2015-05-21

Psychological Predictors of Survival and Disease Recurrence in Women with Breast Cancer Following Cognitive-Behavioral Stress Management

Jamie M. Stagl
University of Miami, jstagl@gmail.com

UNIVERSITY OF MIAMI

PSYCHOLOGICAL PREDICTORS OF SURVIVAL AND DISEASE RECURRENCE IN WOMEN WITH BREAST CANCER FOLLOWING COGNITIVE-BEHAVIORAL STRESS MANAGEMENT

By

Jamie M. Stagl

A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

August 2015

UNIVERSITY OF MIAMI

A doctoral essay submitted in partial fulfillment of
the requirements for the degree of
Doctor of Philosophy

PSYCHOLOGICAL PREDICTORS OF SURVIVAL AND DISEASE RECURRENCE IN WOMEN WITH BREAST CANCER FOLLOWING COGNITIVE-BEHAVIORAL STRESS MANAGEMENT

Jamie M. Stagl

Approved:

_____ Michael H. Antoni, Ph.D. Professor of Psychology	_____ Suzanne C. Lechner, Ph.D. Assistant Professor of Psychiatry & Behavioral Sciences
_____ Charles S. Carver, Ph.D. Professor of Psychology	_____ Gail H. Ironson, M.D., Ph.D. Professor of Psychology & Psychiatry
_____ Stefan Glück, M.D. Professor of Medicine	_____ Dean of the Graduate School

STAGL, JAMIE M. (Ph.D., Psychology)
Psychological Predictors of Survival and Disease Recurrence in Women with Breast Cancer following Cognitive-Behavioral Stress Management (August 2015)

Abstract of a doctoral essay at the University of Miami.

Doctoral essay supervised by Professor Michael H. Antoni.
No. of pages in text. (133)

Women diagnosed with early stage breast cancer experience elevated psychological distress associated with diagnosis and treatment that may have long term implications for disease progression and overall survival. Group-based Cognitive-Behavioral Stress Management (CBSM) has been shown to improve quality of life (QOL) and depressive symptoms in women with early stage breast cancer up to 12 months post-surgery. The current study aimed to examine whether women who received CBSM have better survival, breast cancer specific survival, and disease free interval at 8-15 year follow-up. The study also aimed to determine whether women in the CBSM group report less depressive symptoms and better QOL at the 8-15 year follow-up as compared to women in the control group. Finally, potential mediators of clinical endpoints and psychological outcomes were explored.

From 1998-2005, women (N = 240) with non-metastatic stage 0-IIIb breast cancer were enrolled in a randomized controlled trial comparing a 10-week group-based CBSM intervention to a 1-day group psychoeducational control seminar. Information related to demographic characteristics, treatment, medical history, and psychosocial functioning was collected at baseline (T1), 6 months (T2), 12 months (T3), and 5-years (T5). In 2013, at the 8-15 year (T6) follow-up, information was collected via tumor registry and medical chart review regarding survival, cause and date of death, and status of breast cancer (i.e.,

recurrence or disease free). Women who were reachable and agreeable at T6 (N = 100) completed the Functional Assessment of Cancer Therapy-Breast (FACT-B) and the Center for Epidemiologic Studies-Depression (CES-D) scales. Kaplan-Meier Survival Curves and Cox Proportional Hazards Models were conducted to determine whether women in the CBSM group differed from women in the control group on clinical outcomes of all-cause mortality, breast cancer-related mortality, and disease free interval. Biomedical confounders, specifically age, stage of disease, time elapsed from surgery to baseline assessment, tumor size, HER-2/neu receptor status, chemotherapy receipt, radiation receipt, and hormonal therapy receipt, were included in the Cox Proportional Hazards Models. Linear regressions were conducted to evaluate intervention group differences in QOL and depressive symptoms. Bootstrapped linear regressions were employed to test mediation hypotheses of whether change in affect over the 12-month study period mediated the intervention effects on either clinical or psychological outcomes.

