., 2016; Reyes-Gibby et al., 2008), and fatigue via *IL1B* (Bower et al., 2013; Jim et al., 2012; Reinertsen et al., 2011).

Procedures

Approvals. This study was approved by the University of South Florida Institutional Review Board and Scientific Review Committee for Moffitt Cancer Center (IRB #Ame12_107408) (see Appendix D). All policies for the University of South Florida Institutional Review Board and Scientific Review Committee for Moffitt Cancer Center were adhered to.

Recruitment. Potential participants who met the inclusion criteria were recruited from the breast cancer treatment center clinics at the Moffitt Cancer Center and Research Institute and USF's Carol and Frank Morsani Center for Advanced Healthcare. Health practitioners were provided with a complete description of the study aims and protocol. Consistent with current HIPAA regulations, patients were contacted by Moffitt members and health practitioners who identified eligible patients during routine patient care, and they provided a brief overview of the MBSR(BC) study. Multiple recruitment methods were used. To maintain consistency in participant recruitment, the recruiters followed a template to describe the study. Second, advertisements were placed in Moffitt Cancer Center and Research Institute, which included flyers and brochures. A log was implemented to track contacts made between the study recruiters

and potential participants. Interested patients who met the study inclusion criteria were asked to sign a form to show their interest in participating in the study.

Informed consent. Patients who were interested in the study were invited to an in-person orientation session, in which the principal investigator or the research assistant explained the details of the study and requirements to participate and combined HIPAA and consent documents were obtained. To maximize enrollment and minimize patient dropout, the principal investigator emphasized that, regardless of random assignment, all participants would be able to participate in the MBSR(BC) program and if they were assigned to UC, the program would be available following a wait period. Moreover, it was emphasized that the timing of the intervention was selected to assist in the critical transition period when formal medical care and support had ended, which was at least two weeks but not more than two years after cancer treatment ended. Details of the study were reviewed with the patients, including the six-week schedule of the MBSR(BC) program, information about the blood draw, and the three time points for the questionnaires to be completed. Consent was obtained from all study participants.

Data collection procedures. An in-person collection of demographic data, clinical history data, the Fatigue Symptom Inventory, and Brief Pain Inventory, were performed at baseline, the end of the six-week intervention, and follow-up at 12 weeks, which were collected from all participants who agreed to participate in the study. Five milliliters of blood were drawn at baseline from the 158 participants who consented for genetic analyses and were part of this study. Genomic DNA were isolated from peripheral blood leukocytes with a Qiagen DNA extraction kit (Qiagen, Valencia, CA) with modifications, and stored at Dr. Jong Park's laboratory at Moffitt Cancer Center and Research Institute. For this dissertation study, genotyping was performed using the stored DNA. A total of three candidate SNPs in three genes

(rs1800795 in *IL6*, rs16944 in *IL1B*, rs4680 in *COMT*) were found to be associated with fatigue and pain symptoms during a literature review and a preliminary study (Lengacher et al., 2015b). DNA samples from blood were genotyped using TaqMan allele discrimination PCR analysis method. Different probes were used in the PCR analysis to determine between variant DNA sequences at a single locus. In short, PCR reactions were performed using both 96-well and 384-well plates on separate occasions. The 96-well plates were prepared by combining 10μL TaqMan Universal PCR Master Mix, 0.5μL primer, 5.5μL RNA-free water, and 4μL DNA, for a total of 20μL per well. The 384-well plates were prepared by combining 5μL TaqMan Universal PCR Master Mix, 0.25μL primer, 2.75μL RNA-free water, and 2μL DNA, for a total of 10μL per well. PCR was performed for 45 amplification cycles using the ABI Prism 7900HT. Sequence Detection System (SDS) version 2.3 was used to distinguish between wild-type and polymorphic alleles by identifying homozygous wild-type, homozygous variant, or heterozygous genotype alleles. Assays included two controls and five duplicates as part of quality control.

Description of intervention. The MBSR(BC) program is a six-week complementary alternative medicine program adapted and tested by Lengacher et al. (2009) from Dr. Jon Kabat-Zinn's original eight-week program aimed at reducing stress through self-regulation of symptoms to improve the quality of life in BCS (Lengacher et al., 2009). The intervention components consist of: 1) educational material, 2) formal and informal meditative practice techniques, and 3) group processes related to barriers to the practice of meditation and the application of mindfulness in daily situations (Lengacher et al., 2009). Participants received training in four types of meditation techniques including: 1) sitting meditation, 2) body scan, 3) Gentle Hatha Yoga, and 4) walking meditation. Subjects assigned to the MBSR(BC) group were scheduled for six weekly sessions lasting two hours each, which were conducted by a group

leader trained in MBSR(BC). Class sizes consisted of five to six participants. In addition to the repeated assessment of blood studies and psychological symptoms, physical symptoms, quality of life and mediators at 6 and 12 weeks. MBSR(BC) participants were also asked to record their formal meditation practice times in a daily diary during the intervention period as well as during the following six-week period after the end of the intervention.

The UC group consisted of standard post-treatment follow-up clinic visits and participants were asked to abstain from meditation or yoga techniques. Usual care participants were waitlisted to the MBSR(BC) intervention, giving them the ability to participate in the MBSR(BC) program after study end (after 12 weeks).

Data management. The statistical software used for data entry, management, and analysis was Statistical Package for Social Sciences (SPSS) version 25. All data were de-identified and in order to maintain patients' confidentiality, password-protected files were stored in Dr. Cecile Lengacher's office, the principle investigator of the parent study.

Data Analysis

Sample characteristics were analyzed using descriptive statistics and frequency distributions generated from SPSS. Chi-Square tests were used for categorical variables and t-tests were used for continuous variables, to identify any potential differences between groups not controlled for by randomization.

Aim #1: To identify specific genotypes involved in fatigue and pain symptoms. First, to identify specific genotypes that are significantly associated with fatigue and/or pain symptoms at baseline, a one-way linear trend ANOVA was performed in SPSS for each SNP.

Aim #2: To explore whether single nucleotide polymorphism (SNP) rs1800795 in gene *IL6*, SNP rs16944 in gene *IL1B,* and SNP rs4680 in gene *COMT,* moderate the effects of the

MBSR(BC) intervention on fatigue and/or pain symptoms, a comparison of mean scores on Fatigue Symptom Inventory and Brief Pain Inventory subscales over time at three time points (baseline, 6 weeks, 12 weeks) for each SNP were first examined. A mixed model (MBSR(BC) X time) approach was then performed. Single nucleotide polymorphism variables and MBSR(BC) were analyzed as main effects along with the interaction of MBSR(BC) x SNP and MBSR(BC) x SNP x time (baseline to 12 weeks). A statistically significant interaction between MBSR(BC) x SNP on the slope of symptom change indicates that the relationship between MBSR(BC) and symptoms varies as a function of SNPs. Because we proposed to test a specific intervention (MBSR(BC)) and multiple SNPs in genes with multiple outcomes, a false discovery rate (FDR) approach was used. Given the potential for multiple comparisons of three SNPs in three genes associated with pain and fatigue from a literature review, an FDR rate of 0.10 was adopted. This value means that 10% of the rejected null hypotheses were assumed to be type 1 errors (Benjamini & Hochberg, 1995).

Statistical power. Since the sample size among different races may lack precision, the analyses were limited to Caucasians due to the insufficient number of minorities. A sample size of 158 subjects provides 80% power with 2-sided type I error rate of 0.05 to detect an effect size of 1.2 for the two-way interactions between genotype x time, genotype x assignment (MBSR(BC) versus UC), and assignment x time, analyzed in SPSS using linear mixed models from Aim 2. As these analyses were not designed to be confirmatory, no correction procedure was used for the type I error rate.

Methodological issues and limitations. Due to the modest sample size of 158 patients (MBSR(BC) $n = 75$; UC $n = 83$), the identification of SNPS associated with fatigue and/or pain symptoms and the degree to which they potentially moderate the effects of the MBSR(BC)

program may be subject to uncertainty. However, for Aims 1 and 2, the analysis should not be considered confirmatory, but rather as providing insight into the extent to which specific SNPs may modify the effectiveness of the MBSR(BC) program in reducing levels of pain and fatigue.

Chapter Four

Results

Introduction

This chapter presents the results of the study. First the descriptive characteristics of the sample are presented, followed by the study findings for Aim 1 and Aim 2 identifying specific genotypes associated with fatigue and pain outcomes after breast cancer treatment and exploring whether specific genotypes moderated the effects of MBSR(BC) on fatigue and pain outcomes.

Participant Characteristics

The sample consisted of 158 BCS from the original 322 BCS enrolled in the *R01 Symptoms Cluster Trial for Breast Cancer Survivors*/1R01CA131080, for which DNA had been collected. Participants were enrolled into the study and were randomly assigned to either the MBSR(BC) or UC group using computer-generated randomization, which randomly assigned participants stratified by stage of cancer (Stages 0-III) and type of cancer treatment (lumpectomy versus mastectomy and radiation with or without chemotherapy). Among the 158 participants, there were no significant differences in age, stage of cancer, or type of cancer treatment, between the MBSR(BC) (n = 75) and UC (n = 83) groups. However, there were significantly more (p = .04) participants in the UC group (83.1%) within one year from end of cancer treatment compared to the MBSR(BC) group (69.3%) (see Table 3).

Baseline demographic comparisons were produced for all 158 participants. Furthermore, fatigue and pain symptom data were complete for all 158 participants at baseline, six weeks, and

the 12-week follow-up. All 158 participants completed the study data points. Baseline demographics are illustrated in Table 1. Chi-Square tests were used for categorical variables and t-tests were used for continuous variables (i.e. age), to identify any potential differences between groups not controlled for by randomization.

The mean age for the total sample was 58.4 years, with the mean age for the MBSR(BC) group being 58 years and 58.7 years for the UC group. The majority of participants were white, non-Hispanic (89%), and differences between groups were similar, with the MBSR(BC) group being 89% White, non-Hispanic and the UC group being 88% white, non-Hispanic. There were no significant differences ($p > .05$) between the MBSR(BC) and UC groups on any of the demographic characteristics for age and race/ethnicity. The majority (70.9%, n=112) of participants in the sample were married and this was similar between groups, with 72% (n=54) of participants being married in the MBSR(BC) group, and 69.9% (n=58) being married in the UC group. The total sample's education status was mostly college educated, with 75.3% at least having some college education or an associate's degree. Approximately two-thirds of the participants were unemployed (n=100, or 63.3%), while approximately one-third (n=58, or 36.7%) were working either part time (<32 hours per week) or full time (>32 hours per week). Among the MBSR(BC) group, 33.3% (n=25) were employed, while 39.8% (n=33) of the UC group were employed. Finally, the majority of the sample included those with an annual household income of $40,000 to less than $80,000 (29.1%), and there were no statistically significant differences ($p = .905$) between groups for annual household income. Three subjects declined to report their income, for a total of 2% missing values.

Table 1. *Baseline Demographics (Age, Race/Ethnicity, Marital Status, Education Status, Employment Status, and Annual Household Income of Participants) By Randomization Assignment by Frequency and Percent*

Variable	Total N=158	MBSR(BC) n=75	Usual Care n=83	*p* value
Mean Age + Standard Deviation (years)	58.4±9	58±10	58.7±8	.904
Race, Ethnicity				.948
White, non-Hispanic	140 (89%)	67 (89%)	73 (88%)	
White, Hispanic	18 (11%)	8 (11%)	10 (12%)	
Marital Status, n (%)				.805
Married	112 (70.9%)	54 (72%)	58 (69.9%)	
Divorced	5 (3.2%)	2 (2.7%)	3 (3.6%)	
Single	16 (10.1%)	7 (9.3%)	9 (10.8%)	
Widowed	21 (13.3%)	9 (12%)	12 (14.4%)	
Other	4 (2.5%)	3 (4%)	1 (1.3%)	
Education Status, n (%)				.803
No College				
Some Grade School	1 (0.6%)	1 (1.3%)	0 (0%)	
Some High School	3 (1.9%)	2 (2.7%)	1 (1.3%)	
High School Graduate	26 (16.5%)	11 (14.7%)	15 (18.1%)	
Vocational/Technical School	9 (5.7%)	4 (5.3%)	5 (6%)	
Some College	45 (28.5%)	19 (25.3%)	26 (31.3%)	
College	41 (25.9%)	20 (26.7%)	21 (25.3%)	
Graduate or Professional School	33 (20.9%)	18 (24%)	15 (18.1%)	
Employment Status, n (%)				.812
Employed	58 (36.7%)	25 (33.3%)	33 (39.8%)	
Unemployed	100 (63.3%)	50 (66.7%)	50 (60.2%)	
Annual Household Income, n (%)	19 (12%)	9 (12%)	10 (12%)	.905
<$10,000	25 (15.8%)	13 (17.3%)	12 (14.4%)	
$10,000 to $19,999	31 (19.6%)	12 (16%)	19 (22.9%)	
$20,000 to $39,999	46 (29.1%)	24 (32%)	22 (26.5%)	
$40,000 to $79,999	13 (8.2%)	6 (8%)	7 (8.4%)	
$80,000 to $99,999	21 (13.3%)	10 (13.3%)	11 (13.3%)	
>$100,000	3 (2%)	1 (1.4%)	2 (2.5%)	
Declined to Report				

The results related to clinical characteristics (stage of disease, surgery type, treatment type, and time since treatment) for the participants in the total sample, as well as comparisons of the MBSR(BC) and UC groups, are displayed in Table 2. Cancer staging for the total sample included Stage 0, n=18 (11.4 %); Stage I, n=61 (38.6 %); Stage II, n=54 (34.2 %); and Stage III, n=25 (15.8 %). There were no statistically significant differences (p = .67) between groups. The treatment breakdown included 13.9% (n=22) of total sample participants having chemotherapy only, 25.9% (n=41) had radiation only, 30.4% (n=48) had a combination of chemotherapy and radiation, and 29.7% (n=47) had no chemotherapy or radiation. There was no statistically significant difference (p=.905) between the MBSR(BC) and UC groups for cancer treatment. The majority of total sample participants were treated surgically by mastectomy (n=93, or 58.9%) versus lumpectomy (n=65, or 41.1%). There was similarity between groups, with 61.5% (n=51) of UC and 56% (n=42) of MBSR(BC) participants treated by mastectomy and 38.5% (n=32) of UC and 44% (n=33) of MBSR(BC) participants treated by lumpectomy there was no statistically significant difference between groups (p = .487). Descriptive frequencies showed that for the total sample, 64.6 % (n= 102) of participants had been treated with hormone therapy, which included single or combination medications such as anastrazole, letrozole, levothyroxine, tamoxifen, Herceptin, or other hormone medications. There was no statistically significant difference (p = .233) between MBSR(BC) or UC groups for hormone therapy. At the baseline time point of this study, it had been less than one year for most (n=121, or 76.6%) participants since the end of cancer treatment. There was a statistically significant difference (p=.041) between the MBSR(BC) and UC groups for time since treatment. Between groups, nearly twice as many of the MBSR(BC) group participants (n=23, or 30.7%) were more than one year since cancer treatment end, versus the UC group participants (n=14, or 16.9%).

Table 2. *Clinical History Data (Stage of Disease, Surgery Type, Treatment Type, and Time Since Treatment) for Participants by Randomization Assignment by Frequency and Percent*

Variable	Total N=158	MBSR(BC) n=75	Usual Care n=83	*p* value
Cancer Stage, n (%)				.670
0	18 (11.4%)	7 (9.3%)	11 (13.3%)	
I	61 (38.6%)	28 (37.3%)	33 (39.8%)	
II	54 (34.2%)	29 (38.7%)	25 (30.1%)	
III	25 (15.8%)	11 (14.7%)	14 (16.9%)	
Surgery Type, n (%)				.487
Lumpectomy	65 (41.1%)	33 (44%)	32 (38.5%)	
Mastectomy	93 (58.9%)	42 (56%)	51 (61.5%)	
Treatment Type, n (%)				.905
Chemotherapy	22 (13.9%)	9 (12%)	13 (15.7%)	
Radiation	41 (25.9%)	19 (25.3%)	22 (26.5%)	
Chemotherapy and Radiation	48 (30.4%)	24 (32%)	24 (28.9%)	
No Chemo or Radiation	47 (29.7%)	23 (30.7%)	24 (28.9%)	
Hormonal Therapy Status, n (%)				.233
Yes	102 (64.6%)	23 (30.7%)	33 (39.8%)	
No	56 (35.4%)	52 (69.3%)	50 (60.2%)	
Time Since Treatment, n (%)				.041
<1 Year	121 (76.6%)	52 (69.3%)	69 (83.1%)	
1 to 2 Years	37 (23.4%)	23 (30.7%)	14 (16.9%)	

The demographic characteristics within this study's subset (N = 158) were similar to those found within the parent study. The average age among BCS in this study was 58.4 years, versus 56.5 years among the 322 BCS in the parent study (Lengacher et al., 2016). Among BCS in the parent study, 69.4% of participants were white, non-Hispanic, which is lower than in this study's sample (89%). This is due to the exclusion of other races and ethnicities, as the sample size would not allow for genetic analyses among those groups. Most BCS were married in both the parent study (64.4%) and this study (70.9%). Most BCS were college educated in both the parent study (some college or above = 82.2%) and this study (some college or above = 75.3%),

and two-thirds were not working in both studies. A majority of BCS had an annual household income of $40,000 to less than $80,000 in both the parent study (24.2%) and this study (29.1%).

The clinical characteristics within this study's subset (N = 158) were also similar to those found within the parent study. However, more patients were diagnosed with Stage II cancer in the parent study (35.7%), whereas more patients were diagnosed with Stage I cancer in this study's subsample (38.6%). A majority of patients in both studies received mastectomy (parent study, 53.4%; this study, 58.9%) versus lumpectomy and a combination of chemotherapy and radiation (parent study, 35.7%; this study, 30.4%) versus other types of treatments. Finally, the majority of patients were also on hormone treatment in both the parent study (55.9%) and this study's subsample (64.6%) as well.

In summary, randomization successfully controlled for most potential differences between groups (MBSR(BC) and UC) in demographic and clinical history data characteristics. However, the MBSR(BC) and UC groups were significantly different for time since treatment, with more time since treatment (at least one year) for the MBSR(BC) group than the UC group. Demographic and clinical characteristics were similar among BCS within the parent study and this study's subset.

Characteristics in Candidate SNPs

Prior to analysis of the associations of the SNPs (rs4680, rs16944, rs1800795) with pain and fatigue outcomes, characteristics of the SNPs were identified and presented in Table 3. The wild-type alleles for this sample were determined to be (A) for *COMT* SNP rs4680, (G) for *IL1B* SNP rs16944, and (G) for *IL6* SNP rs1800795. The minor allele frequency (MAF) for each SNP was determined to be 0.46 for SNP rs4680, 0.32 for rs16944, and 0.38 for rs1800795. The genotype distributions for the SNPs in this study were tested for and passed Hardy-Weinberg

equilibrium, with no statistically significant differences (*p's* > .05). Hardy-Weinberg equilibrium suggests that if the general population have allele frequencies of a and b, the sample should have allele frequencies of a^2, 2ab, and b^2. This method was used to reduce the likelihood of false results from genotyping error.