At a median follow-up of 11 years, 47 women had a breast cancer recurrence and 30 women were deceased, with 22 having had breast-cancer related mortalities. Results of Cox Proportional Hazards analyses controlling previously stated covariates showed that women with early stage breast cancer who were randomly assigned to the CBSM group had a 79% reduced risk of all-cause mortality (95% CI [0.05, 0.91]; $p = .037$) compared to the control group. Risk for breast cancer recurrence was 56% lower than the control group (95% CI [0.18, 1.04]; $p = .062$) although not significantly lower. Similarly, risk for breast-cancer specific mortality was lower in the CBSM group, HR = 0.23 (95% CI [0.05, 1.08]), but not significantly so ($p = .063$). Women in the CBSM group reported

greater physical (p =.003) and emotional well-being (p =.053) on the FACT-B and less depressive symptoms (p =.036) and negative affect (p =.032) on the CES-D at T6. Mediation hypotheses were not supported in bootstrapped linear regressions.

A CBSM intervention may provide long-term protective effects for women with early stage breast cancer by reducing risk of all-cause mortality, lowering depressive symptoms, and improving quality of life. The mediators of these effects remain unknown. This research bolsters the evidence for the effects of psychosocial interventions on physical and psychological health outcomes in breast cancer patients and has implications for clinical practice.

TABLE OF CONTENTS

Page

LIST OF TABLES v

LIST OF FIGURES vi

LIST OF APPENDICES vii

Chapter

1 CHAPTER 1: Introduction 1
Stress, Disease Progression and Survival in Breast Cancer..... 1
Psychosocial Interventions, Survival, and Disease Progression in Breast Cancer..... 4
Potential Biopsychosocial Mechanisms..... 6
Immune Regulation, Inflammatory and Metastatic Processes 7
Psychosocial Processes 8
Quality of Life and Depression in Breast Cancer Survivors 9
Long-term Effects of Psychosocial Interventions 12
Study Objectives 13
Specific Study Aims 15

2 CHAPTER 2: Methods 16
Participants..... 16
Intervention..... 16
Psychoeducation Seminar Control 17
Assessments 18
Data Collection Procedures 19
Measures 25
Analytic Strategy 28

3 CHAPTER 3: Results 41
Contacting Participants..... 41
Medical Chart Reviews..... 42
Participant Sample Characteristics 43
Aim 1 Full Sample Unadjusted Kaplan-Meier Curves 46
Adjusted Cox Proportional Hazards Models (all covariates) 47
Adjusted Cox Proportional Hazards Models (minimally controlled) 49
Aim 2 Intervention Effects on Psychosocial Outcomes 51
Quality of Life 51
Depressive Symptoms 53
Aim 3 Mediation 55
Aim 3a Mediation Effects on Clinical Outcomes 55

Aim 3b Mediation Effects on Psychosocial Outcomes 56

4 CHAPTER 4: Discussion 57
Psychosocial Interventions, Survival, and Disease Progression in Breast Cancer 57
Long-term Effects on Psychosocial Outcomes 62
Long-term Effects of Psychosocial Interventions 66
Mechanisms of Psychosocial Interventions 68
Strengths and Limitations 71
Clinical Implications 74
Future Research 75
Conclusion 78

REFERENCES..... 79

TABLES 98

FIGURES..... 104

APPENDICES..... 119

LIST OF TABLES

Table 1 98
Table 2 100
Table 3 101
Table 4 102
Table 5 103

LIST OF FIGURES

Figure 1 104
Figure 2 105
Figure 3 106
Figure 4 107
Figure 5 108
Figure 6 109
Figure 7 110
Figure 8 111
Figure 9 112
Figure 10 113
Figure 11 114
Figure 12 115
Figure 13 116
Figure 14 117
Figure 15 118

LIST OF APPENDICES

APPENDIX A Forms Mailed in Packet 119
APPENDIX B Psychosocial Measures and Scoring 125