Table 3. *Characteristics of Candidate SNPs*

					Poly/HT/WT			
Gene Symbol	SNP ID	Chr/Or	Allele (P/W)	MAF	MBSR(BC) (*n* = 75)	UC (*n* = 83)	HWE	Function
COMT	rs4680	22/For	G/A	0.46	13/38/24	21/38/24	0.96	Missense Val158Met affects dopamine levels in the brain (Stein et al., 2006)
IL1B	rs16944	2/For	A/G	0.32	10/38/27	4/35/44	0.85	Affects plasma levels of IL1B
IL6	rs1800795	7/For	C/G	0.38	11/36/28	10/41/32	0.94	Affects plasma levels of IL6

Note. SNP = single nucleotide polymorphism; Chr = chromosome; Or = orientation; *COMT* = catechol-O-methyltransferase; *IL1B* = interleukin 1, beta; *IL6* = interleukin 6; Allele (P/W) = polymorphic/wild; MAF = minor allele frequency; Poly/HT/WT = homozygous polymorphic/heterozygous polymorphic/wild; For = forward.

Results Aim 1

The first aim of this study was to identify specific genotypes related to symptoms of fatigue and pain. The hypothesis for this aim was that specific genotypes are associated with higher or lower levels of pain and fatigue among BCS. To identify what specific genotypes of the three candidate SNPs were significantly associated with fatigue and pain symptoms at baseline, trend analyses using one-way linear ANOVAs were performed in SPSS among all participants (MBSR(BC), N = 75; and UC, N = 83), but found no statistically significant correlations (see Tables 4-6).

First, for SNP rs4680 in *COMT* gene, neither AA, AG, nor GG genotype were associated with a difference in mean scores on fatigue severity, fatigue interference, pain severity, or pain interference (see Table 4). For fatigue severity, there was no linear relationship among mean scores from AA to AG to GG, with mean scores of 14.63, 14.33, and 15.59 respectively. For fatigue interference, there was no linear relationship in mean scores as well, with mean scores of 27.17, 25.68, and 27.15 for AA, AG, and GG respectively. The same occurred for pain severity, with no linear pattern for AA, AG, and GG with mean scores of 8.88, 8.63, and 9.32 respectively. Although genotype did follow a linear pattern for mean scores for pain interference, with a consistent increase in mean scores from AA to GG (AA = 13.15; AG = 14.64; GG = 16.79), this was not statistically significant (p = .328).

Table 4. *One-Way ANOVA Linear Trend Analysis between SNP rs4680 in gene COMT and Pain and Fatigue Scores*

Symptom Outcome Measure	Genotype	Mean	SD	*F*	*p*-value
Fatigue Severity					
	AA	14.63	8.06	.285	.594
	AG	14.33	8.16		
	GG	15.59	7.77		
Fatigue Interference					
	AA	27.17	19.63	.000	.997
	AG	25.68	21.77		
	GG	27.15	18.54		
Pain Severity					
	AA	8.88	8.27	.059	.808
	AG	8.63	8.21		
	GG	9.32	8.22		
Pain Interference					
	AA	13.15	14.53	.963	.328
	AG	14.64	17.84		
	GG	16.79	16.38		

Note. COMT = catechol-O-methyltransferase; SNP = single nucleotide polymorphism

Second, for SNP rs1800795 in gene *IL6*, neither CC, CG, or GG genotypes were associated with a difference in mean scores on fatigue severity, fatigue interference, pain severity, or pain interference (see Table 5). For fatigue severity, there was no linear relationship among mean scores for CC, CG, and GG genotypes, with mean scores of 14.35, 14.22, and 15.42 respectively. For fatigue interference, there was no linear relationship in mean scores as well, with mean scores of 24.67, 24.18, and 29.98 for CC, CG, and GG respectively. For pain severity, there did appear to be a linear pattern among scores for CC, CG, and GG with mean scores of 8.81, 8.82, and 8.92 respectively, however, this was not significant ($p = .959$). The same occurred for pain interference, with a linear increase in scores from CC to CG to GG, however, this also was not significant ($p = .506$).

Table 5. *One-Way ANOVA Trend Analysis Between SNP rs1800795 in gene IL6 and Pain and Fatigue Scores*

Symptom Outcome Measure	Genotype	Mean	SD	*F*	*p*-value
Fatigue Severity					
	CC	14.35	7.84	.274	.601
	CG	14.22	8.46		
	GG	15.42	7.54		
Fatigue Interference					
	CC	24.67	19.06	1.067	.303
	CG	24.18	20.19		
	GG	29.98	20.84		
Pain Severity					
	CC	8.81	8.17	.003	.959
	CG	8.82	8.76		
	GG	8.92	7.54		
Pain Interference					
	CC	13.14	15.20	.445	.506
	CG	14.05	17.26		
	GG	15.95	16.20		

Note. *IL6* = interleukin 6; SNP = single nucleotide polymorphism

Finally, for SNP rs16944 in gene IL1B, neither AA, AG, or GG genotypes were associated with a difference in mean scores on fatigue severity, fatigue interference, pain severity, or pain interference (see Table 6). There was no linear pattern from AA to AG to GG for fatigue severity, with mean scores of 14.36, 13.81, and 15.66 respectively. Although there did appear to be a linear pattern among scores for AA, AG, and GG for fatigue interference, with mean scores of 24.14, 24.42, and 28.99 respectively, this was not significant ($p = .417$). There was no linear pattern for pain severity genotypes, with AA, AG, and GG scores of 10.01, 7.60, and 9.90 respectively. Finally, was no linear pattern for pain interference, with mean scores for AA, AG, and GG genotypes of 15.93, 11.97, and 17.15 respectively.

Table 6. *One-Way ANOVA Trend Analysis Between SNP rs16944 in gene IL1B and Pain and Fatigue Scores*

Symptom Outcome Measure	Genotype	Mean	SD	*F*	*p*-value
Fatigue Severity					
	AA	14.36	7.59	.310	.578
	AG	13.81	8.12		
	GG	15.66	7.98		
Fatigue Interference					
	AA	24.14	20.41	.662	.417
	AG	24.42	20.04		
	GG	28.99	20.68		
Pain Severity					
	AA	10.07	7.18	.005	.943
	AG	7.60	7.91		
	GG	9.90	8.55		
Pain Interference					
	AA	15.93	15.57	.065	.799
	AG	11.97	15.74		
	GG	17.15	17.29		

Note. *IL1B* = interleukin 1 beta; SNP = single nucleotide polymorphism

In summary, the results of the aim 1 one-way linear ANOVAs that explored the relationships between specific genotypes and fatigue or pain scores found no statistically significant correlations (*p's* > .05) for all SNPs.

Results Aim 2

The second aim of this study was to explore whether single nucleotide polymorphism (SNP) rs1800795 in gene *IL6*, SNP rs16944 in gene *IL1B,* and SNP rs4680 in gene *COMT,* moderate the effects of the MBSR(BC) intervention on fatigue and/or pain symptoms. Although there were no linear relationships between genotypes and mean scores on FSI and BPI measurements from Aim 1, the possibility of genetic moderation of FSI and BPI scores from MBSR(BC) remained, as Aim 1 and Aim 2 were not conditional upon one another. Groups were

compared by assignment (MBSR(BC) versus UC) and genotype (AA, AG, GG or CC, CG, GG) to show the changes for mean fatigue and pain scores over 12 weeks between groups. This allowed the exploration of potential genetic moderators of fatigue and/or pain symptoms in BCS as well as moderation of fatigue and/or pain symptom outcomes resulting from the MBSR(BC) intervention. Three models were used (Additive, Dominant, and Recessive for the polymorphic alleles) and the model that fit the hypotheses best was included. To further explore genetic moderation of fatigue and pain outcomes resulting from MBSR(BC), Linear Mixed Model (LMM) analyses were performed. Again, three models (Additive, Dominant, and Recessive) were used and the model that fit the hypotheses best was included.

COMT. For *COMT* SNP rs4680, when comparing mean scores between groups by assignment (MBSR(BC) versus UC) and genotype (AA, AG, GG) during the active time of the intervention (baseline to six weeks) through 12-week follow-up, it appeared that genotype may have had an impact on fatigue severity scores (see Figure 3). In Figure 3, MBSR(BC) participants with GG genotype scored higher for fatigue severity than other participants within other groups at baseline. MBSR(BC) may have had a positive effect on fatigue severity for those with GG genotype, as fatigue severity scores were higher at baseline and decreased more than those with other genotypes (AA or AG) from baseline and 12 weeks. However, in this study, the sample size was small and because the minor allele for SNP rs4680 was (G) and there were only 13 participants in the MBSR(BC) group with GG genotype (see table 3), this may have affected the results as the higher baseline mean score among that group may have influenced the regression to the mean.

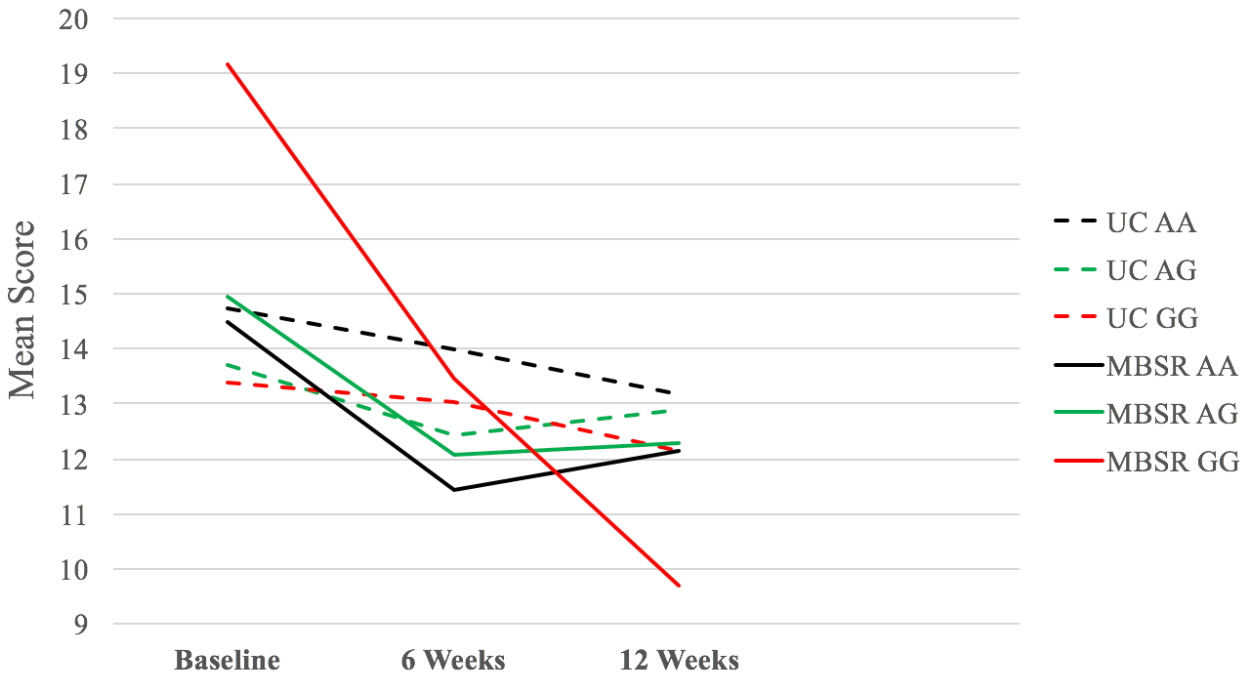


Figure 3. Fatigue Severity Scores from Baseline to 6 and 12 Weeks for COMT. A comparison of means was used to compare improvement in fatigue severity scores between groups and explore potential genetic moderation of outcomes. MBSR = mindfulness-based stress reduction for breast cancer survivor group; UC = usual care group; UC AA = usual care group with AA genotype; UC AG = usual care group with AG genotype; UC GG = usual care group with GG genotype; MBSR AA = MBSR group with AA genotype; MBSR AG = MBSR group with AG genotype; MBSR GG = MBSR group with GG genotype

To further explore the possibility that genotype moderated fatigue severity symptoms and the effects of MBSR(BC), linear mixed models (LMM) were used to assess interactions between time (baseline to 6 and 12 weeks), assignment (MBSR(BC) versus UC), and genotype (AA, AG, or GG), which resulted in no significant findings.

Table 7 illustrates that the results of LMM show that fatigue severity scores seemed to improve over time, regardless of assignment to MBSR(BC) or UC, which approached significance F (2, 156) = 2.458, p = .089. However, there were no significant interactions between time and genotype, time and assignment, or genotype and assignment at p*'s* > .05.

Table 7. Linear Mixed Model Results for Fatigue Severity by Genotype, Assignment, and Time for COMT rs4680

Source	df (num, den)	*F* value	*p* value
Time	(2, 156)	2.458	.089
Assignment	(1, 156)	.557	.457
COMT Additive	(1, 156)	.391	.677
Time**COMT* Additive	(4, 156)	1.070	.374
Time*Assignment	(2, 156)	1.383	.254
COMT Additive*Assignment	(2, 154)	1.667	.192

Note. *COMT* = Catechol-O-methyltransferase gene; df = degrees of freedom; num = numerator; den = denominator

There were also no significant findings for genetic moderation of fatigue interference for *COMT* SNP rs4680. Figure 4 illustrates that genotype did not have an effect on scores in the MBSR(BC) group, as participants with either AA, AG, or GG genotype all similarly benefited from the intervention. However, among those with GG genotype, those in the MBSR(BC) group had a decrease in fatigue interference scores from baseline to six weeks, whereas scores increased in the UC group. To further explore the possibility that genotype moderated fatigue interference and/or the effects of MBSR(BC), LMM were used and found no significant interactions of time, assignment, or genotype.

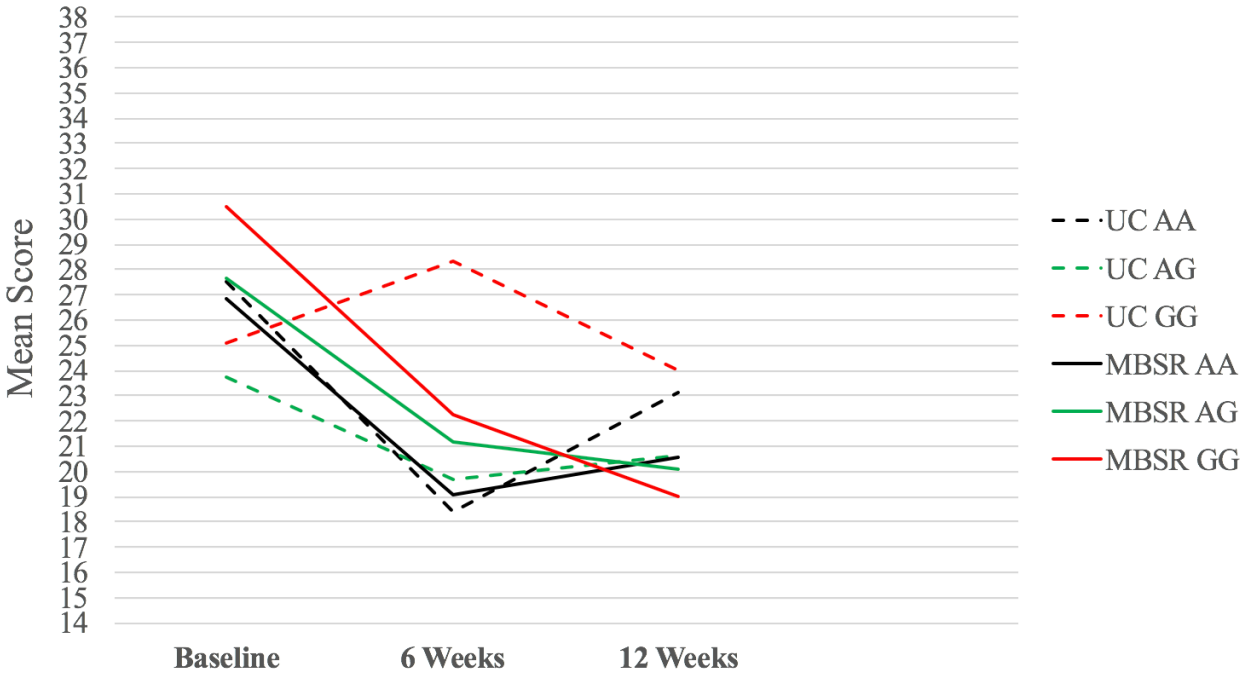


Figure 4. Fatigue Interference Scores from Baseline to 6 and 12 Weeks for COMT. A comparison of means was used to compare improvement in fatigue interference scores between groups and explore potential genetic moderation of outcomes. MBSR = mindfulness-based stress reduction for breast cancer survivor group; UC = usual care group; UC AA = usual care group with AA genotype; UC AG = usual care group with AG genotype; UC GG = usual care group with GG genotype; MBSR AA = MBSR group with AA genotype; MBSR AG = MBSR group with AG genotype; MBSR GG = MBSR group with GG genotype

Table 8 illustrates that neither time, MBSR(BC), or genotype affected fatigue interference scores. This means that whether time passed, if participants were in the UC or MBSR(BC) group, or if they had a specific genotype, these interactions did not contribute to a decrease in fatigue interference.

Table 8. Linear Mixed Model Results for Fatigue Interference by Genotype, Assignment, and Time for COMT rs4680

Source	df (num, den)	*F* value	*p* value
Time	(2, 156)	2.088	.127
Assignment	(1, 156)	.528	.469
COMT Additive	(2, 156)	.297	.744
Time**COMT* Additive	(4, 156)	1.018	.400
Time*Assignment	(2, 156)	1.211	.301
COMT Additive*Assignment	(2, 154)	.371	.690

Note. *COMT* = Catechol-O-methyltransferase gene; df = degrees of freedom; num = numerator; den = denominator

A similar result occurred for pain severity scores for *COMT* SNP rs4680, with no significant findings, Although Figure 5 illustrates that participants with GG genotype may have benefited more from the MBSR(BC) intervention between baseline and six weeks than those with AA or AG genotype, LMM were implemented and found no significant interaction.

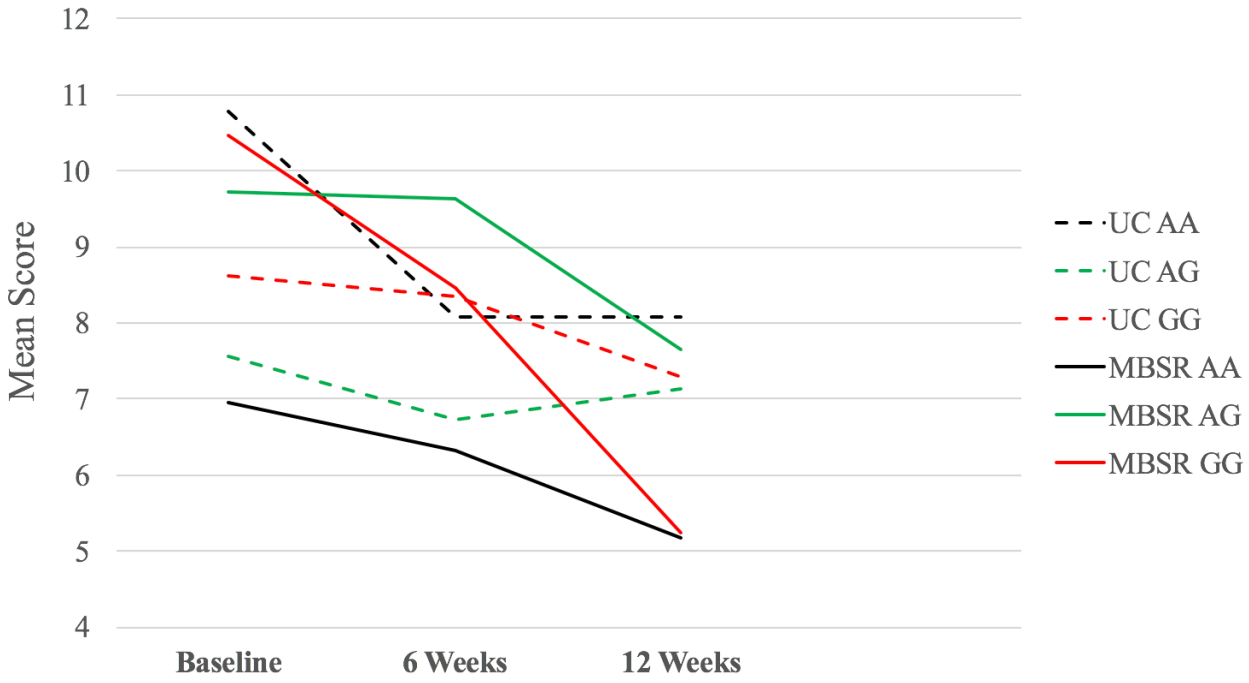


Figure 5. Pain Severity Scores from Baseline to 6 and 12 Weeks for COMT. A comparison of means was used to compare improvement in pain severity scores between groups and explore potential genetic moderation of outcomes. MBSR = mindfulness-based stress reduction for breast cancer survivor group; UC = usual care group; UC AA = usual care group with AA genotype; UC AG = usual care group with AG genotype; UC GG = usual care group with GG genotype; MBSR AA = MBSR group with AA genotype; MBSR AG = MBSR group with AG genotype; MBSR GG = MBSR group with GG genotype

Table 9 illustrates the results of LMM, which show that pain severity scores may have improved over time, regardless of assignment to MBSR(BC) or UC, as the main effect of time approached significance F (2, 156) = 2.548, p = .081. However, there were no significant interactions for the main effects of assignment or genotype, nor interactions between time and genotype, time and assignment, or genotype and assignment.