Chapter 1

Breast cancer is the leading cancer in women in the United States (US). Of all cancer diagnoses, 29% (226,870) are breast cancer. Of all cancer-related deaths, 14% (39,510) are breast cancer-related (Jemal, Bray, Center, Ferlay, Ward & Forman, 2011; DeSantis, Siegel, Bandi & Jemal, 2011; Siegel, Naishadham & Jemal, 2012). In the recent years, mortality rates have decreased in large part due to screening mammography procedures and enhanced medical treatment (Berry et al., 2005; Berry et al., 2006; Tabar, Yen, Vitak, Chen, Smith & Duffy, 2003; Kalager, Haldorsen, Bretthauer, Hoff, Thoresen & Adami, 2009). Specifically, improved characterization of tumor types allows for identification of targeted therapies, rather than a "one-size fits all" approach to treatment (Toriola & Colditz, 2013). Research suggests that there are other contributing factors to mortality that are not as easily quantifiable such as biologic changes in the tumor and healthcare factors. In terms of healthcare factors, improved multidisciplinary breast cancer care has been estimated to account for 33% of improved survival (Kalager et al., 2009). Multidisciplinary care aims to improve the well-being of the whole patient, including psychological and emotional well-being. Women diagnosed with non-metastatic breast cancer often experience increased psychological and physical distress associated with diagnosis and treatment (Montazeri, 2008). The implications of psychological well-being have been investigated in the context of disease progression and overall survival (Antoni & Lutgendorf, 2007).

Stress, Disease Progression and Survival in Breast Cancer

A determining factor in one's psychological well-being is the influence of stressful life events. The association between stressful life events and breast cancer risk is

modest at best, though statistically significant (Duijts, Zeegers, Borne, 2003). Specifically results from meta-analyses estimating the influence of psychosocial stress on clinical disease endpoints in cancer reveals hazard ratios (HRs) of 1.06 (95% CI 1.02-1.11, $p = 0.005$) for studies examining the role of psychosocial stress on cancer incidence, 1.03 (95% CI 1.02-1.04, $p < 0.001$) for studies examining all-cause mortality, and 1.29 (95% CI 1.16-1.44, $p < 0.001$) for those examining cancer mortality (Chida, Hamer, Wardle & Steptoe, 2008).

In the context of breast cancer, a stronger relationship exists between stress-related factors and survival, as opposed to incidence (Chida et al., 2008). Combined psychosocial factors are associated with a 13% increase in HR's for breast cancer survival (Chida et al., 2008). Evidence suggests that psychological factors such as stress, depression and social isolation may be related to disease progression (Palesh et al., 2007; Satin, Linden & Phillips, 2009; Steel et al., 2007). Life-event stress is associated with a 15% increase in HRs for cancer-related mortality. Depression affected cancer incidence with a 29% increase in HRs, an 8% increase in HRs for all-cause mortality, and a 34% increase in HRs for cancer-related mortality (Chida et al., 2008).

Disease progression and cancer-related-mortality are most likely a direct result of cancer metastasis, which involves several complex steps including angiogenesis, tumor invasion of adjacent tissue, embolization and evasion of normal immune surveillance (Fidler, 2003). Multiple steps of the metastatic cascade have the potential to be altered by stress response pathways (Lutgendorf, Sood & Antoni, 2010). Psychological states of chronic stress, depression and social isolation are key players in the downregulation of the cellular immune response (Kiecolt-Glaser, Fisher, Ogrocki, Stout, Speicher & Glaser,

1987; Zorrilla et al., 2001; Irwin, 2002) and are also shown to be associated with fundamental elements in metastatic processes in both human and animal models (Lutgendorf et al., 2009; Cole, Hawkley, Arevalo, Sung, Rose, Cacioppo, 2007; Williams, et al., 2009).

Animal models show that chronic stress initiates tumor progression via the suppression of type 1 (Th1) cytokines, cytotoxic activities of T cells and natural killer (NK) cells and impaired antigen presentation (Saul, 2005; Ben-Eliyahu, Yirmiya, Liebeskind, Taylor & Gale, 1991; Ben-Eliyahu, Page, Yirmiya & Shakhar, 1999; Greenfeld et al., 2007). Clinical studies demonstrate the relationship between stress and cellular immune markers post-surgery for breast cancer evidenced by lower T-cell production of Th1 vs. Th2 cytokines (Blomberg et al., 2009), impaired NK cell cytotoxicity, and weakened T-cell response to mitogen stimulation (Andersen et al., 1998; Thornton, Andersen, Crespin & Carson, 2007). The autonomic nervous system and the hypothalamic-pituitary-adrenal axis are activated in response to stress and are identified as potential mediators of the relationship between psychosocial factors and cancer progression (Lutgendorf et al., 2010). A study with metastatic breast cancer patients showed that women with flatter cortisol slopes had lower circulating NK cells as well as overall NK cell activity. Cancer-related mortality was significantly predicted by cortisol slope, where flatter slopes predicted shorter survival time (Sephton, Sapolsky, Kraemer & Spiegel, 2000). Greater urinary cortisol output and disturbances in circadian secretion of cortisol are associated with stress, depression and decreased social support, suggesting that cortisol alterations may mediate the effects of the psychosocial factors on cancer-related processes (Antoni, 2003a; Sephton & Spiegel, 2003).