Table 9. Linear Mixed Model Results for Pain Severity by Genotype, Assignment, and Time for COMT rs4680

Source	df (num, den)	*F* value	*p* value
Time	(2, 156)	2.548	.081
Assignment	(1, 156)	.364	.547
COMT Additive	(2, 156)	.087	.917
Time**COMT* Additive	(4, 156)	.710	.586
Time*Assignment	(2, 156)	.196	.822
COMT Additive*Assignment	(2, 154)	1.939	.147

Note. *COMT* = Catechol-O-methyltransferase gene; df = degrees of freedom; num = numerator; den = denominator

When comparing mean scores from baseline to six and 12 weeks for pain interference for *COMT* SNP rs4680, it did not appear that genotype had an effect on scores or moderated the effects of MBSR(BC), as shown in Figure 6. MBSR(BC) participants with either AA, AG, or GG genotype similarly benefited during the intervention (baseline to six weeks).

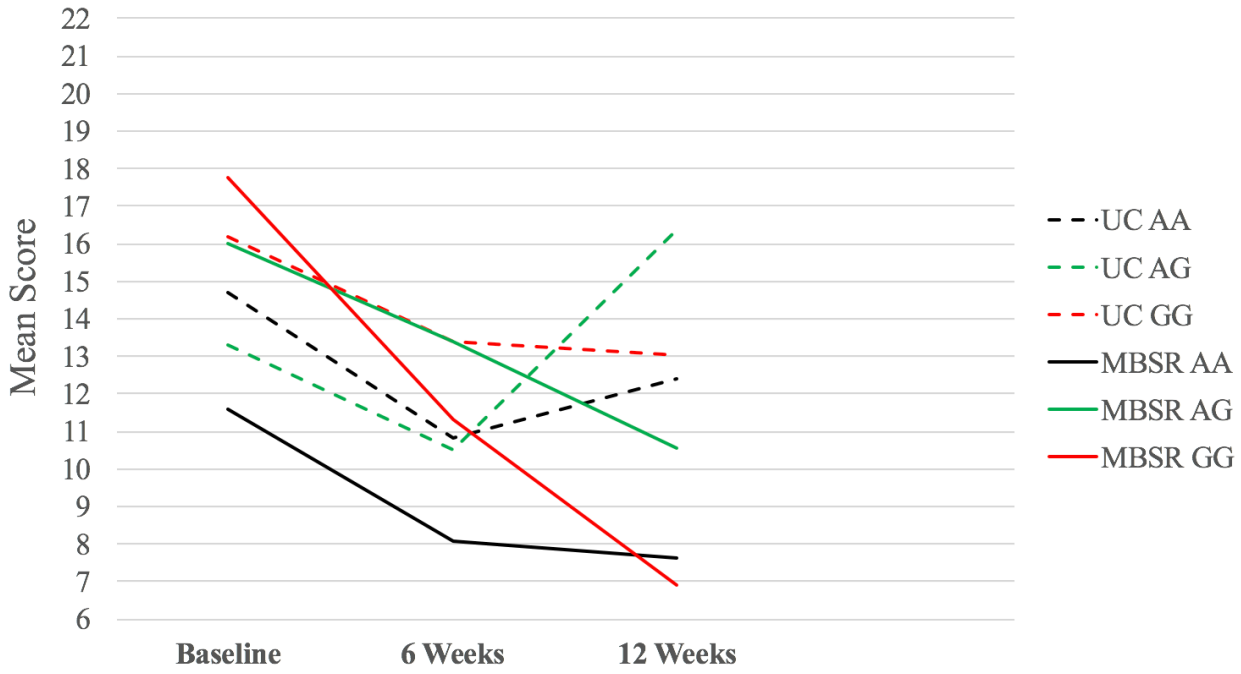


Figure 6. Pain Interference Scores from Baseline to 6 and 12 Weeks for COMT. A comparison of means was used to compare improvement in pain severity scores between groups and explore potential genetic moderation of outcomes. MBSR = mindfulness-based stress reduction for breast cancer survivor group; UC = usual care group; UC AA = usual care group with AA genotype; UC AG = usual care group with AG genotype; UC GG = usual care group with GG genotype; MBSR AA = MBSR group with AA genotype; MBSR AG = MBSR group with AG genotype; MBSR GG = MBSR group with GG genotype

Table 10 illustrates the results of LMM, which further explored the possibility that genotype moderated pain interference and the effects of MBSR(BC). Results suggest no significant interactions for the main effects of time, assignment, or genotype, or the interactions between time and genotype, time and assignment, and genotype by assignment.

Table 10. Linear Mixed Model Results for Pain Interference by Genotype, Assignment, and Time for COMT rs4680 (Additive Model)

Source	df (num, den)	*F* value	*p* value
Time	(2, 156)	2.122	.123
Assignment	(1, 156)	.153	.696
COMT Additive	(2, 156)	.266	.767
Time**COMT* Additive	(4, 156)	.935	.445
Time*Assignment	(2, 156)	.460	.632
COMT Additive*Assignment	(2, 154)	.526	.592

Note. *COMT* = Catechol-O-methyltransferase gene; df = degrees of freedom; num = numerator; den = denominator

IL1B. For *IL1B* SNP rs16944, when comparing mean scores from baseline to six and 12 weeks for fatigue severity, it did not appear that genotype had an effect on scores or moderated the effects of MBSR(BC) (see Figure 7). MBSR(BC) participants with either AA, AG, or GG genotype similarly benefited from the intervention between baseline and six weeks.

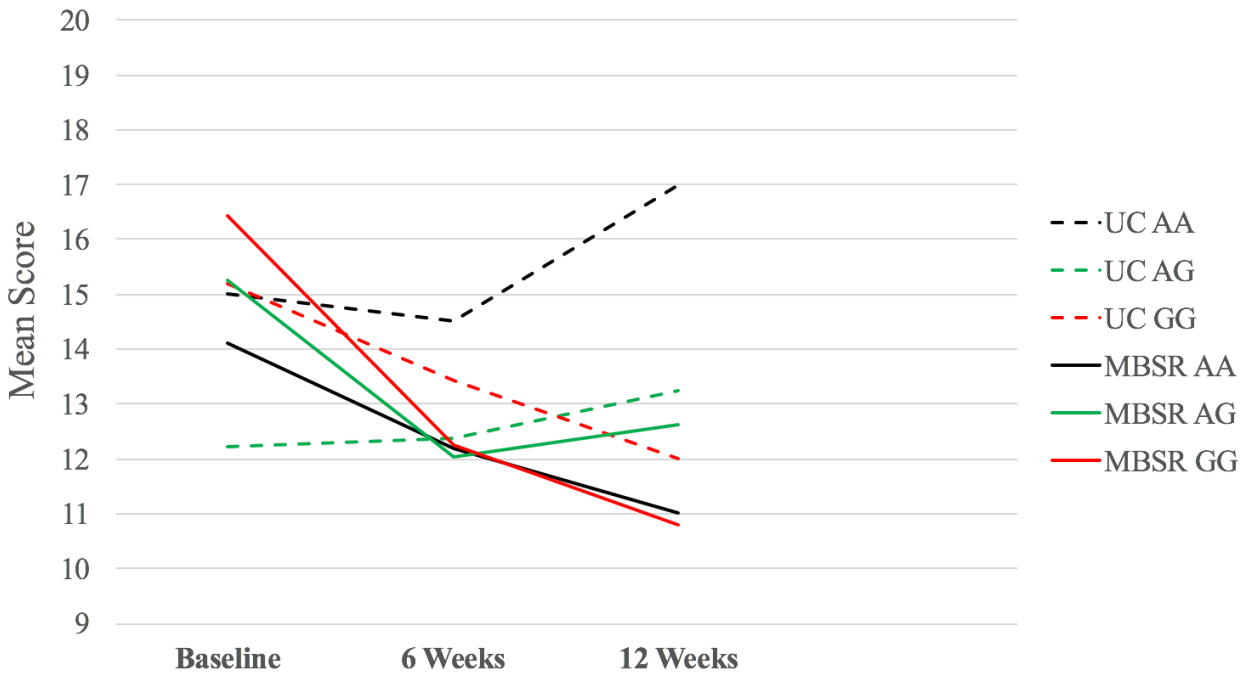


Figure 7. Fatigue Severity Scores from Baseline to 6 and 12 Weeks for IL1B. A comparison of means was used to compare improvement in fatigue severity scores between groups and explore potential genetic moderation of outcomes. MBSR = mindfulness-based stress reduction for breast cancer survivor group; UC = usual care group; UC AA = usual care group with AA genotype; UC AG = usual care group with AG genotype; UC GG = usual care group with GG genotype; MBSR AA = MBSR group with AA genotype; MBSR AG = MBSR group with AG genotype; MBSR GG = MBSR group with GG genotype

Table 11 illustrates the results of LMM, which further explored the possibility that genotype moderated fatigue severity and/or the effects of MBSR(BC). Results show that fatigue severity scores may have improved over time, regardless of assignment to MBSR(BC) or UC, as the main effect of time approached significance F (2, 156) = 2.670, p = .072. However, there were no significant interactions for the main effects of assignment or genotype, nor interactions between time and genotype, time and assignment, or genotype and assignment.

Table 11. Linear Mixed Model Results for Fatigue Severity by Genotype, Assignment, and Time for IL1B rs16944

Source	df (num, den)	*F* value	*p* value
Time	(2, 156)	2.670	.072
Assignment	(1, 156)	.642	.424
IL1B Additive	(2, 156)	.035	.966
Time**IL1B* Additive	(4, 156)	.691	.599
Time*Assignment	(2, 156)	1.287	.279
IL1B Additive*Assignment	(2, 154)	.369	.692

Note. *IL1B* = Interleukin 1 beta gene; df = degrees of freedom; num = numerator; den = denominator

When comparing mean scores from baseline to six and 12 weeks for fatigue interference for *IL1B* SNP rs16944, it did appear that genotype may have moderated the effects of MBSR(BC) (see Figure 8). Among those with AA genotype, those in the MBSR(BC) group had a decrease in fatigue interference scores from baseline to six and 12 weeks, whereas scores increased in the UC group. However, in this study, the sample size was small and because the minor allele for SNP rs16944 was (A), this may have affected the results.

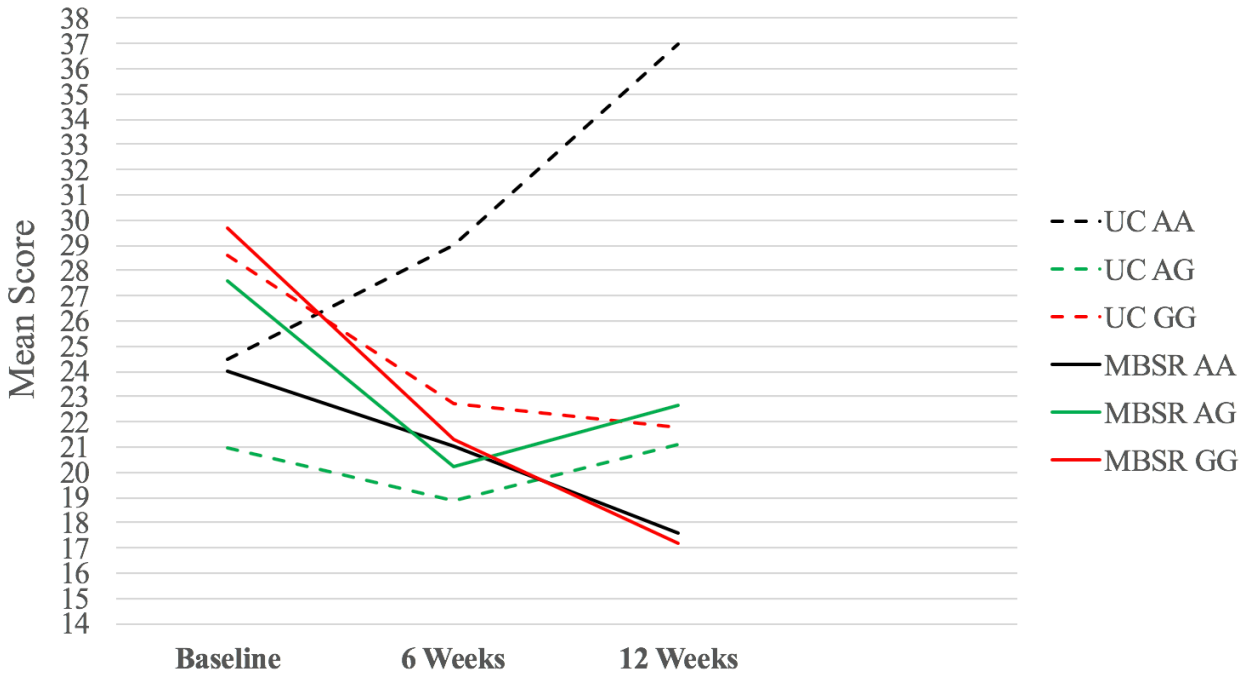


Figure 8. Fatigue Interference Scores from Baseline to 6 and 12 Weeks for IL1B. A comparison of means was used to compare improvement in fatigue interference scores between groups and explore potential genetic moderation of outcomes. MBSR = Mindfulness-based stress reduction for breast cancer survivor group; UC = Usual care group; UC AA = usual care group with AA genotype; UC AG = usual care group with AG genotype; UC GG = usual care group with GG genotype; MBSR AA = MBSR group with AA genotype; MBSR AG = MBSR group with AG genotype; MBSR GG = MBSR group with GG genotype

To further explore the possibility that genotype moderated the effects of MBSR(BC) on fatigue interference, LMM were implemented. Table 12 illustrates a decrease in fatigue interference scores over time among both MBSR(BC) and UC groups, which approached significance F (2, 156) =2.531, p = .083. This means that fatigue interference may have improved over time, regardless of assignment or genotype. However, there were no significant interactions for the main effect of assignment or genotype, nor for the interactions between time and assignment, time and genotype, or genotype and assignment.

Table 12. Linear Mixed Model Results for Fatigue Interference by Genotype, Assignment, and Time for IL1B rs16944

Source	df (num, den)	F value	*p* value
Time	(2, 156)	2.531	.083
Assignment	(1, 163)	.604	.438
IL1B Additive	(2, 156)	.041	.960
Time**IL1B* Additive	(4, 156)	.653	.625
Time*Assignment	(2, 156)	1.104	.334
IL1B Additive*Assignment	(2, 154)	.484	.617

Note. *IL1B* = Interleukin 1 beta gene; df = degrees of freedom; num = numerator; den = denominator

When comparing mean scores from baseline to six and 12 weeks for *IL1B* SNP rs16944, it appeared that genotype possibly moderated pain severity in the MBSR(BC) group, as those with AG genotype seemed to benefit less from the intervention (baseline to six weeks) than those with AA or AG genotype (see Figure 9).

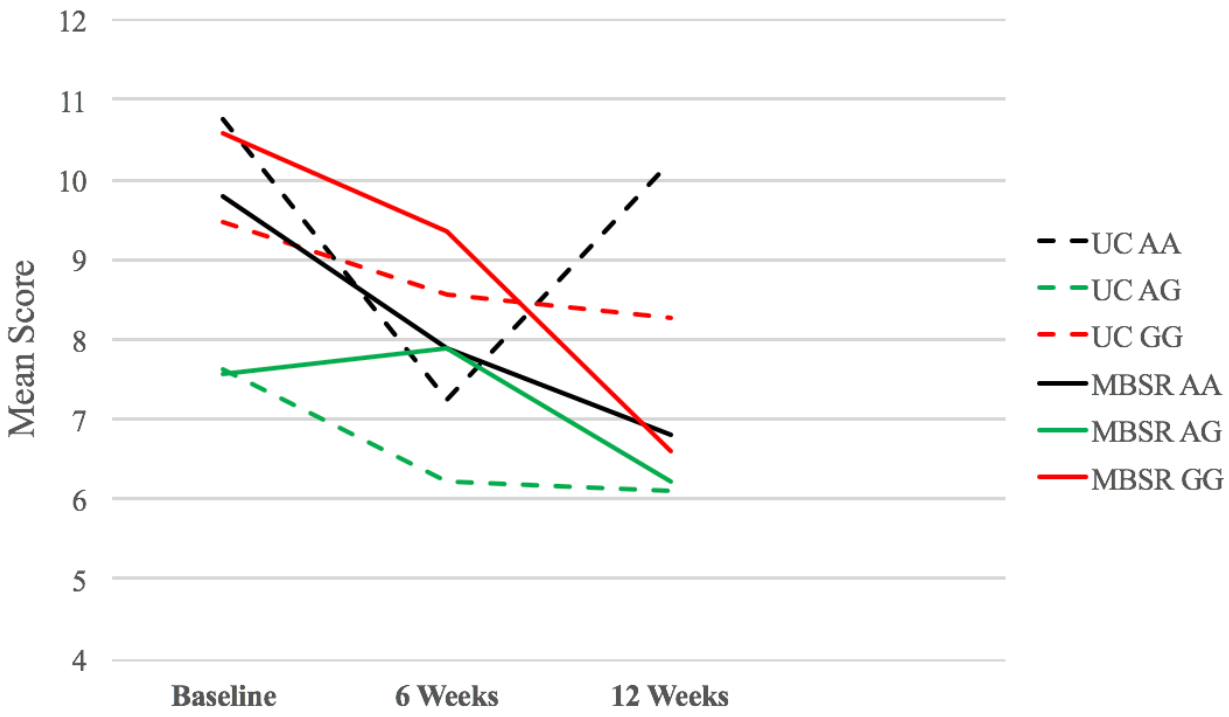


Figure 9. Pain Severity Scores from Baseline to 6 and 12 Weeks for IL1B. A comparison of means was used to compare improvement in pain severity scores between groups and explore potential genetic moderation of outcomes. MBSR = Mindfulness-based stress reduction for breast cancer survivor group; UC = Usual care group; UC AA = usual care group with AA genotype; UC AG = usual care group with AG genotype; UC GG = usual care group with GG genotype; MBSR AA = MBSR group with AA genotype; MBSR AG = MBSR group with AG genotype; MBSR GG = MBSR group with GG genotype

To further explore the possibility that genotype moderated pain severity and/or the effects of MBSR(BC), LMM were implemented. Table 13 illustrates that LMM resulted in no significant findings for the main effects of time, assignment, or genotype, nor for interactions between time and genotype, time and assignment, or genotype and assignment.

Table 13. Linear Mixed Model Results for Pain Severity by Genotype, Assignment, and Time for IL1B rs16944

Source	df (num, den)	F value	*p* value
Time	(2, 156)	.638	.530
Assignment	(1, 158)	.730	.394
IL1B Additive	(2, 156)	.623	.538
Time**IL1B* Additive	(4, 156)	.301	.877
Time*Assignment	(2, 156)	.381	.684
IL1B Additive*Assignment	(2, 154)	.110	.896

Note. *IL1B* = Interleukin 1 beta gene; df = degrees of freedom; num = numerator; den = denominator

When comparing mean scores from baseline to six and 12 weeks for *IL1B* SNP rs16944, it did not appear that genotype moderated pain interference or the effects of MBSR(BC) (see Figure 10). However, Figure 10 illustrates the lasting effects of MBSR(BC), as intervention participants experienced a decrease in pain interference even after the end of six weeks, which continued until 12-week follow up.

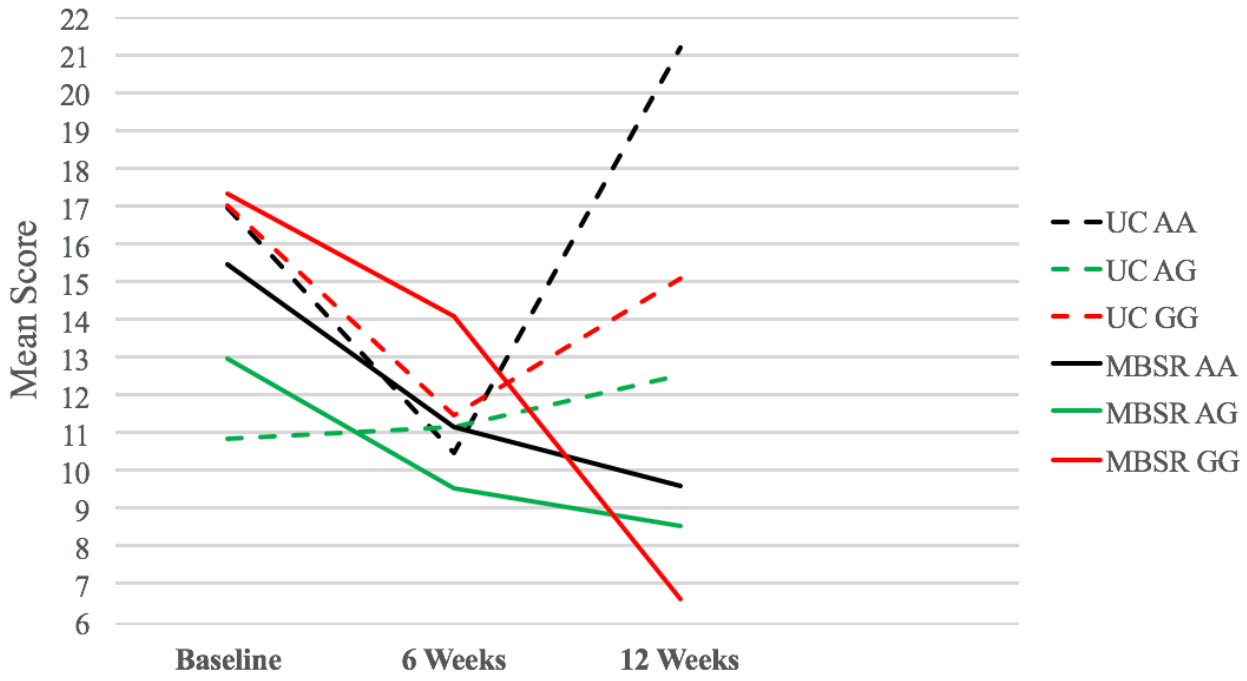


Figure 10. Pain Interference Scores from Baseline to 6 and 12 Weeks for IL1B. A comparison of means was used to compare improvement in pain interference scores between groups and explore potential genetic moderation of outcomes. MBSR = Mindfulness-based stress reduction for breast cancer survivor group; UC = Usual care group; UC AA = usual care group with AA genotype; UC AG = usual care group with AG genotype; UC GG = usual care group with GG genotype; MBSR AA = MBSR group with AA genotype; MBSR AG = MBSR group with AG genotype; MBSR GG = MBSR group with GG genotype

Lastly, to further explore the possibility that genotype moderated pain interference and/or the effects of MBSR(BC), LMM were used but found no significant results. However, table 14 illustrates a decrease in pain interference scores over time among both MBSR(BC) and UC groups, which approached significance F (2, 156) =2.959, p = .055. This means that pain interference may have improved over time, regardless of assignment or genotype. However, there were no significant results for the main effects of assignment or genotype, nor for the interactions between time and genotype, time and assignment, or genotype and assignment.

Table 14. Linear Mixed Model Results for Pain Interference by Genotype, Assignment, and Time for IL1B rs16944

Source	df (num, den)	F value	*p* value
Time	(2, 156)	2.959	.055
Assignment	(1, 161)	.279	.598
IL1B Additive	(2, 156)	.137	.872
Time**IL1B* Additive	(4, 156)	1.658	.163
Time*Assignment	(2, 156)	.449	.639
IL1B Additive*Assignment	(2, 154)	.143	.867

Note. *IL1B* = Interleukin 1 beta gene; df = degrees of freedom; num = numerator; den = denominator

IL6. For *IL6* SNP rs1800795, when comparing mean scores from baseline to six and 12 weeks for fatigue severity for *IL6* SNP rs1800795, it did appear that genotype and assignment had a moderating effect on fatigue severity (see Figure 11). Among those with CG genotype, participants in the MBSR(BC) group experienced a decrease in fatigue severity scores during the active time of the intervention (baseline to six weeks).

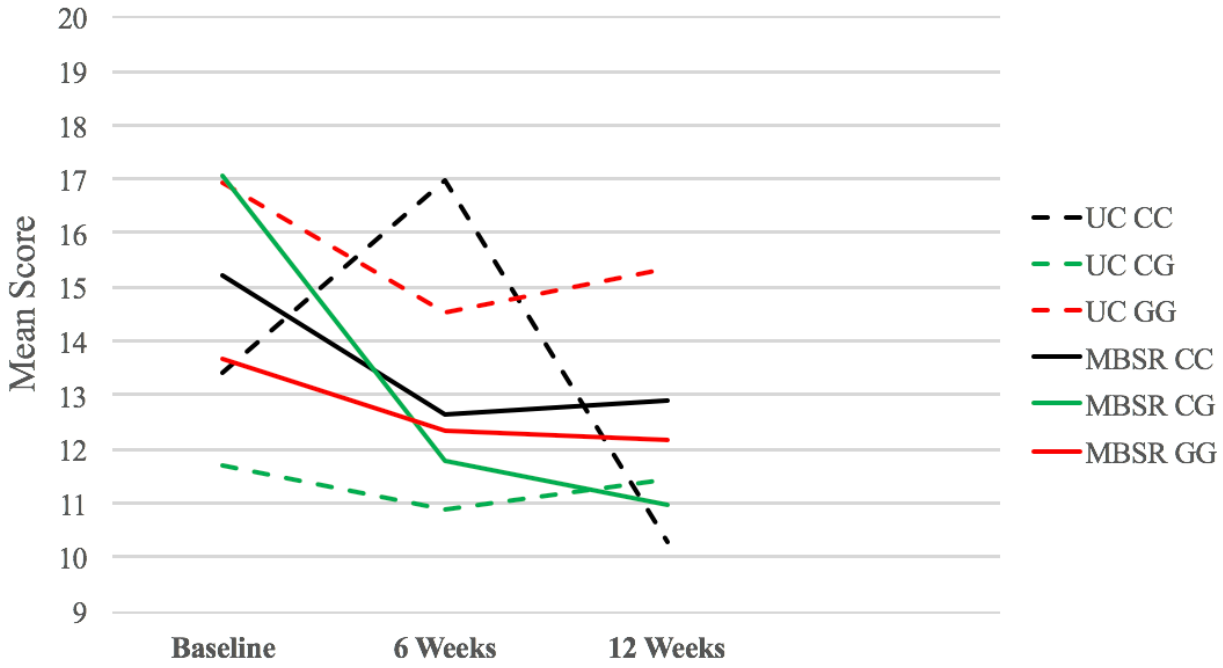


Figure 11. Fatigue Severity Scores from Baseline to 6 and 12 Weeks for IL6. A comparison of means was used to compare improvement in fatigue severity scores between groups and explore potential genetic moderation of outcomes. MBSR = Mindfulness-based stress reduction for breast cancer survivor group; UC = Usual care group; UC CC = usual care group with CC genotype; UC CG = usual care group with CG genotype; UC GG = usual care group with GG genotype; MBSR CC = MBSR group with CC genotype; MBSR CG = MBSR group with CG genotype; MBSR GG = MBSR group with GG genotype

To further explore the possibility that assignment and genotype moderated the outcome of fatigue severity, LMM were used and found a significant interaction F (2, 154) = 5.172, p = .007 (see table 15). This suggests that being in the MBSR(BC) group and having a specific genotype affected fatigue severity scores.

Table 15. Linear Mixed Model Results for Fatigue Severity by Genotype, Assignment, and Time for IL6 rs1800795

Source	df (num, den)	F value	*p* value
Time	(2, 156)	1.305	.274
Assignment	(1, 156)	.714	.399
IL6 Additive	(2, 156)	1.944	.147
Time**IL6* Additive	(4, 156)	1.065	.376
Time*Assignment	(2, 156)	1.727	.181
IL6 Additive*Assignment	(2, 154)	5.172	.007*

Note. *IL6* = Interleukin 6 gene; df = degrees of freedom; num = numerator; den = denominator; *$p<.05$

Table 16 reports mean scores and standard deviations for fatigue severity at baseline and 12 weeks for *IL6* by assignment and genotype, which further supports the results displayed in Figure 11. It may be interpreted that MBSR participants with CG genotype experienced the largest drop in fatigue severity scores from 17.08 at baseline to 10.97 at 12 weeks, with a medium to large effect size of $d = 0.72$.

Table 16. Mean Scores and Standard Deviations for Fatigue Severity at Baseline and 12 Weeks for IL6 rs1800795 by Assignment and Genotype

Group	Baseline		12 Weeks	
Assignment and Genotype	Mean	Standard Deviation	Mean	Standard Deviation
UC CC	13.40	8.396	10.27	7.754
UC CG	11.71	7.191	11.42	8.397
UC GG	16.94	8.207	15.35	9.120
MBSR CC	15.21	7.591	12.91	8.093
MBSR CG	17.08	8.977	10.97	7.829
MBSR GG	13.68	6.412	12.18	6.532

There was a similar finding when comparing mean scores from baseline to six and 12 weeks for fatigue interference for *IL6* SNP rs1800795. Figure 12 illustrates that it did appear that genotype had a moderating effect on the decrease in scores resulting from MBSR(BC). Overall, participants in the MBSR(BC) group seemed to experience a greater decrease in mean scores for fatigue interference if they had CG genotype versus CC or GG genotypes.

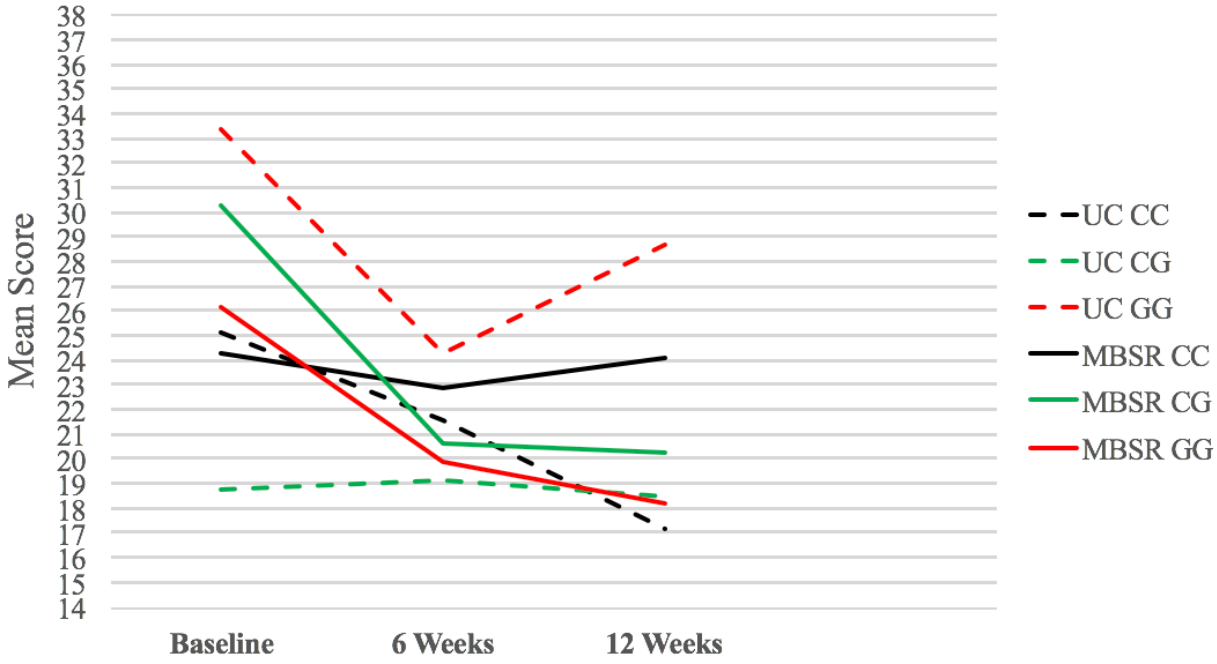


Figure 12. Fatigue Interference Scores from Baseline to 6 and 12 Weeks for IL6. A comparison of means was used to compare improvement in fatigue interference scores between groups and explore potential genetic moderation of outcomes. MBSR = Mindfulness-based stress reduction for breast cancer survivor group; UC = Usual care groupUC CC = usual care group with CC genotype; UC CG = usual care group with CG genotype; UC GG = usual care group with GG genotype; MBSR CC = MBSR group with CC genotype; MBSR CG = MBSR group with CG genotype; MBSR GG = MBSR group with GG genotype

To further explore this possibility, LMM were implemented and found a significant interaction F (2, 154) = 3.548, p = .031 between genotype and assignment (see table 16). This suggests that being in the MBSR(BC) group and having a specific genotype affected fatigue interference scores.

Table 17. Linear Mixed Model Results for Fatigue Interference by Genotype, Assignment, and Time for IL6 rs1800795

Source	df (num, den)	F value	*p* value
Time	(2, 156)	1.066	.347
Assignment	(1, 158)	.600	.440
IL6 Additive	(2, 155)	1.817	.166
Time**IL6* Additive	(4, 156)	1.143	.339
Time*Assignment	(2, 156)	1.538	.218
IL6 Additive*Assignment	(2, 154)	3.548	.031*

Note. *IL6* = Interleukin 6 gene; df = degrees of freedom; num = numerator; den = denominator; *$p<.05$

Table 18 reports mean scores and standard deviations for fatigue interference at baseline and 12 weeks for *IL6* by assignment and genotype, which further supports the results displayed in Figure 12. It may be interpreted that MBSR participants with CG genotype experienced the largest drop in fatigue interference scores from 30.31 at baseline to 20.29 at 12 weeks, with a small to medium effect size of $d = 0.48$.

Table 18. Mean Scores and Standard Deviations for Fatigue Interference at Baseline and 12 Weeks for IL6 rs1800795 by Assignment and Genotype

Group	Baseline		12 Weeks	
Assignment and Genotype	Mean	Standard Deviation	Mean	Standard Deviation
UC CC	25.10	20.212	17.20	14.242
UC CG	18.80	16.629	18.45	18.970
UC GG	33.34	21.977	28.74	21.288
MBSR CC	24.27	18.932	24.09	23.704
MBSR CG	30.31	22.280	20.29	19.170
MBSR GG	26.14	19.125	18.18	12.681

When comparing mean scores from baseline to six and 12 weeks for pain severity for *IL6* SNP rs1800795, it did appear that genotype had a moderating effect on the decrease in scores resulting from MBSR(BC) (see Figure 13). Participants with CG genotype appeared to benefit more from MBSR(BC) from baseline to six weeks than those with CC or GG genotypes. From baseline to six weeks, pain severity scores actually increased in MBSR(BC) participants with CC

genotype, and at 12 weeks, pain severity scores returned to baseline levels, showing no benefit of MBSR(BC). Similarly, MBSR(BC) participants with GG genotype experienced an increase in pain severity scores from baseline to six weeks, showing no benefit during the intervention period.

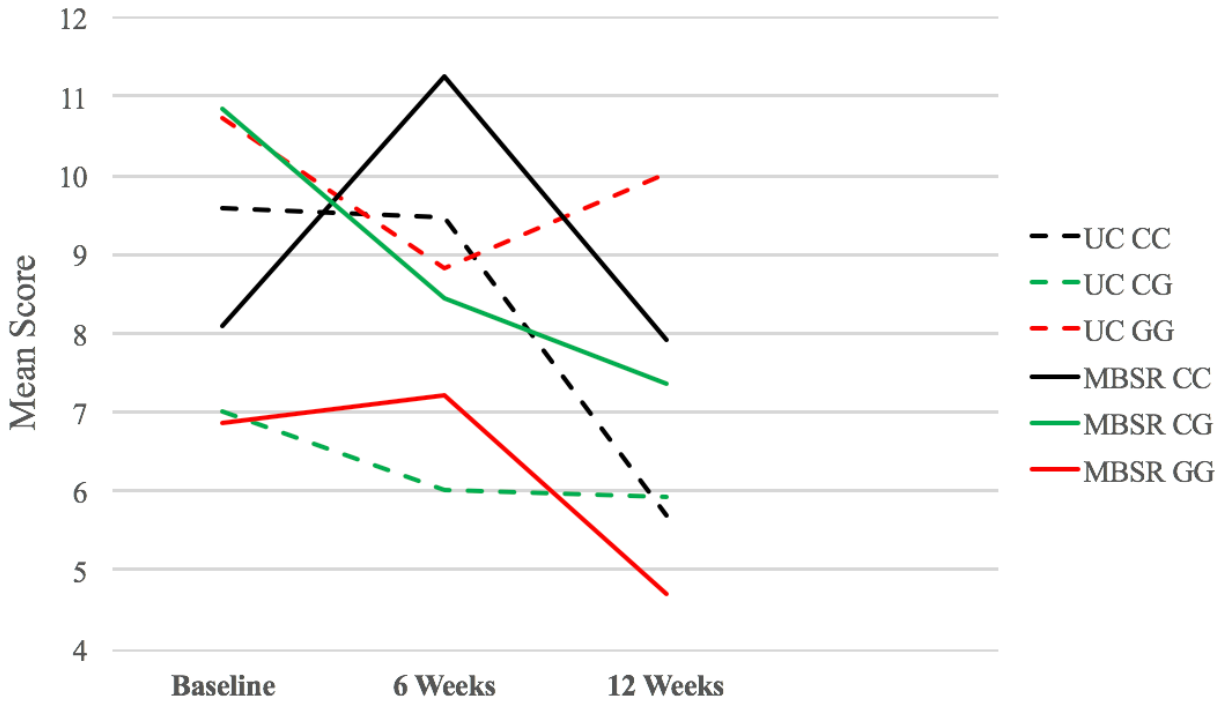


Figure 13. Pain Severity Scores from Baseline to 6 and 12 Weeks for IL6. A comparison of means was used to compare improvement in pain severity scores between groups and explore potential genetic moderation of outcomes. MBSR = Mindfulness-based stress reduction for breast cancer survivor group; UC = Usual care groupUC CC = usual care group with CC genotype; UC CG = usual care group with CG genotype; UC GG = usual care group with GG genotype; MBSR CC = MBSR group with CC genotype; MBSR CG = MBSR group with CG genotype; MBSR GG = MBSR group with GG genotype

To further explore the possibility that genotype moderated the outcome of pain severity within the MBSR(BC) group, LMM were used and confirmed a significant interaction between genotype and assignment F (2, 154) = 4.294, p = .015 (see table 17).