These in vitro, in vivo, and clinical studies show increasing evidence for the role of stress-related neuroendocrine processes in cancer progression (Lutgendorf et al., 2010). A meta-analysis concludes that psychological stress, defined as "the emotional and physiological reactions experienced when an individual confronts a situation in which the demands go beyond their coping resources", is associated with poorer cancer survival (National Cancer Institute, 2008; Chida, et al., 2008). The fact that stress is related with poorer survival, and that stressful events and depression are prevalent in the population (Creed & Dickens, 2007) reinforces the importance of managing stress and depressive symptoms in cancer patients especially (Chida et al., 2008). Therefore, research highlights the importance of psychosocial interventions to improve psychological adaptation to breast cancer diagnosis and treatment with the goal of modulating stress-related pathways that may ultimately lead to disease progression and mortality (Antoni et al., 2006a, Antoni et al., 2006c, Lutgendorf et al., 2010).

Psychosocial Interventions, Survival, and Disease Progression in Breast Cancer

Psychosocial interventions that teach behavioral methods for stress management are important for modulating stress-related pathways (Lutgendorf et al., 2010). Subsequently, psychosocial interventions that reduce psychosocial stress and depression or depressive symptoms may be beneficial to breast cancer patients in terms of clinical disease outcomes. However, controversial research findings from randomized controlled trials leave unanswered questions about whether psychosocial interventions can actually impact the course of breast cancer progression and mortality (Spiegel 2002; Coyne, Stefanek & Palmer 2007, Andersen et al., 2008). A study by Kissane and colleagues (2007) enrolled women with metastatic breast cancer who received a 12-month course of

weekly group-based supportive expressive therapy, but findings did not show a survival advantage related to the intervention (Kissane et al., 2007). A study for women with metastatic breast cancer examined the effects of group supportive therapy with self-hypnosis compared to a control condition. Women in the intervention group reported significantly less anxiety, depression and pain. At the 10-year follow-up, findings showed significantly improved survival for women in the intervention group as compared to the control group (Spiegel, Bloom, Kraemer & Gottheil, 1989). However, efforts to replicate these findings in metastatic breast cancer patients have not been completely successful. For instance, Goodwin et al (2001) conducted a study examining the influence of group-based supportive expressive therapy in women with metastatic breast cancer (N=235). While the intervention group experienced improvements in pain and psychological symptoms, survival was not statistically different between study conditions (Goodwin et al., 2001). In addition, efforts to replicate the study by Spiegel and colleagues (1989) also did not show a survival advantage, except in a small subset of women who had estrogen receptor (ER)-negative tumor types (Spiegel et al., 2007). While patients in the previously mentioned studies had metastatic breast cancer, there has only been one randomized controlled trial to date to demonstrate beneficial effects of a cognitive-behavioral intervention on survival and recurrence in women with non-metastatic breast cancer (Andersen et al., 2008).