Table 19. Linear Mixed Model Results for Pain Severity by Genotype, Assignment, and Time for IL6 rs1800795 (Additive Model)

Source	df (num, den)	F value	*p* value
Time	(2, 156)	.974	.380
Assignment	(1, 156)	.430	.513
IL6 Additive	(2, 155)	.722	.488
Time**IL6* Additive	(4, 156)	.658	.622
Time*Assignment	(2, 156)	.250	.779
IL6 Additive*Assignment	(2, 154)	4.294	.015*

Note. *IL6* = Interleukin 6 gene; df = degrees of freedom; num = numerator; den = denominator; *$p<.05$

Table 20 reports mean scores and standard deviations for pain severity at baseline and 12 weeks for *IL6* by assignment and genotype, which further supports the results displayed in Figure 13. It may be interpreted that MBSR participants with CG genotype experienced the largest drop in pain severity scores from 10.86 at baseline to 7.38 at 12 weeks, with a small to medium effect size of $d = 0.41$.

Table 20. Mean Scores and Standard Deviations for Pain Severity at Baseline and 12 Weeks for IL6 rs1800795 by Assignment and Genotype

Group	Baseline		12 Weeks	
Assignment and Genotype	Mean	Standard Deviation	Mean	Standard Deviation
UC CC	9.60	9.97	5.70	7.24
UC CG	7.02	7.65	5.93	6.37
UC GG	10.72	7.50	10.02	7.79
MBSR CC	8.09	6.55	7.91	9.04
MBSR CG	10.86	9.57	7.38	7.39
MBSR GG	6.86	7.17	4.71	7.29

Finally, for pain interference, a comparison of mean scores from baseline to six and 12 weeks for *IL6* SNP rs1800795 suggested that genotype had a moderating effect on pain interference scores resulting from MBSR(BC) (see Figure 14).

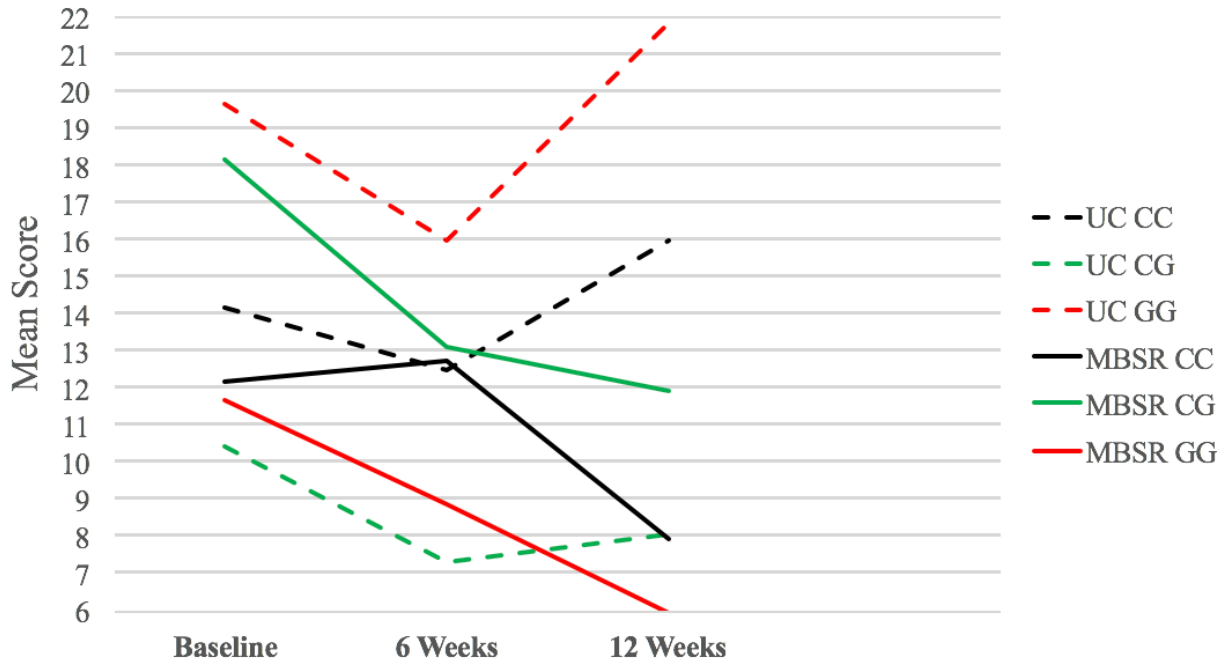


Figure 14. Pain Interference Scores from Baseline to 6 and 12 Weeks for IL6. A comparison of means was used to compare improvement in pain interference scores between groups and explore potential genetic moderation of outcomes. MBSR = Mindfulness-based stress reduction for breast cancer survivor group; UC = Usual care group; UC CC = usual care group with CC genotype; UC CG = usual care group with CG genotype; UC GG = usual care group with GG genotype; MBSR CC = MBSR group with CC genotype; MBSR CG = MBSR group with CG genotype; MBSR GG = MBSR group with GG genotype

To further explore the possibility that genotype moderated the outcome of pain interference within the MBSR(BC) group, LMM were implemented and confirmed a significant interaction between genotype and assignment F (2, 154) = 3.577, p = .030 (see table 18). This means that among MBSR(BC) participants, having a specific genotype affected pain interference scores.

Table 21. Linear Mixed Model Results for Pain Interference by Genotype, Assignment, and Time for IL6 rs1800795

Source	df (num, den)	F value	*p* value
Time	(2, 156)	1.147	.320
Assignment	(1, 157)	.221	.639
IL6 Additive	(2, 155)	1.508	.224
Time**IL6* Additive	(4, 156)	.761	.552
Time*Assignment	(2, 156)	.660	.518
IL6 Additive*Assignment	(2, 154)	3.577	.030*

Note. *IL6* = Interleukin 6 gene; df = degrees of freedom; num = numerator; den = denominator; *$p<.05$

Table 22 reports mean scores and standard deviations for pain interference at baseline and 12 weeks for *IL6* by assignment and genotype, which further supports the results displayed in Figure 14. It may be interpreted that MBSR participants with CG genotype experienced the largest drop in pain interference scores from 18.19 at baseline to 11.95 at 12 weeks, with a small to medium effect size of $d = 0.38$.

Table 22. Mean Scores and Standard Deviations for Pain Interference at Baseline and 12 Weeks for IL6 rs1800795 by Assignment and Genotype

Group	Baseline		12 Weeks	
Assignment and Genotype	Mean	Standard Deviation	Mean	Standard Deviation
UC CC	14.20	18.16	16.00	24.55
UC CG	10.41	14.72	8.08	11.61
UC GG	19.66	16.95	21.84	26.46
MBSR CC	12.18	12.77	7.95	12.40
MBSR CG	18.19	19.13	11.95	13.81
MBSR GG	19.66	16.95	21.84	26.46

In summary, there were no significant findings for SNP rs4680 in *COMT* or SNP rs16944 in *IL1B*. However, the results from LMM analyses suggest that time may have been in a factor in the improvement of fatigue severity and pain severity when assessing *COMT* and for fatigue severity, fatigue interference, and pain severity when assessing *IL1B*. Several significant findings

resulted from LMM when assessing *IL6*. First, LMM resulted in a significant interaction between genotype and assignment. Second, a comparison of means suggests that participants in the MBSR(BC) group who had CG genotype benefited more from the intervention than those with CC or GG genotypes for fatigue severity, fatigue interference, pain severity, and pain interference, with small to large effect sizes ranging from $d = 0.38$ to $d = 0.72$.

Chapter Five

Summary, Discussion, Conclusions, Implications, and Recommendations for Future Study

Introduction

The final chapter of the dissertation includes a summary of the study and a discussion of the results, conclusions including limitations, implications for nursing, and future research recommendations. The purpose of this study was to identify specific genotypes involved in fatigue and pain symptoms and explore whether SNP rs16944 in gene *IL1B*, SNP rs4680 in gene *COMT*, and SNP rs1800795 in gene *IL6* moderate fatigue and/or pain outcomes in BCS and whether the effects of the MBSR(BC) intervention on fatigue and/or pain are moderated by these SNPs. This genetic study and secondary data analysis conducted within the *R01 MBSR Symptom Cluster Trial for Breast Cancer Survivors*, 1R01CA131080.

Discussion and Conclusions

This study yielded several important findings. First, in this study of 158 BCS, most participants were married, college-educated (75.3%), with an average age of 58.4 years, and had an average annual household income of $40,000-$80,000, which were similar to the demographic characteristics within the parent R01 study (N = 322). The subsample of this study (N = 158) were not racially diverse as the sample size was too small to compare genetic associations across different racial groups and was therefore limited to non-Hispanic and Hispanic whites. In terms of clinical characteristics, most BCS were diagnosed with Stage I-II BC (72.8%), received mastectomy (58.9%), and received a combination of chemotherapy and

radiation (30.4%), and received hormone treatment (64.6%), which were similar to clinical characteristics in the parent study. Among the 158 participants in this study, there were no significant differences in age, stage of cancer, or type of cancer treatment, between MBSR(BC) (n = 75) and UC (n = 83) groups in this study. However, there were significantly more (p = .04) participants in the UC group (83.1%) within one year from end of cancer treatment compared to the MBSR(BC) group (69.3%), which may help explain why UC participants also experienced an improvement in fatigue and pain symptoms during the study, as they were closer to treatment end and may have been focused on trying to overcome adverse symptoms to continue with daily activities.

A second finding of this study was that there were no significant correlations between SNPs *COMT* rs4680, *IL1B* rs16944, and *IL6* rs1800975, and fatigue and pain symptoms at baseline. The results from one-way linear ANOVAs, which were implemented to identify specific genotypes associated with fatigue and pain symptoms from Aim 1, found no linear relationships between genotypes and mean scores on FSI and BPI measurements. Previous research has found associations between pain and SNPs in *COMT* rs4680, *IL1B* rs16944, and *IL6* rs1800795. For SNP *COMT* rs4680, the results from previous research have been mixed for associations between +/- pain severity and (A) and (G) alleles, with two studies (Knisely et al., 2018; Tammimaki & Mannisto, 2012) reporting positive associations between (A) alleles and increased pain, and another study (Rut et al., 2014) reporting a positive association between (G) alleles and increased pain. The *COMT* enzyme is responsible for metabolizing catechol neurotransmitters (dopamine, adrenaline, and noradrenaline) in the brain's prefrontal cortex. The (G) allele codes for valine amino acid, which results in more *COMT* enzyme available to metabolize catechol neurotransmitters and thus less extracellular dopamine, which may result in

a higher pain threshold and resilience to stress (Stein, Newman, Savitz, & Ramesar, 2006). Considering the previous research results between genotypes for SNP *COMT* rs4680 and pain have been mixed, and there were no significant associations found in this study, more research is needed in this area to confirm the genetic effects on the pain symptom experience. Second, for SNP *IL1B* rs16944, the results from previous research on the associations between genotype and fatigue have also been mixed. A study by Kober et al., 2016 reported an association between CG or GG genotype and higher levels of fatigue, a study by Jim et al., 2012 found no association, and a study by Collado-Hidalgo et al., 2008 reported an association between CC genotype and higher levels of fatigue. The *IL1B* gene provides instructions for producing pro-inflammatory IL1B cytokine protein, an important mediator involved in the inflammatory response, increased plasma levels of IL1B promote inflammation. It is unclear which genotypes promote increases in plasma *IL1B*. Considering the previous research results between genotypes for SNP *IL1B* rs16944 and fatigue have been mixed, and there were no significant associations found in this study, more research is needed in this area to confirm the genetic effects on the fatigue symptom experience. Finally, for SNP *IL6* rs1800795, the results from previous research have been mixed for associations between +/- fatigue severity and genotype, with one study (Collado-Hidalgo et al., 2008) reporting an association between both GG or CC genotype and higher levels of fatigue versus CG genotype, two studies (Bower et al., 2013; Shi et al., 2014) reporting an association between GG genotype and higher levels of fatigue, and one study (Jim et al., 2012) reporting an association between CG genotype and higher levels of fatigue. Similar to the actions of the *IL1B* gene, the *IL6* gene provides instructions for producing pro-inflammatory IL6 cytokine protein that is an important mediator involved in the inflammatory response and increased plasma levels of IL6 promote inflammation. It is unclear which genotypes promote increases in plasma IL6 and

considering previous research findings have been mixed for associations between SNP *IL6* rs16944 and +/- fatigue severity, more research is needed to confirm its effects on the fatigue symptom experience.

A third finding of this study is that those in the MBSR(BC) group who had CG genotype for *IL6* benefited more from the intervention than those with CC or GG genotypes for fatigue severity ($p = .007$, $d = 0.72$), fatigue interference ($p = .031$, $d = 0.48$), pain severity ($p = .015$, $d = 0.41$), and pain interference ($p = .030$, $d = 0.38$. Although there were no significant findings identified from Aim 1, this did not mean that genotype could not moderate a change in symptom scores resulting from an intervention such as MBSR(BC). Therefore, a mixed model approach was then implemented to explore whether SNP rs1800795 in gene *IL6*, SNP rs16944 in gene *IL1B,* and SNP rs4680 in gene *COMT,* moderated the effects of the MBSR(BC) intervention on fatigue and/or pain symptoms from Aim 2. Linear mixed models analyzed genotype, assignment, and time as main effects along with the interaction of genotype x time, genotype x assignment (MBSR(BC) versus UC), and assignment x time. First, an interesting finding from Aim 2 results was that regardless of assignment, participants experienced an improvement in symptoms over time. This may mean that MBSR(BC) was an effective treatment for participants within the intervention group during the active time of the intervention, and control group participants may have become more attentive and concerned over their symptoms and found other ways to improve their symptoms. In the parent study, MBSR(BC) was demonstrated as an effective therapy for fatigue severity and interference ($p's < .01$), with a small effect size for fatigue severity ($d = 0.27$) (Lengacher et al., 2016). Additional research has supported MBSR for the treatment of fatigue symptoms (Carlson & Garland, 2005) and although the parent study did not find benefit from MBSR for pain symptoms, another study found

promising results (Kvillemo & Branstrom, 2011). In this study, the significant interaction found between genotype and assignment suggests that MBSR(BC) participants with CG genotype for *IL6* experience a greater improvement in fatigue severity, fatigue interference, pain severity, and pain interference than those with CC or GG genotypes. Among other genetic studies, the results have been mixed, with some studies (Collado-Hidalgo et al., 2008; Jim et al., 2012) suggesting that CC or CG genotype predicts more fatigue and other studies (Bower et al., 2013; Collado-Hidalgo et al., 2008) suggesting GG genotype predicts higher levels of fatigue. There are no positive findings on the association between pain and SNP *IL6* rs1800795 among BCS in the literature. However, previous research suggests that increased plasma levels of pro-inflammatory cytokine IL6 are associated with pain and SNP rs1800795 influences its expression rate (Kovacs et al., 2016). Results from this study provide preliminary evidence that SNPs in genes associated with inflammatory pathways moderate the effects of MBSR(BC) on improvements fatigue and pain symptoms in BCS and supports the hypothesis that MBSR reduces symptoms by improving the stress response (Kabat-Zinn, 1990; Kabat-Zinn et al., 1985, 1992). Fatigued BCS have been found to have increased plasma levels of IL6, IL1B, and other markers of inflammation (Bower et al., 2007; Collado-Hidalgo et al., 2006). Considering mind-body therapies have been found to reduce plasma levels of inflammatory cytokines such as IL6 (Morgan et al., 2014), a speculation may be made that stress-reducing programs such as MBSR(BC) help decrease inflammation in the body by reducing inflammatory cytokine levels and thus improve fatigue and/or pain symptoms.

Exploring these associations and disseminating findings will contribute to symptom science and precision medicine by targeting optimal therapies for BCS based on their genetic profiles, which may help improve quality of life. As the symptom experience varies by

individual based on genetic and environmental backgrounds, medicine should not follow a "one-size-fits-all" approach. Mind-body therapies such as MBSR(BC) are finally entering the spotlight in medicine research. Although this study is the first reported study to explore the genetic moderation of fatigue and/or pain symptoms in BCS participating in a MBSR(BC) program, it further supports previous research (Lengacher et al., 2015b) which found genetic moderation of MBSR(BC) on cognitive impairment in BCS. The major benefit of this study is to support future genetic research and precision medicine to help predict which treatments are more advantageous for patients based on their individual genes. The major aim of the Precision Medicine Initiative is to expand cancer genomics to develop better treatment methods and during President Barack Obama's State of the Union address, $215 million was invested towards biomedical advances to help supply healthcare providers with new knowledge and tools to personalize treatments for the best outcomes (The White House, 2015). By first discovering genetic changes and their associations, further research can then test targeted interventions on patients to determine the best outcomes. This genetic study is a step towards both identifying genetic associations with adverse symptoms such as pain and fatigue experienced by BCS, and exploring the genetic moderation of MBSR(BC) on such symptoms.

Limitations

There are several limitations of this study that should be mentioned. First, the sample size was small for a genetic study. Sufficient statistical power is critical for the detection of genetic association and moderation studies. Testing one SNP requires 248 cases, under the assumption of an odds ratio of 2, 5% prevalence, 5% minor allele frequency, 1:1 case/control ratio, and a 5% error rate (Hong & Park, 2012). This current study had enrolled 158 participants and tested three SNPs: *COMT* rs4680, *IL1B* rs16944, and *IL6* rs1800795. However, this study was exploratory in

nature with a goal of identifying associations and moderation of effects that should be researched in larger future studies. A second limitation was that this study explored the presence or absence of SNPs and their association with symptoms experienced by BCS, however, it does not address gene expression. The results of this study do not bridge the gap between the presence of SNPs and their effects on protein synthesis. The study of gene expression can help explain the variability of a SNP's effect on symptoms and increase the power of detecting their overall effects (Huang, VanderWeele, & Lin, 2014). Another limitation is that although specific genotypes were explored among genes involved in inflammatory and anti-inflammatory pathways, there were no direct measures of systemic levels of circulating *IL6* and *IL1B*, which would have provided additional information on the underlying mechanisms for pain and fatigue severity. Current empirical research has primarily focused on circulating inflammatory markers, which has generally shown a positive association with fatigue and pain, particularly after the end of cancer treatment (Miaskowski & Aouizerat, 2012). In addition, since there was no assessment of fatigue or pain prior to a breast cancer diagnosis, so it is impossible to determine if there were pre-existing symptoms prior to cancer treatment. Since there was no healthy control group, inferences cannot be made about the relationship between these genetic variations and fatigue and pain in the general population or in people with other types of cancer (prostate, lung, etc.). Furthermore, this study included only Hispanic and non-Hispanic white women; generalizations to women of other races and men are limited. Finally, even though participants were randomized, the MBSR(BC) and UC groups were significantly ($p < .05$) different in terms of time since the end of their cancer treatment. The UC group was closer to cancer treatment end (< 1 year) than the MBSR(BC) group, which may have diminished the potential to determine the true influence of the MBSR(BC) intervention.

Implications for Nursing

The nurse caring for BCS should be knowledgeable of the individual variations in fatigue and pain experiences, which may be influenced by genetic background. As healthcare moves forward into the era of precision medicine, the nurse should also be aware that because of these genetic differences, some patients may respond more or less to treatments aimed at improving adverse symptoms experienced by patients after cancer treatment. As the implementation of precision medicine moves forward, nurses must continue providing care while optimizing patient outcomes. The nurse should also be informed of non-pharmacological treatments such as MBSR(BC), as discussions between the nurse and patient may occur regarding unpleasant symptoms resulting from cancer treatment and/or the cancer experience, and the nurse should be prepared to discuss what is available to the patient. Finally, educational programs should be further implemented to provide nurses a basic understanding of precision medicine, to help them understand how genetics influence subjective symptoms as well as treatment outcomes.

Recommendations for future research. This was the first study to explore whether SNPs moderate the effects of a MBSR(BC) intervention on pain and/or fatigue. Although the exact mechanisms for fatigue and pain resulting from cancer treatment are largely unknown, genetic factors play a role (Doong et al., 2015; Shi et al., 2015) and genetic studies can contribute to the field of precision medicine, to tailor complementary and alternative medicine therapies to best suit patients' needs (Grady & Gough, 2015). The future research recommendations, based on the findings of this current study as well as the existing scientific literature in this area of research, include the following:

1. To conduct additional research exploring associations between SNPs in genes and other distressing symptoms experienced by BCS after treatment.

2. To conduct a study exploring genetic moderation of symptom outcomes resulting from MBSR(BC) with a larger sample size and include a healthy (non-cancer) control group.
3. To perform a study similar to this but including other racial backgrounds. This study was conducted only on Hispanic and non-Hispanic whites and the findings may not apply to BCS with more diverse racial backgrounds. Although nucleotide diversity between humans is about 0.1 percent, this study was limited to whites only since the sample size would lack precision for other races, which were very few in the parent study.
4. Combine studies of SNP analysis, gene expression, and measurement of circulating inflammatory and ant-inflammatory markers in a study involving BCS participating in a MBSR(BC) program for pain and fatigue.

References

Abrahams, H.J., Gielissen, M.F., Schmits, I.C., Verhagen, C.A., Rovers, M.M., & Knoop, H. (2016). Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: A meta-analysis involving 12,327 breast cancer survivors. *Annals of Oncology 27*(6), 965-974.

American Cancer Society. (2017). *Breast Cancer Facts & Figures 2017-2018*. Atlanta: American Cancer Society, Inc.

American Cancer Society. (2016). *Cancer-related fatigue.* Retrieved from https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fatigue/what-is-cancer-related-fatigue.html

Andersen, S., & Skorpen, F. (2009). Variation in the COMT gene: Implications for pain perception and pain treatment. *Pharmacogenomics, 10*(4), 669-684.

Avis, N.E., Levine, B., Marshall, S.A., & Ip, E.H. (2017). Longitudinal examination of symptom profiles among breast cancer survivors. *Journal of Pain and Symptom Management, 53*(4), 703-710.

Barbosa, F.R., Matsuda, J.B., Mazucato, M., de Castro Franca, S., Zingaretti, S.M., da Silva, L.M., … Facnin, A.L. (2012). Influence of catechol-O-methyltransferase (*COMT*) gene polymorphisms in pain sensibility of Brazilian fibromyalgia patients. *Rheumatology International, 32*(2), 427-430. doi: 10.1007/s00296-010-1659-z

Belfer, I., & Segall, S. (2011). COMT genetic variants and pain. *Drugs Today, 47*(6), 457-467.

Berger, A.M., Abernethy, A.P., Atkinson, A., et al. (2010). Cancer-related fatigue. *Journal of the National Comprehensive Cancer Network, 8*(8), 904-931.

Binns-Turner, P.G., Wilson, L.L., Pryor, E.R., Boyd, G.L., & Prickett, C.A. (2011). Perioperative music and its effects on anxiety, hemodynamics, and pain in women undergoing mastectomy. *American Association of Nurse Anesthetists Journal, 79*(4 suppl), S21-S27.

Blaes, A.H., Kreitzer, M.J., Torkelson, C., & Haddad, T. (2011). Non-pharmacologic complementary therapies in symptom management for breast cancer survivors. *Seminars in Oncology, 38*(3), 394-402.

Bower, J.E., Ganz, P.A., Desmond, K.A., Rowland, J.H., Meyerowitz, B.E., & Belin, T.R. (2000). Fatigue in breast cancer survivors: Occurrence, correlates and impact on quality of life. *Journal of Clinical Oncology, 18*, 743-753. doi: 10.1200/JCO.2012.46.2143

Bower, J.E., Ganz, P.A., Irwin, M.R., Castellon, S., Arevalo, J., & Cole, S.W. (2013). Cytokine genetic variations and fatigue among patients with breast cancer. *Journal of Clinical Oncology, 31*(13), 1656-1661.

Bower, J.E. (2014). Cancer-related fatigue: Mechanisms, risk factors, and treatments. *Nature Reviews Clinical Oncology, 11*(10), 597-609.

Branford, R., Droney, J., & Ross, J.R. (2012). Opioid genetics: The key to personalized pain control? *Clinical Genetics, 82*(4), 301-310.

Brown, J.C., Mao, J.J., Stricker, C., Hwang, W.T., Tan, K.S., & Schmitz, K.H. (2014). Aromatase inhibitor associated musculoskeletal symptoms are associated with reduced physical activity among breast cancer survivors. *Breast Journal, 20*(1), 22-28.

Carlson, L.E., & Garland, S. (2005). Impact of Mindfulness-Based Stress Reduction on sleep, mood, stress, and fatigue symptoms in cancer outpatients. *International Journal of Behavioral Medicine, 12*(4), 278-285.

Carlson, L. E., Doll, R., Stephen, J., Faris, P., Tamagawa, R., Drysdale, E., & Speca, M. (2013). Randomized controlled trial of mindfulness-based cancer recovery versus supportive expressive group therapy for distressed survivors of breast cancer. *Journal of Clinical Oncology,, 31*(25), 3119-3126. doi: 10.1200/JCO.2012.47.5210

Cleelend, C.S. (2009). *The Brief Pain Inventory: User Guide*. Retrieved from https://www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf

Cleveland Clinic. (2017). *Fatigue and Cancer Fatigue.* Retrieved from https://my.clevelandclinic.org/health/articles/cancer-related-fatigue

Collado-Hidalgo, A., Bower, J.E., Ganz, P.A., Cole, S.W., & Irwin, M.R. (2006). Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clinical Cancer Research, 12,* 2759-2766.

Collado-Hidalgo, A., Bower, J.E., Ganz, P.A., Irwin, M.R., & Cole, S.W. (2008). Cytokine gene polymorphisms and fatigue in breast cancer survivors: Early findings. *Brain, Behavior, and Immunity, 22*(8), 1197-1200.

De Jesus, S., Fitzgeorge, L., Unsworth, K., Massel, D., Suskin, N., Prapavessis, H., & Sanatani, M. (2017). Feasibility of an exercise intervention for fatigued breast cancer patients at a community-based cardiac rehabilitation program. *Cancer Management Research, 9,* 29-39. doi: 10.2147/CMAR.S117703. PMID: 28228661

De Sanctis, V., Agolli, L., Visco, C., Monaco, F., Muni, R., Spagnoli, A., … Enrici, R.M. (2014). Cytokines, fatigue, and cutaneous erythema in early stage breast cancer patients receiving adjuvant radiation therapy. *BioMed Research International*., Epub ahead of print.

Dodd, M.J., Miaskowski, C., & Paul, S.M. (2001). Symptom clusters and their effect on the functional status of patients with cancer. *Oncology Nursing Forum, 28*(3), 465-470.

Donovan, K.A., & Jacobsen, P.B. (2010). The Fatigue Symptom Inventory: A systematic review of its psychometric properties. *Support Care Cancer, 19*, 169-185.

Doong, S. H., Dhruva, A., Dunn, L. B., West, C., Paul, S. M., Cooper, B. A., . . . Miaskowski, C. (2015). Associations between cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression in patients prior to breast cancer surgery. *Biological Research in Nursing, 17*(3), 237-247. doi: 10.1177/1099800414550394

Ehlers, D.K., Aguinaga, S., Cosman, J., Severson, J., Kramer, A.F., & McAuley, E. (2017). The effects of physical activity and fatigue on cognitive performance in breast cancer survivors. *Breast Cancer Research & Treatment, 165*(3), 699-707.

Evans, M.E. (1992). Using a model to structure psychosocial nursing research. *Journal of Psychosocial Nursing and Mental Health Services, 30*(8), 27-36.

Finan, P.H., Zautra, A.J., Davis, M.C., Lemery-Chalfant, K., Covault, J., & Tennen, H. (2011). *COMT* moderates the relation of daily maladaptive coping and pain in fibromyalgia. *Pain, 152*(2), 300-307. doi: 10.1016/j.pain.2010.10.024

Evans, M.E. (1992). Using a model to structure psychosocial nursing [corrected]. *Journal of Psychosocial Nursing and Mental Health Services, 30*(8), 27-32.

Fang C.Y., Reibel D.K., Longacre M.L., Rosenzweig S., Campbell D.E., & Douglas S.D. (2010). Enhanced psychosocial well-being following participation in a mindfulness-based stress reduction program is associated with increased natural killer cell activity. *Journal of Alternative and Complementary Medicine, 16*, 531–538.

Fernandez-de-las-Penas, C., Ambite-Quesada, S., Gil-Crujera, A., Cigaran-Mendez, M., & Penacoba-Puente, C. (2012). Catechol-O-methyltransferase Val158Met polymorphism influences anxiety, depression, disability, but not pressure pain sensitivity, in women with fibromyalgia syndrome. *Journal of Pain, 13*(11), 1068-1074.

Fijal, B., Perlis, R.H., Heinloth, A.N., & Houston, J.P. (2010). The association of single nucleotide polymorphisms in the catechol-O-methyltransferase gene and pain scores in female patients with major depressive disorder. *Journal of Pain, 11*(9), 910-915. doi: 10.1016/j.jpain.2009.12.016

Fishman, D., Faulds, G., Jeffery, R., Mohamed-Ali, V., Yudkin, J.S., Humphries, S., … Woo, P. (1998). The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *Journal of Clinical Investigation, 102*(7), 1369-1376.

FitzHenry, F., Wells, N., Slater, V., Dietrich, M.S., Wisawatapnimit, P., & Chakravarthy, A.B. (2014). A randomized placebo-controlled pilot study of the impact of healing touch on fatigue in breast cancer patients undergoing radiation therapy. *Integrative Cancer Therapies*, *13,* 105-113.

Galantino, M.L., Capito, L., Kane, R.J., Ottey, N., Switzer, S., Packel, L. (2003). The effects of Tai Chi and walking on fatigue and body mass index in women living with breast cancer: A pilot study. *Rehabilitation Oncology, 21*, 17-22

Galiano-Castillo, N., Cantarero-Villanueva, I., Fernandez-Lao, C., Ariza-Garcia, A., Diaz-Rodriguez, L., Del-Moral-Avila, R., & Arroyo-Morales, M. (2016). Telehealth system: A randomized controlled trial evaluating the impact of an internet-based exercise intervention on quality of life, pain, muscle strength, and fatigue in breast cancer survivors. *Cancer, 122*(20), 3166-3174.

Gavric, Z., & Vukovic-Kostic, X. (2016). Assessment of quality of life of women with breast cancer. *Global Journal of Health Science, 8*(9), 52792.

Genetics Home Reference. (2018a). *What is a gene?* Retrieved from https://ghr.nlm.nih.gov/primer/basics/gene

Genetics Home Reference. (2018b). *What is a single nucleotide polymorphism?* Retrieved from https://ghr.nlm.nih.gov/primer/genomicresearch/snp

Glare, P.A., Davies, P.S., Finlay, E., Gulati, A., Lemanne, D., Moryl, N., … Syrjala, K.L. (2014). Pain in cancer survivors. *Journal of Clinical Oncology*, 32(16), 1739-1747.

Grady, P.A., & Gough, L.L. (2015). Nursing science: Claiming the future. *Journal of Nursing Scholarship, 47*(6), 512-521.

Greenlee, H., DuPont-Reyes, M.J., Balneaves, L.G., Carlson, L.E., Cohen, M.R., Deng, G., … Tripathy, D. (2017). Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA: A Cancer Journal for Clinicans, 67*, 194-232.

Hamer, J., McDonald, R., Zhang, L., Verma, S., Leahey, A., Ecclestone, C., … Chow, E. (2016). Quality of life and symptom burden in patients with breast cancer. *Support Care Cancer*, Epub ahead of print.

Hamood, R., Hamood, H., Merhasin, I., & Keinan-Boker, L. (2017). Chronic pain and other symptoms among breast cancer survivors: Prevalence, predictors, and effects on quality of life. *Breast Cancer Research and Treatment, 167*(1), 157-169. DOI 10.1007/s10549-017-4485-0

Hickey, O.T., Nugent, N.F., Burke, S.M., Hafeez, P., Mudrakouski, A.L., & Shorten, G.D. (2011). Persistent pain after mastectomy with reconstruction. *Journal of Clinical Anesthesia,* 23, 482-488.

Hong, E.P., & Park, J.W. (2012). Sample size and statistical power calculation in genetic association studies. *Genomics Inf, 10*(2), 117-122.

Howlader, N., Noone, A.M., Krapcho, M., Garshell, J., Miller, D., Altekruse, S.F., … Cronin, K.A. (2014). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission.

Huang, H.P., He, M., Wang, H.Y., & Zhou, M. (2016). A meta-analysis of the benefits of mindfulness-based stress reduction (MBSR) on psychological function among breast cancer survivors. *Breast Cancer, 23*(4), 568-576.

Huang, Y.T., VanderWeele, T.J., & Lin, X. (2014). Joint analysis of SNP and gene expression data in genetic association studies of complex diseases. *The Annals of Applied Statistics, 8*(1), 352-376.

IASP Task Force on Taxonomy. (2017). *Pain*. Retrieved from: http://www.iasp-pain.org/Taxonomy - Pain

Jacobsen, L.M., Schistad, E.I., Storesund, A., Pedersen, L.M., Rygh, L.I., Roe, C., & Gjerstad, J. (2012). The *COMT* rs4680 Met allele contributes to long-lasting low back pain, sciatica

and disability after lumbar disc herniation. *European Journal of Pain, 16*(7), 1064-1069. doi: 10.1002/j.1532-2149.2011.00102.x

Jefford, M., Ward, A.C., Lisy, K., Lacey, K., Emery, J.D., Glaser, A.W., … Bishop, J. (2017). Patient-reported outcomes in cancer survivors: A population-wide cross-sectional study. *Supportive Care in Cancer*, 1-9. DOI 10.1007/s00520-017-3725-5

Jim, H.S., Park, J.Y., Permuth-Wey, J., Rincon, M.A., Phillips, K.M., Small, B.J., & Jacobsen, P.B. (2012). Genetic predictors of fatigue in prostate cancer patients treated with androgen deprivation therapy: Preliminary findings. *Brain, Behavior, and Immunity, 26*(7), 1030-1036.

Johns, S.A., Brown, L.F., Beck-Coon, K., Monahan, P.O., Tong, Y., & Kroenke, K. (2014). Randomized controlled pilot study of mindfulness-based stress reduction for persistently fatigued cancer survivors. *Psycho-Oncology, 24*(8), 885-893. 10.1002/pon.3648

Johns, S.A., Brown, L.F., Beck-Coon, K., Talib, T.L., Monahan, P.O., Giesler, R.B., … Kroenke, K. (2016a). Randomized controlled pilot trial of mindfulness-based stress reduction compared to psychoeducational support for persistently fatigued breast and colorectal cancer survivors. *Support Care Cancer, 24*(10), 4085-4096.

Johns, S.A., Von Ah, D., Brown, L.F., Beck-Coon, K., Talib, T.L., Alyea, J.M., … Giesler, R.B. (2016b). Randomized controlled pilot trial of mindfulness-based stress reduction for breast and colorectal cancer survivors: Effects on cancer-related cognitive impairment. *Journal of Cancer Survivorship, 10*(3), 437-448.

Kabat-Zinn, J. (1990). *Full catastrophe living: Using the wisdom of your body and mind to face stress*. New York, NY: Bantam Books.

Kabat-Zinn, J., Lipworth, L., & Burney, R. (1985). The clinical use of mindfulness meditation for the self-regulation of chronic pain. *Journal of Behavioral Medicine, 8,* 163-190.

Kabat-Zinn, J., Massion, A.O., Kristeller, J., Peterson, L.G., Fletcher, K.E., Pbert, L., … Santorelli, S.F. (1992). Effectiveness of a medication-based stress reduction program in the treatment of anxiety disorders. *American Journal of Psychiatry, 149*, 936-943.

Kim, H., Lee, H., Rowan, J., Brahim, J., & Dionne, R.A. (2006). Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. *Molecular Pain, 2*, 24.

Kinkead, B., Schettler, P.J., Larson, E.R., Carroll, D., Sharenko, M., Nettles, J., … Rapaport, M.H. (2018). Massage therapy decreases cancer-related fatigue: Results from a randomized early phase trial. *Cancer, 124*(3), 546-554.

Knisely, M.R., Conley, Y.P., Kober, K.M., Smoot, B., Paul, S.M., Levine, J.D., & Miaskowski, C. (2018). Associations between catecholaminergic and serotonergic genes and persistent breast pain phenotypes following breast cancer surgery. *Journal of Pain,* Epub ahead of print.

Kober, K.M., Smoot, B., Paul, S.M., Cooper, B.A., Levine, J.D., & Miaskowski, C. (2016). Polymorphisms in cytokine genes are associated with higher levels of fatigue and lower levels of energy in women after breast cancer surgery. *Journal of Pain and Symptom Management, 52*(5), 695-708).

Kovacs, D., Eszlari, N., Petschner, P., Pap, D., Vas, S., Kovacs, P., … Juhasz, G. (2016). Interleukin-6 promoter polymorphism interacts with pain and life stress influencing depression phenotypes. *Journal of Neural Transmitters, 123*(5), 541-548. doi: 10.1007/s00702-016-1506-9

Kvillemo, P., & Branstrom, R. (2011). Experiences of a mindfulness-based stress-reduction intervention among patients with cancer. *Cancer Nursing, 34*(1), 24-31.

Lacourt, T.E. & Heijnen, C.J. (2017). Mechanisms of neurotoxic symptoms as a result of breast cancer and its treatment: Considerations on the contribution of stress, inflammation, and cellular bioenergetics. *Current Breast Cancer Reports, 9*(2), 70-81.

Larkey, L., Huberty, J., Pedersen, M.S., & Weihs, K. (2016). Qigong/Tai Chi Easy for fatigue in breast cancer survivors: Rationale and design of a randomized clinical trial. *Contemporary Clinical Trials, 50*, 222-228.

Lee, B.N., Dantzer, R., Langley, K.E., Bennett, G.J., Dougherty, P.M., Dunn, A.J., … Cleeland, C.S. (2004). A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation, 11*(5), 279-292.