Andersen and colleagues (2008) enrolled 227 women with stage II to III non-metastatic breast cancer in the weeks following surgery. Women were randomly assigned to either standard of care control group or the group-based cognitive-behavioral therapy intervention condition. Women in the intervention group received 4 months of weekly

sessions followed by 8 months of monthly sessions of cognitive-behavioral therapy plus health education aimed to improve QOL, reduce distress, improve health behaviors, and enhance treatment and medical compliance and follow-up. Topics addressed in the intervention included progressive muscle relaxation, problem-solving, identifying and enhancing social support, assertive communication, coping with treatment side effects, and improving nutrition and physical activity. At the 7-13 year follow up (11-year median follow-up) women in the intervention group had a significant reduction in breast cancer –specific (HR = .44, p = 0.016*)* and all-cause mortality rates (HR = 0.51, p = 0.028). Intervention participants also had a lowered risk of breast cancer recurrence (HR = 0.55, p = 0.034; Andersen et al, 2008). These findings have yet to be replicated. Mechanisms of how the psychological interventions reduced recurrence and improved survival in both the Andersen et al. (2008) and Spiegel et al. (1989) studies have been proposed but have not been thoroughly investigated in clinical trials (Lutgendorf et al., 2010; Antoni, 2013). For instance, women in the intervention group in the Andersen (2008) study showed significant psychological and behavioral improvements including reduced distress and improved health behaviors at 12 months (Andersen et al., 2008). Furthermore, findings showed that the participants who had disease recurrence were more likely to have higher cortisol in the months prior to detection (Andersen et al., 2008). Researchers suggest that this stress reduction via a psychosocial intervention may mediate the intervention effect on disease progression (Bunt et al., 2007)

Potential Biopsychosocial Mechanisms

A growing body of research provides evidence for the relationship between stress-related psychosocial factors and cancer survival (Chida et al., 2008). Specifically, stress,

depression and social isolation have been linked to disease progression, potentially via down regulation of the cellular immune response and subsequent metastatic processes discussed earlier (Palesh et al., 2007; Satin et al., 2009; Steel et al., 2007; Lutgendorf et al., 2010). Distress and anxiety may negatively affect neuroendocrine and immune regulation (Segerstrom & Miller, 2004). As mentioned previously, social support may be a factor in survival, as cancer patients who are married have been shown to survive longer than those who are not married (Kennedy, Kiecolt-Glaser & Glaser, 1988; Goodwin, Hunt, Key & Samet, 1987). Researchers purport that the improved survival rates in Spiegel's 1989 study may be related to women having a supportive environment in which to express their feelings and share a sense of belonging (Friedman, Baer, Nelson, Lane, Smith & Dworkin, 1988). In addition to improving social support, meaning making and benefit finding by "working through" stressors such as breast cancer may be another avenue leading to a more positive affect and improved immune function (Antoni et al., 2009; McGregor, Antoni, Boyers, Alferi, Blomberg & Carver, 2004).

Immune Regulation, Inflammatory and Metastatic Processes

Stress management interventions that improve affect and psychological mood states via re-appraisal of the stressful breast cancer experience may modify stress-related immune suppression and neuroendocrine dysregulation such that immune surveillance is restored or even enhanced (Antoni & Lutgendorf, 2007). Given both psychosocial and immunosuppressive effects of cancer treatments such as chemotherapy and radiation, enhanced immune surveillance may be crucial to buffer the cascade of the seeding and growth of micro-metastases (Antoni & Lutgendorf, 2007). This further emphasizes the

potential health relevance of psychosocial interventions that improve psychological well-being (McGregor et al., 2004).

Recent work by our lab demonstrated the effect of a psychological intervention on leukocyte expression of pro-inflammatory and pro-metastatic genes in women with breast cancer. Women assigned to CBSM showed changes in leukocyte transcriptional dynamics, including down-regulation of pro-inflammatory (e.g., NF-kB, IL-1) and metastasis-related (e.g., matrix metallopeptidase-9 [MMP-9]) genes, and up-regulation of glucocorticoid receptor expression and type I IFN response genes (Antoni et al., 2012). Findings also showed links between negative affective states and increased leukocyte expression of pro-inflammatory genes, which imply that that anxiety and mood-related processes may play a mediating role (Antoni et al., 2012). These effects all persisted at 12-month follow-up after controlling for all relevant sociodemographic, disease, treatment, and health behavior covariates. These findings are the first to show that a psychosocial intervention in the context of breast cancer, as well as negative affective states, can influence immune cell changes by altering the basal leukoctye transcriptome in ways that could explain effects on increased cellular immunity on the one hand and decreased inflammatory signaling on the other.

Psychosocial Processes

As mentioned previously, work in our lab showed that a 10-week group-based Cognitive-Behavioral Stress Management (CBSM) program is efficacious in enhancing physiological adaptation as women recover from surgical intervention and undergo active adjuvant treatments for non-metastatic breast cancer. Women also showed enhanced psychological adaptation, in that women assigned to the CBSM intervention reported less

social disruption, interviewer-rated anxiety symptoms, and cancer-specific anxiety and greater emotional well-being, positive states of mind, benefit finding, positive lifestyle changes, and positive affect over the 12 months after surgery as compared to the control group (Antoni et al., 2006a; Antoni et al., 2006c). At the 5-year follow-up, women who were in the CBSM group reported significantly less depressive symptoms than those in the control group (Stagl et al., 2013). Given evidence of the relationship between depression and cancer risk and survival (Creed & Dickens, 2007), it is plausible that neuroendocrine changes related to distress are responsible for the effects of psychological adaptation on clinical outcomes (Antoni et al., 2006b). Prior work has shown that women with the largest psychological improvements during CBSM showed the greatest immune effects (e.g, lymphocyte proliferative response) (McGregor et al., 2004). Thus, CBSM-related changes in mood and affect may play a role in altering physiological parameters such as immune functioning which might in turn affect disease progression and survival.

Quality of Life and Depression in Breast Cancer Survivors

While survival rates have increased due to medical advances and treatment personalization, women surviving breast cancer remain at high risk for psychological distress and mood disorders (Deshields, Tibbs, Fan & Taylor, 2006). Although life-saving, treatments such as chemotherapy, radiation, and systemic hormonal therapy for breast cancer produce long term and late onset effects such as pain in surgical areas, lymphedema, reduced vaginal lubrication, and hot flashes (Casso, Buist & Taplin, 2004). In addition, persistent fear and anxiety related to disease recurrence and possible death results in a psychological discomfort related to anger, low self-esteem, low emotional support and depression even years after diagnosis and treatment (Spiegel, 1997).

Depressive symptoms and breast cancer. The association between depression, depressive symptoms and breast cancer is quite strong (Reddick, Nanda, Campbell, Ryman, Gaston-Johansson, 2005) and is pervasive beyond the phases of active treatment (Burgess, Cornelius, Love, Graham, Richards & Ramirez, 2005). Prevalence rates in patients with cancer are estimated to be 15-30% or higher (McDaniel, Musselman, Porter, Reed & Nemeroff, 1995; Miovic & Block, 2007; Reyes-Gibby, Anderson, Morrow, Shete & Hassan, 2012). The consequences of chronic depression are of concern as depression relates to disease severity (Spiegel & Giese-Davis, 2003; Kreitler, Chaitchik, Rapoport & Algor, 1995) and cancer mortality (Giese-Davis, Collie, Rancourt, Neri, Kraemer & Spiegel, 2011; Somerset, Sout, Miller & Musselman, 2004). Depression has also been shown to be associated with fatigue, pain and insomnia (Patrick et al., 2003; Reyes-Gibby et al., 2012), with fatigue and depression often grouped together as a symptom cluster in cancer-related research (Thornton et al., 2010; Cleeland et al., 2003).

Quality of life and breast cancer. Depression negatively affects interpersonal relationships, occupational performance and perceptions of health and physical symptoms (Badger, Braden, Mishel & Longman, 2004; Somerset et al., 2004). It also weighs heavily on the overall quality of life (QOL) of breast cancer survivors (Casso et al., 2004; Reich, Lesur, Perdrizet-Chevallier, 2008; Reyes-Gibby et al., 2012). The concept of QoL is defined as "an appraisal of and satisfaction with one's current level of functioning compared to what one believes is possible or ideal" (Cella & Cherin, 1988). It is often measured in terms of a person's life satisfaction and overall well-being, with respect to physical, functional, emotional, and social domains of functioning (Cella & Tulsky, 1990). Previous work has demonstrated that more depressed breast cancer patients have

worse QOL (Montazeri, 2008). Both poor QOL and depression can negatively impact treatment adherence and medical follow-up, and lower health-related QOL is associated with poorer cancer survival in breast cancer patients (Quinten et al., 2009).