Lengacher, C.A., Johnson-Mallard, V., Post-White, J., Moscoso, M.S., Jacobsen, P.B., Klein, T.W., … Kip, K.E. (2009). Randomized controlled trial of mindfulness-based stress reduction (MBSR) for survivors of breast cancer. *Psycho-Oncology, 18*(12), 1261-1272.

Lengacher, C.A., Reich, R.R., Post-White, J., Moscoso, M., Shelton, M.M., Barta, M., … Budhrani, P. (2012). Mindfulness-based stress reduction in post-treatment breast cancer patients: An examination of symptoms and symptom clusters. *Journal of Behavioral Medicine, 35*(1), 86-94.

Lengacher, C.A., Kip, K.E., Post-White, J., Fitzgerald, S., Newton, C., Barta, M., … Klein, T.W. (2013). Lymphocyte recovery after breast cancer treatment and mindfulness-based (MBSR) therapy. *Biological Research for Nursing, 15*(1), 37-47.

Lengacher, C.A., Shelton, M.M., Riech, R.R., Barta, M.K., Johnson-Mallard, V., Moscoso, M.S., … Kip, K.E. (2014). Mindfulness based stress reduction (MBSR(BC)) in breast cancer:

Evaluating fear of recurrence as a mediator of psychological and physical symptoms in a randomized control trial (RCT). *Journal of Behavioral Medicine, 37*(2), 185-195.

Lengacher, C.A., Kip, K.E., Reich, R.R., Craig, B.M., Mogos, M., Ramesar, S., … Pracht, E. (2015a). A cost-effective mindfulness stress reduction program: A randomized control trial for breast cancer survivors. *Nursing Economics, 33*(4), 210-218, 232.

Lengacher, C.A., Reich, R.R., Kip, K.E., Paterson, C.L., Park, H.Y., Ramesar, S., … Park, J.Y. (2015b). Moderating effects of genetic polymorphisms on improvements in cognitive impairment in breast cancer survivors participating in a 6-week mindfulness-based stress reduction program. *Biological Research in Nursing, 17*(4), 393-404.

Lengacher, C.A., Reich, R.R., Paterson, C.L., Jim, H.S., Ramesar, S., Alinat, C.B., … Kip, K.E. (2015c). The effects of mindfulness-based stress reduction on objective and subjective sleep parameters in women with breast cancer: A randomized controlled trial. *Psycho-Oncology, 24*(4), 424-432.

Lengacher, C.A., Reich, R.R., Paterson, C.L., Ramesar, S., Park, J.Y., Alinat, C.B., … Kip, K.E. (2016). Examination of broad symptom improvement resulting from mindfulness-based stress reduction in breast cancer survivors: A randomized controlled trial. *Journal of Clinical Oncology, 34*(24), 2827-2834.

Lengacher, C.A., Reich, R.R., Ramesar, S., Alinat, C.B., Moscoso, M., Cousin, L., … Park, J.Y. (2017). Feasibility of the Mobile Mindfulness-Based Stress Reduction for Breast Cancer (mMBSR(BC)) program for symptom improvement among breast cancer survivors. *Psycho-Oncology,* Epub ahead of print.

Leyson, L., Beckwee, D., Nijs, J., Pas, R., Bilterys, T., Vermeir, S., & Adriaenssens, N. (2017). Risk factors of pain in breast cancer survivors: A systematic review and meta-analysis. *Support Care Cancer, 25*(12), 3607-3643.

Li, X.M., Zhou, K.N., Yan, H., Wang, D.L., & Zhang, Y.P. (2012). Effects of music therapy on anxiety of patients with breast cancer after radical mastectomy: A randomized clinical trial. *Journal of Advanced Nursing, 68*, 1145-1155.

Ludwig, D.S., & Kabat-Zinn, J. (2008). Mindfulness in medicine. *JAMA, 300,* 1350-1352.

Lynch, M. (2001). Pain as the fifth vital sign. *Journal of Intravenous Nursing*, 24(2), 85-94

Martinez-Jauand, M., Sitges, C., Rodriguez, V., Picornell, A., Ramon, M., Buskila, D., & Montoya, P. (2013). Pain sensitivity in fibromyalgia is associated with catechol-O-methyltransferase (*COMT*) gene. *European Journal of Pain, 17*(1), 16-27. doi: 10.1002/j.1532-2149.2012.00153.x

Miaskowski, C., & Aouizerat, B. E. (2012). Biomarkers: Symptoms, survivorship, and quality of life. *Seminars in Oncology Nursing, 28*, 129–138. doi:10.1016/j.soncn.2012.03.008

Miaskowski, C., Aouizerat, B.E., Dodd, M., & Cooper, B. Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. *Journal of the National Cancer Institute Monographs, 37,* 39-46.

Montgomery, G.H., Weltz, C.R., Seltz, M., & Bovjerg, D.H. (2002). Brief pre-surgery hypnosis reduces distress and pain in excisional breast biopsy patients. *International Journal of Clinical and Experimental Hypnosis, 50*, 17-32.

Montgomery, G.H., Bovbjerg, D.H., Schnur, J.B., David, D., Goldfarb, A., Weltz, C.R., … Silverstein, J.H. (2007). Randomized clinical trial of a brief hypnosis intervention to

control side effects in breast surgery patients. *Journal of the National Cancer Institute, 99*(17), 1304-1312.

Morgan, N., Irwin, M.R., Chung, M., & Wang, C. (2014). The effects of mind-body therapies on the immune system: A meta-analysis. *PLoS One, 9* (7), e100903.

Mustian, K.M., Katula, J.A., Gill, D.L., Roscoe, J.A., Lang, D., & Murphy, K. (2004). Tai Chi Chuan, health-related quality of life and self-esteem: A randomized trial with breast cancer survivors. *Support Care Cancer, 12,* 871-876.

National Cancer Institute. (2015). *Strategic priorities: Symptom management and quality of life steering committee*. Retrieved from https://www.cancer.gov/about-nci/organization/ccct/steering-committees/2015-SxQoLSC-StrategicPriorities

National Cancer Institute. (2017). *Fatigue (PDQ)-Health Professional Version*. Retrieved from https://www.cancer.gov/about-cancer/treatment/side-effects/fatigue/fatigue-hp-pdq#cit/section_1.13

National Human Genome Research Institute. (2018). *Genotype*. Retrieved from https://www.genome.gov/glossary/index.cfm?id=93

Nicholl, B.I., Holliday, K.L., Macfarlane, G.J., Thomson, W., Davies, K.A., O'Neill, T.W., … McBeth, J. (2010). No evidence for a role of the catechol-O-methyltransferase pain sensitivity haplotypes in chronic widespread pain. *Annals of the Rheumatic Diseases, 69*(11), 2009-2012.

Niv, D., & Kreitier, S. (2001). Pain and quality of life. *Pain Practice, 1*(2), 150-161.

Omair, A., Lie, B.A., Reikeras, O., Holden, M., & Brox, J.I. (2012). Genetic contribution of catechol-O-methyltransferase variants in treatment outcome of low back pain: A prospective genetic association study. *BMC Musculoskeletal Disorders, 13*, 76.

Palesh, O., Scheiber, C., Kesler, S., Mustian, K., Koopman, C., & Schapira, L. (2017). Management of side effects during and post-treatment in breast cancer survivors. *The Breast Journal, 24*(2), 167-175.

Post-White, J., Kinney, M.E., Savik, K., Gau, J.B., Wilcox, C., & Lerner, I. (2003). Therapeutic massage and healing touch improve symptoms in cancer. *Integrative Cancer Therapies, 2,* 332-344.

Radiation Therapy Oncology Group. (2010). *Fatigue Symptom Inventory*. Retrieved from https://www.rtog.org/LinkClick.aspx?fileticket=NGE3JA-Xav0%3D&tabid=118

Rakvag, T.T., Ross, J.R., Sato, H., Skorpen, F., Kaasa, S., & Klepstad, P. (2008). Genetic variation in the catechol-O-methyltransferase (*COMT*) gene and morphine requirements in cancer patients with pain. *BMC Molecular Pain, 4*, 64. doi: 10.1186/1744-8069-4-64

Rausch, S.M., Robins, J., Walter, J.M., & McCain, N.L. (2006). Tai chi as a biobehavioral intervention for women with breast cancer. *Brain, Behavior and Immunity, 20*, 58-59.

Reich, R.R., Lengacher, C.A., Kip, K.E., Shivers, S.C., Schell, M.J., Shelton, M., … Klein, T.W. (2014). Baseline immune biomarkers as predictors of MBSR(BC) treatment success in off-treatment breast cancer patients. *Biological Research for Nursing, 16*(4), 429-437.

Reich, R.R., Lengacher, C.A., Alinat, C.B., Kip, K.E., Paterson, C., Ramesar, S., … Park, J. (2017a). Mindfulness-Based Stress Reduction in post-treatment breast cancer patients: Immediate and sustained effects across multiple symptom clusters. *Journal of Pain and Symptom Management, 53*(1), 85-95.

Reich, R.R., Lengacher, C.A., Klein, T.W., Newton, C., Shivers, S., Ramesar, S., … Kip, K.E. (2017b). A randomized controlled trial of the effects of Mindfulness-Based Stress

Reduction on levels of inflammatory biomarkers among recovering breast cancer survivors. *Biological Research in Nursing, 19*(4), 456-464.

Reinertsen, K.V., Grenaker Alnaes, G.I., Landmark-Hoyvik, H., Loge, J.H., Wist, E., Kristensen, V.N., … Edvardsen, H. (2011). Fatigued breast cancer survivors and gene polymorphisms in the inflammatory pathway. *Brain, Behavior, and Immunity, 25*(7), 1376-1383. doi: 10.1016/j.bbi.2011.04.001

Ren, K., & Torres, R. (2009). Role of interleukin-1beta during pain and inflammation. *Brain Research Reviews, 60*(1), 57-64.

Reyes-Gibby, C.C., El Osta, B., Spitz, M.R., Parsons, H., Kurzrock, R., Wu, X., … Bruera, E. (2008). The influence of tumor necrosis factor-alpha -308 G/A and IL-6 -174 G/C on pain and analgesia response in lung cancer patients receiving supportive care. *Cancer Epidemiology, Biomarkers, and Prevention, 17*(11), 3262-3267. doi: 10.1158/1055-9965.EPI-08-0125

Rim, C.H., Ahn, S.J., Kim, J.H., Yoon, W.S., Chun, M., Yang, D.S., … Cha, J. (2017). An assessment of quality of life for early phase after adjuvant radiotherapy in breast cancer survivors: A Korean multicenter survey (KROG 14-09). *Health Quality Life Outcomes*, *15*, 96. 10.1186/s12955-017-0673-1

Rosenberg, K. (2016). Acupressure reduces breast cancer-related fatigue. *American Journal of Nursing 116*(10), 61-62.

Runowicz, C.D., Leach, C.R., Henry, N.L., Henry, K.S., Mackey, H.T., Cowens-Alvarado, R.L., … & Cannady, R.S. (2016). American Cancer Society/ American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *Journal of Clinical Oncology, 34*(6), 611-635.

Rut, M., Machoy-Mokrzynska, A., Reclawowicz, D., Sloniewski, P., Kurzawski, M., Drozdzik, M., … Bialecka, M. (2014). Influence of variation in the catechol-O-methyltransferase gene on the clinical outcome after lumbar spine surgery for one-level symptomatic disc disease: A report on 176 cases. *Acta Neurochirurgica: The European Journal of Neurosurgery, 156(*2), 245-252.

Sarenmalm, E.K., Martensson, L.B., Andersson, B.A., Karlsson, P., & Bergh, I. (2017). Mindfulness and its efficacy for psychological and biological responses in women with breast cancer. *Cancer Medicine, 6*(5), 1108-1122.

Serra, M.C., Ryan, A.S., Ortmeyer, H.K., Addison, O., & Goldberg, A.P. (2018). Resistance training reduces inflammation and fatigue and improves physical function in older breast cancer survivors. *Menopause, 25*(2), 211-216. doi: 10.1097/GME.0000000000000969

Shi, Q., Wang, X. S., Li, G., Shah, N. D., Orlowski, R. Z., Williams, L. A., . . . Cleeland, C. S. (2015). Racial/ethnic disparities in inflammatory gene single-nucleotide polymorphisms as predictors of a high risk for symptom burden in patients with multiple myeloma 1 year after diagnosis. *Cancer, 121*(7), 1138-1146. doi: 10.1002/cncr.29154

Siegel, R.L., Miller, K.D., & Jemal, A. (2018). Cancer Statistics, 2018. *CA: A Cancer Journal for Clinicians, 68*(1), 7-30.

Smith, S.B., Reenila, I., Mannisto, P.T., Slade, G.D., Maixner, W., Diatchenko, L., & Nackley, A.G. (2014). Epistasis between polymorphisms in *COMT*, *ESR1,* and *GCH1* influences *COMT* enzyme activity and pain. *Pain, 155*(11), 2390-2399.

Stein, D.J., Newman, T.K., Savitz, J., & Ramesar, R. (2006). Warriors versus worriers: The role of *COMT* gene variants. *CNS Spectrums, 11*(10), 745-748.

Tammimaki, A., & Mannisto, P.T. (2012). Catechol-O-methyltransferase gene polymorphism and chronic human pain: A systematic review and meta-analysis. *Pharmacogenetics and Genomics, 22*(9), 673-691.

Tao, W.W., Jiang, H., Tao, X.M., Jiang, P., Sha, L.Y., & Sun, X.C. (2016). Effects of acupuncture, tuina, tai chi, qigong, and traditional Chinese medicine five-element music therapy on symptom management and quality of life for cancer patients: A meta-analysis. *Journal of Pain and Symptom Management, 51*(4), 728-747.

The White House. (2015). *Fact Sheet: President Obama's Precision Medicine Initiative.* Retrieved from https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative

United States (U.S.) Breast Cancer Statistics. (2018). Retrieved from http://www.breastcancer.org/symptoms/understand_bc/statistics

Vargas-Alarcon, G., Fragoso, J.M., Cruz-Robles, D., Vargas, A., Vargas, A., Lao-Villadoniga, J.I., … Martinez-Lavin, M. (2007). Catechol-O-methyltransferase gene haplotypes in Mexican and Spanish patients with fibromyalgia. *Arthritis Research and Therapy, 9*(5), R110.

Vichaya, E.G., Chiu, G.S., Krukowski, K., Lacourt, T.E., Kavelaars, A., Dantzer, R., … Walker, A.K. (2015). Mechanisms of chemotherapy-induced behavioral toxicities. *Frontiers in Neuroscience, 9*, 131.

Wang, X.S., Song, H.B., Chen, S., Zhang, W., Liu, J.Q., Huang, C., … Chu, Q. (2015). Association of single nucleotide polymorphisms of *ABCB1*, *OPRM1* and *COMT* with pain perception in cancer patients. *Journal of Huazhong University of Science and Technology, Med Sciences, 35*(5), 752-758.

Wang, X.S., & Woodruff, J.F. (2015). Cancer-related and treatment-related fatigue. *Gynecological Oncology, 136*(3), 446-452.

Witek-Janusek, L., Albuquerque, K., Chroniak, K.R., Durazo-Arvizu, R., & Mathews, H.L. (2008). Effect of mindfulness-based stress reduction on immune function, quality of life, and coping in women newly diagnosed with early stage breast cancer. *Brain, Behavior, and Immunity, 22*, 969-981.

Yeh, C.H., Chien, L.C., Lin, W.C., Bovbjerg, D.H., & van Londen, G.J. (2016). Pilot randomized controlled trial of auricular point acupressure to manage symptom clusters of pain, fatigue, and disturbed sleep in breast cancer patients. *Cancer Nursing, 39*(5), 402-410.

Ziegelstein, R.C. (2017). Personomics: The missing link in the evolution from precision medicine to personalized medicine. *Journal of Personalized Medicine, 7*(4), 11.

Zomkowski, K., de Souza, B.C., da Silva, F.P., Moreira, G.M., de Souza Cunha, N., & Sperandio, F.F. (2018). Physical symptoms and working performance in female breast cancer survivors: A systematic review. *Journal of Disability and Rehabilitation, 40*(13), 1485-1493.

Zubieta, J.K., Heitzeg, M.M., Smith, Y.R., Bueller, J.A., Xu, K., Xu, Y., … Goldman, D. (2003). *COMT* val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science, 299*(5610), 1240-1243.

Appendices

Appendix A. Clinical History Forms

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐ Group #: ☐☐

Patient Demographics

Patient Information:

Sex: ○ Female ○ Male

What is your ethnic or racial background? (choose all that apply)

- ○ White, non-Hispanic
- ○ White, Hispanic
- ○ Black, non-Hispanic
- ○ Black, Hispanic
- ○ Chinese
- ○ Japanese
- ○ Filipino
- ○ Native American, Eskimo or Aleutian
- ○ Hawaiian
- ○ Korean
- ○ Vietnamese
- ○ Ashkenazi Jewish (European origin)
- ○ Don't know
- ○ Other

If "Other", please specify: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

What is your current marital status? (choose only one response)

- ○ Married
- ○ Single
- ○ Widowed
- ○ Divorced
- ○ Other

What is your current educational status? (choose only one response)

- ○ Some grade school
- ○ Some high school
- ○ High school graduate
- ○ Vocational/Technical beyond high school
- ○ Some college or associate's degree
- ○ College
- ○ Graduate or Professional school
- ○ Other

What is your current employment status? (choose only one response)

- ○ Employed >= 32 hrs/wk
- ○ Employed < 32 hrs/wk
- ○ Full time student
- ○ Part time student
- ○ Homemaker
- ○ On medical leave
- ○ Disabled
- ○ Unemployed
- ○ Retired
- ○ Employed < 32 hrs/wk & part time student
- ○ Other

Appendix A. Clinical History Forms (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐ Group #: ☐☐

What is your income? (choose only one response)

- ○ Less than $10,000
- ○ $10,000 to < $20,000
- ○ $20,000 to < $40,000
- ○ $40,000 to < $80,000
- ○ $80,000 to < $100,000
- ○ $100,000 or more

Type of employment (choose only one response)

- ○ Forestry, fishing, hunting and agricultural support
- ○ Mining
- ○ Utilities
- ○ Construction
- ○ Manufacturing
- ○ Wholesale trade
- ○ Retail trade
- ○ Transportation and warehousing
- ○ Information
- ○ Finance and Insurance
- ○ Real estate and rental and leasing
- ○ Professional, scientific, and technical services
- ○ Management of companies and enterprises
- ○ Administration, support, waste management, remediation services
- ○ Educational services
- ○ Health care and social assistance
- ○ Arts, entertainment, and recreation
- ○ Accommodation and food services
- ○ Other services

Appendix A. Clinical History Forms (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐ Group #: ☐☐

Clinical History

1. Medical History

Current Episode of Breast

Please enter the details of this episode here:

1. Type of breast cancer:

- O Lobular carcinoma in-situ (LCIS)
- O Ductal carcinoma in-situ (DCIS)
- O Not specified
- O Other
- O Invasive lobular
- O Invasive ductal
- O Unknown

Date of diagnosis (mm/dd/yyyy)

☐☐ / ☐☐ / ☐☐☐☐

Side

O Left O Right O Both O Unknown

If "Other", please describe:

Treatment

O Chemotherapy O Radiation therapy
O Hormone therapy O Surgery

Personal History of Cancers Other than Breast Cancer: O Yes O No O Unknown

If "Yes", please enter the details here:

1.

Year of diagnosis ☐☐☐☐

Treatment (check all that apply)

O Chemotherapy O Radiation therapy O None
O Hormone therapy O Surgery O Other

2.

Year of diagnosis ☐☐☐☐

Treatment

O Chemotherapy O Radiation therapy O None
O Hormone therapy O Surgery O Other

Which option below best describes your current level of physical activity WITHIN THE PAST WEEK? Please choose only one response.

- O Fully active, able to carry on all usual activities without restrictions
- O Restricted in physically strenuous activity, but can walk and is able to carry out light housework
- O Can walk and take care of yourself, but unable to carry out any work activities. Up more than half a day
- O Need some help taking care of yourself, spend more than half a day in bed or a chair
- O Cannot take care of yourself at all, and spend all of time in bed or a chair

Do you perform Breast self exams: O No O Weekly O Monthly O Occasionally

Appendix A. Clinical History Forms (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐ Group #: ☐☐

Clinical History

2. Medical History (Please answer **ALL** of the following questions related to your health)

Have you ever had a heart attack?	O No	O Yes
Have you ever been treated for heart failure? (You may have been short of breath and the doctor may have told you that you had fluid in your lungs or that your heart was not pumping.)	O No	O Yes
Have you ever had an operation to unclog or bypass the arteries in your arms or legs?	O No	O Yes
Have you ever had a stroke, cerebrovascular accident, blood clot or bleeding in the brain or transient ischemic attack (TIA)?	O No	O Yes
If Yes, do you have difficulty moving an arm or leg as a result of a stroke or a cerebrovascular accident?	O No	O Yes
Do you have asthma, emphysema, chronic bronchitis or chronic obstructive lung disease?	O No	O Yes
If Yes, take medication for your condition (either on a regular basis or just for flare-ups)?	O No	O Yes
Do you have stomach ulcers or peptic ulcer disease?	O No	O Yes
If Yes, was this condition diagnosed by endoscopy (whre a doctor looks into your stomach through a scope), or an upper GI or barium swallow study (where you swallow chalky dye and then x-rays are taken)?	O No	O Yes
Do you have diabetes or high blood sugar?	O No	O Yes
If Yes, please answer the following questions:		
Is it treated by monitoring your diet?	O No	O Yes
Is it treated by medications taken by mouth?	O No	O Yes
Is it treated by insulin injections?	O No	O Yes
Has your diabetes caused problems with your kidneys or problems with your eyes treated by an opthalmologist?	O No	O Yes
Have you ever had problems with your kidneys?	O No	O Yes
If Yes, please answer the following questions:		
Have you had poor kidney function with blood tests showing high creatinine levels?	O No	O Yes
Have you used hemodialysis or peritoneal dialysis?	O No	O Yes
Have you received a kidney transplant?	O No	O Yes
Do you have rheumatoid arthritis?	O No	O Yes
If Yes, do you take medication for your arthritis regularly?	O No	O Yes
Do you have lupus (systemic lupus erythrematosus) or polymyalgia rheumatica?	O No	O Yes
Do you have Alzheimer's Disease or another form of dementia?	O No	O Yes
Do you have cirrhosis or sever liver disease?	O No	O Yes
Do you have leukemia or polycythemia vera?	O No	O Yes
Do you have lymphoma?	O No	O Yes
Do you have AIDS (HIV)? This question is optional.	O No	O Yes
Do you have any other cancer (other than breast cancer, skin cancer, leukemia or lymphoma)?	O No	O Yes
If Yes, has the cancer spread or metastasized to other parts of your body?	O No	O Yes

Do you have any other medical problems?

If Yes, please describe the problem(s) here:

Appendix A. Clinical History Forms (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐ Group #: ☐☐

Clinical History

3. Past Surgical History

Hysterectomy (Removal of the uterus): O Yes O No O Unknown

Date of hysterectomy (mm/dd/yyyy): ☐☐ / ☐☐ / ☐☐☐☐

Reason for hysterectomy:
O Excessive bleeding
O Uterine fibroid
O Cancer
O Endometriosis
O Unknown
O Other

If "Other", please specify:

Oophorectomy (Removal of an ovary): O Yes O No O Unknown

Date of oophorectomy (mm/dd/yyyy): ☐☐ / ☐☐ / ☐☐☐☐

Side of oophorectomy: O Left O Right O Bilateral O Unknown

Reason for oophorectomy:
O During hysterectomy
O Ovarian cancer
O Ovarian cyst
O Benign ovarian mass
O Endometrial cancer
O Other

If "Other", please specify:

4. Diagnostic Studies

Mammograms

Date of most recent mammogram (mm/dd/yyyy): ☐☐ / ☐☐ / ☐☐☐☐

Age at most recent mammogram (years): ☐☐☐

Location of most recent mammogram (Name of facility):

Result of most recent mammogram: O Normal O Abnormal O Unknown

Was this your first mammogram: O Yes O No

Appendix A. Clinical History Forms (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐ Group #: ☐☐

Clinical History

5. Current Medications

Please list any medications you are now taking, including vitamins and non-prescription drugs. If there are more than 10, please write other medications below.

	Medication Name	Date Started	Reason for Use
1.		☐☐ / ☐☐ / ☐☐☐☐	
2.		☐☐ / ☐☐ / ☐☐☐☐	
3.		☐☐ / ☐☐ / ☐☐☐☐	
4.		☐☐ / ☐☐ / ☐☐☐☐	
5.		☐☐ / ☐☐ / ☐☐☐☐	
6.		☐☐ / ☐☐ / ☐☐☐☐	
7.		☐☐ / ☐☐ / ☐☐☐☐	
8.		☐☐ / ☐☐ / ☐☐☐☐	
9.		☐☐ / ☐☐ / ☐☐☐☐	
10.		☐☐ / ☐☐ / ☐☐☐☐	
11.		☐☐ / ☐☐ / ☐☐☐☐	
12.		☐☐ / ☐☐ / ☐☐☐☐	
13.		☐☐ / ☐☐ / ☐☐☐☐	
14.		☐☐ / ☐☐ / ☐☐☐☐	
15.		☐☐ / ☐☐ / ☐☐☐☐	
16.		☐☐ / ☐☐ / ☐☐☐☐	
17.		☐☐ / ☐☐ / ☐☐☐☐	
18.		☐☐ / ☐☐ / ☐☐☐☐	
19.		☐☐ / ☐☐ / ☐☐☐☐	
20.		☐☐ / ☐☐ / ☐☐☐☐	

19372

Appendix A. Clinical History Forms (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐ Group #: ☐☐

Clinical History

6. Social History

Marital status: O Married O Single O Widowed O Divorced

Where were you born? ☐

Where were you raised? ☐

How many years have you been in Florida? ☐☐

Current/Former occupation: ☐

Do you smoke cigarettes? O Yes, currently O No, previously O No

If yes, please answer the following:

Total years as a smoker: ☐☐☐

Number of cigarettes per week: (1 pack = 20 cigarettes) ☐☐☐ Packs per day: ☐☐

Date started: ☐☐ / ☐☐ / ☐☐☐☐

Date stopped: ☐☐ / ☐☐ / ☐☐☐☐

Do you drink alcoholic beverages? O Yes O No

Note: If you drink only occasionally, please answer "0":

How many beers do you drink per week: O 0 O 1-2 O 3-4 O Greater than 5

How many glasses of wine do you drink per week: O 0 O 1-2 O 3-4 O Greater than 5

How much hard liquor do you drink per week: O 0 O 1-2 O 3-4 O Greater than 5

Do you drink caffeinated beverages? O Yes O No

How many cups of coffee or tea per day? ☐☐☐

How many soft drinks (soda) per day? ☐☐☐

What type? ☐

Appendix A. Clinical History Forms (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐ Group #: ☐☐

Clinical History

6. Social History (Cont.)

Diet:

In the last 5 days, how many fruits per day have you had? ☐☐☐

How many vegetables have you had per day? ☐☐☐

Exercise:

How many days a week do you exercise? ☐

How many times a day do you exercise? ☐☐

What type(s) of exercise do you engage in? ☐

Therapy:

1. Do you regularly use a support group to assist you with your recovery? O Yes O No
2. Do you regularly use meditation to assist you with your recovery? O Yes O No
3. Do you regularly use prayer to assist you with your recovery? O Yes O No
4. Do you regularly use guided imagery to assist you with your recovery? O Yes O No
5. Do you regularly use hypnosis to assist you with your recovery? O Yes O No
6. Do you regularly use counseling to assist you with your recovery? O Yes O No
7. Do you regularly use yoga to assist you with your recovery? O Yes O No
8. Do you regularly engage in other stress reducing techniques to assist you with your recovery? O Yes O No

Appendix A. Clinical History Forms (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐ Group #: ☐☐

Clinical History

8. Family History (cont.)

Family history of benign breast conditions: O Yes O No O Unknown

If "Yes", please enter the details here:

	Family member*	Age at diagnosis
1.	☐☐	☐☐☐
2.	☐☐	☐☐☐
3.	☐☐	☐☐☐
4.	☐☐	☐☐☐
5.	☐☐	☐☐☐

Family member key

* Please use the following key when filling in "Family Member" information. Maternal refers to your mother's side of the family and Paternal refers to your father's side of the family.

1 = Mother
2 = Father
3 = Sister
4 = Brother
5 = Daughter
6 = Son
7 = Maternal grandmother
8 = Maternal grandfather
9 = Paternal grandmother
10 = Paternal grandfather
11 = Maternal aunt
12 = Maternal uncle
13 = Paternal aunt
14 = Paternal uncle
15 = Cousin (maternal or paternal)

Family history of other cancer (including breast cancer): O Yes O No O Unknown

If "Yes", please enter the details here (*please use the Family Member key at the top of this page):

	Family member*	Age at diagnosis	Status of family member	Type of cancer	Death due to cancer	Age of death
1.	☐☐	☐☐☐	O Alive O Dead O Unknown		O Yes O No O Unknown	☐☐☐
2.	☐☐	☐☐☐	O Alive O Dead O Unknown		O Yes O No O Unknown	☐☐☐
3.	☐☐	☐☐☐	O Alive O Dead O Unknown		O Yes O No O Unknown	☐☐☐
4.	☐☐	☐☐☐	O Alive O Dead O Unknown		O Yes O No O Unknown	☐☐☐
5.	☐☐	☐☐☐	O Alive O Dead O Unknown		O Yes O No O Unknown	☐☐☐
6.	☐☐	☐☐☐	O Alive O Dead O Unknown		O Yes O No O Unknown	☐☐☐
7.	☐☐	☐☐☐	O Alive O Dead O Unknown		O Yes O No O Unknown	☐☐☐

Appendix B. Fatigue Symptom Inventory

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐☐ Group #: ☐☐

FSI

For each of the following, circle the **one number** that best indicates how that item applies to you.

1. Rate your level of fatigue on the day you felt **MOST** fatigued during the past week:

0	1	2	3	4	5	6	7	8	9	10
Not at all fatigued										**As fatigued as I could be**

2. Rate your level of fatigue on the day you felt **LEAST** fatigued during the past week:

0	1	2	3	4	5	6	7	8	9	10
Not at all fatigued										**As fatigued as I could be**

3. Rate your level of fatigue on the **AVERAGE** during the past week:

0	1	2	3	4	5	6	7	8	9	10
Not at all fatigued										**As fatigued as I could be**

4. Rate your level of fatigue **RIGHT NOW**:

0	1	2	3	4	5	6	7	8	9	10
Not at all fatigued										**As fatigued as I could be**

5. Rate how much, in the past week, fatigue interfered with your **general level of activity**:

0	1	2	3	4	5	6	7	8	9	10
No interference										**Extreme interference**

6. Rate how much, in the past week, fatigue interfered with your **ability to bathe and dress yourself**:

0	1	2	3	4	5	6	7	8	9	10
No interference										**Extreme interference**

7. Rate how much, in the past week, fatigue interfered with your **normal work activity** (includes both work outside the home and housework):

0	1	2	3	4	5	6	7	8	9	10
No interference										**Extreme interference**

Appendix B. Fatigue Symptom Inventory (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐☐ Group #: ☐☐

8. Rate how much, in the past week, fatigue interfered with your **ability to concentrate**:

0	1	2	3	4	5	6	7	8	9	10
No interference										**Extreme interference**

9. Rate how much, in the past week, fatigue interfered with your **relations with other people**:

0	1	2	3	4	5	6	7	8	9	10
No interference										**Extreme interference**

10. Rate how much, in the past week, fatigue interfered with your **enjoyment of life**:

0	1	2	3	4	5	6	7	8	9	10
No interference										**Extreme interference**

11. Rate how much, in the past week, fatigue interfered with your **mood**:

0	1	2	3	4	5	6	7	8	9	10
No interference										**Extreme interference**

12. Indicate **how many days**, in the past week, you felt fatigued for any part of the day:

0	1	2	3	4	5	6	7
Days							**Days**

13. Rate **how much of the day**, on average, you felt fatigued in the past week:

0	1	2	3	4	5	6	7	8	9	10
None of the day										**The entire day**

14. Indicate which of the following best describes the **daily pattern** of your fatigue in the past week:

0	1	2	3	4
Not at all fatigued	**Worse in the morning**	**Worse in the afternoon**	**Worse in the evening**	**No consistent daily pattern of fatigue**

Appendix C. Brief Pain Inventory

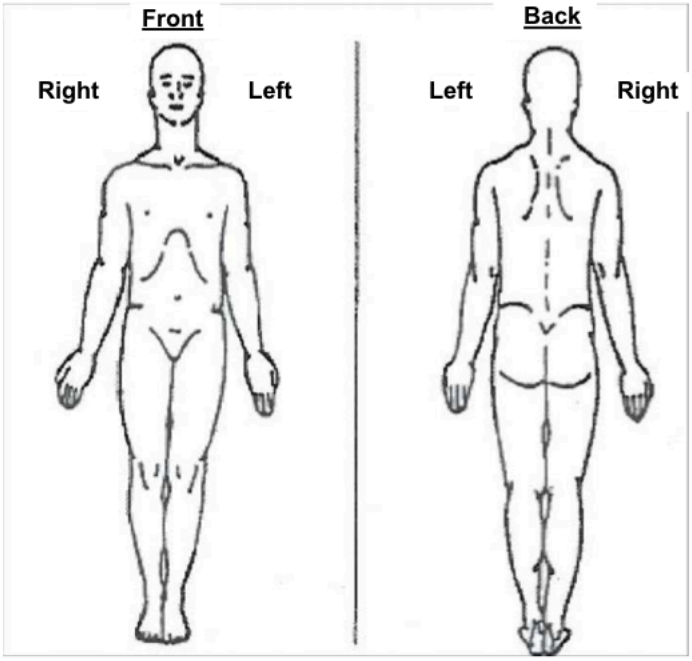
Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐ Group #: ☐☐

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

○ **Yes** ○ **No**

2. On the diagram, shade in the areas where you feel pain. Put an **X** on the area that hurts the most.



Office Use Only - Please do not write in this section

☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

Appendix C. Brief Pain Inventory (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐☐ Group #: ☐☐

3. Please rate your pain by circling the number that best describes your pain at its **WORST** in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										**Pain as bad as you can imagine**

4. Please rate your pain by circling the number that best describes your pain at its **LEAST** in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										**Pain as bad as you can imagine**

5. Please rate your pain by circling the number that best describes your pain on the **AVERAGE**.

0	1	2	3	4	5	6	7	8	9	10
No pain										**Pain as bad as you can imagine**

6. Please rate your pain by circling the number that tells how much pain you have **RIGHT NOW**.

0	1	2	3	4	5	6	7	8	9	10
No pain										**Pain as bad as you can imagine**

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No relief										**Complete relief**

Appendix C. Brief Pain Inventory (Continued)

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐ Randomization #: ☐☐☐☐☐☐ Group #: ☐☐

9. Please circle the number that describes how, during the past 24 hours, pain has interfered with your:

a. General activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

b. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

c. Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

d. Normal work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

e. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

f. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

g. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Appendix D: Institutional Review Board Approval

USF
UNIVERSITY OF
SOUTH FLORIDA

RESEARCH INTEGRITY AND COMPLIANCE
Institutional Review Boards, FWA No. 00001669
12901 Bruce B. Downs Blvd., MDC035 • Tampa, FL 33612-4799
(813) 974-5638 • FAX(813)974-7091

8/21/2017

Cecile Lengacher , Ph.D.
USF College of Nursing
12901 Bruce B. Downs Blvd. MDC-22
Tampa, FL 33612

RE: **Expedited Approval of Amendment**
IRB#: Ame12_107408
Title: Mindfulness-Based Stress Reduction (MBSR) Symptom Cluster Trial for Breast Cancer Survivors

Dear Dr. Lengacher :

On 8/20/2017, the Institutional Review Board (IRB) reviewed and **APPROVED** your Amendment. The submitted request and all documents contained within have been approved, including those outlined below, as described by the study team:

Other changes: Allowing a doctoral student access to a deidentified data set for secondary analysis. The doctoral student is Carissa Alinat and she has received a grant from Sigma Theta Tau International (STTI) to fund her secondary analysis for her grant entitled "Genetic Moderation of Pain and Fatigue in Breast Cancer Survivors Utilizing Mindfulness-Based Stress Reduction"

Justification: The secondary analysis on the deidentified data set will allow this doctoral student candidate to analyze the data specific to the Single Nucleotide Polymorphisms (SNPs) identified without using any PHI. The purpose of this SITI grant is for the candidate to apply their knowledge and related research by utilizing the data available through this R01 project. The purpose of her research will assess whether specific SNPs (rs1800795 of gene IL6 and rs16944 in gene ILB1b moderate fatigue, and whether SNP rs4680 of COMT moderates pain) are associated with any improvement with these symptoms after a behavioral intervention, the Mindfulness-Based Stress Reduction for Breast Cancer (MBSR(BC)) program, which are within the scope of the parent R01. There will no new data or samples to be collected for this secondary data analysis.

As the principal investigator of this study, it is your responsibility to conduct this study in accordance with USF HRPP policies and procedures and as approved by the USF IRB. Any changes to the approved research must be submitted to the IRB for review and approval via an

Appendix D. Institutional Review Board Approval (Continued)

amendment. Additionally, all unanticipated problems must be reported to the USF IRB within five (5) calendar days.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

V Jorgensen MD

E. Verena Jorgensen, M.D., Chairperson
USF Institutional Review Board

About the Author

Carissa Alinat is a triple graduate of the University of South Florida, earning a Bachelor of Arts in English Literature, a Bachelor of Science in Nursing, and a Master of Science in Nursing, before reaching doctoral candidacy for a PhD in Nursing Science. She is a board-certified Advanced Registered Nurse Practitioner specializing in Adult-Gerontology Primary Care and manages a health and wellness clinic in the Tampa Bay area in which she practices. In addition, she has multiple years of experience working as a Graduate Research Assistant and Graduate Teaching Assistant. Her research interests include genetics, complementary and alternative medicine, and symptom management, and has a strong interest in precision medicine.

Carissa received multiple awards for her graduate education, including but not limited to a Jonas Nurse Leaders Scholarship, University of South Florida Graduate Fellowship Award, and Sigma Theta Tau International Honor Society for Nursing's Rising Stars of Research award. She also received funding for her dissertation research through a grant from Sigma Theta Tau, Delta-Beta-at-Large chapter. Carissa served as Vice President and Secretary of the Doctoral Nursing Student Organization at the University of South Florida and has served on the Abstract Review Committees for the American Psychosocial Oncology Society, International Society for Nurses in Genetics, and the Southern Nursing Research Society. She has been a member of Sigma Theta Tau International Honor Society for Nursing, International Society of Nurses in Genetics, Southern Nursing Research Society, American Psychosocial Oncology Society, American Academy of Nurse Practitioners, and the Institute of Functional Medicine.

Carissa has had the opportunity to co-author multiple peer-reviewed publications and has presented at several conferences across the United States. She hopes to continue her research in Florida.