Psychosocial interventions, depression and quality of life. One of the major targets of cognitive-behavioral therapy interventions for cancer patients is to improve depression as well as QOL (Kissane, Grabsch, Love, Clarke, Bloch & Smith, 2004; Antoni, 2011). Meta-analyses examining outcomes of group psychological interventions in breast cancer patients have shown moderate to strong effects in reduction of depression and moderate effects in QOL improvements (Naaman et al., 2009). Findings suggested that psychological interventions focused on coping and social support building were most efficacious (Naaman et al., 2009). Most research objectives focus on understanding QOL during the early years of breast cancer treatment, mainly in the 5 years post-initial diagnosis (Ganz, Rowland, Desmond, Meyerowitz & Wyatt, 1998).

Fewer studies have evaluated depression and QOL in the years following active treatment (Ganz, Desmond, Leedham, Rowland, Meyerowitz & Thomas, 2002; Dorval, Maunsell, Deschenes, Brisson & Mâsse, 1998). A study by Casso, Buist & Taplin (2004) examined the QOL of younger long-term breast cancer survivors. The purpose of this study was to improve the assessment of relevant factors affecting women living beyond breast cancer. Women were between ages 40-49 years old when they were diagnosed with breast cancer. Findings showed that women who did not receive systemic adjuvant therapy had higher QOL than those who did receive systemic adjuvant therapy, and the amount of reported breast cancer related symptoms and pain were significantly associated with a person's life satisfaction as measured by QOL (Casso et al., 2004). While breast

cancer survivors report more depression and worse QOL than the general population, rates of anxiety and depressive disorders are higher in those who have a breast cancer recurrence, and estimated to be greater than 40% (Okamura et al., 2000). Given these disparities, more studies are needed to address the long-term effects of psychosocial interventions beyond the acute phase of treatment (Ganz et al., 2002).

Long-term Effects of Psychosocial Interventions

It has long been acknowledged that psychological interventions are efficacious in managing symptoms and side effects from treatment as well as decreasing stress (Hewitt, Herdmann & Holland, 2004). In a study by Ganz and colleagues (2002), the quality of social support received by survivors was one of the largest contributors to health-related QOL. Authors concluded that psychosocial interventions which increase social support following the acute treatment phase may be crucial to breast cancer survivors' care over the years (Ganz et al., 2002). However, less is known about whether women who received CBSM post-surgery for breast cancer benefit from the intervention in the years after treatment leading into survivorship phases.

Giese-Davis and colleagues (2011) found that decreases in depression over the first year of their study were related to increased survival for women with metastatic breast cancer (Giese-Davis et al., 2011). In addition, a follow-up analysis of the trial by Andersen et al (2008) showed that of the women who had a breast cancer recurrence, those who were in the intervention group had a significantly longer post-recurrence survival time than those in the control group. Furthermore, although women in both study arms were similarly distressed at the time of recurrence diagnosis, those who received the

intervention reported declines in negative mood over time as opposed to the control group (Andersen et al., 2010).

Work in our research lab has shown that women with non-metastatic breast cancer who are assigned to a 10-week group-based CSBM while recovering from surgery and beginning active adjuvant treatment report improved psychosocial adaptation as compared to controls (Antoni et al., 2006a, Antoni et al., 2006c). Preliminary analyses have been conducted to examine whether women who received CBSM differ on psychological outcomes 5-years post diagnosis as compared with those in the control group. Women assigned to the CBSM group reported significantly less depressive symptoms on the Center for Epidemiologic Studies Depression (CES-D; Radloff, 1977) Scale than those in the control group at the 5-year follow-up assessment. This is one of the first studies to show long-term improvement in depressive symptoms in breast cancer survivors who received CBSM during the initial phases of treatment (Stagl et al., 2013)

Given these findings showing potential long-term effects of CBSM as well as evidence for long-term effects of psychosocial intervention on breast cancer disease progression and survival, there is a rationale to look further into these processes.

Study Objectives

There is a need to attempt to replicate the psychosocial intervention findings from the Andersen et al (2008) study on survival and recurrence using a comparable intervention, patient population, sample size, and follow-up time period. Furthermore, there is justification to evaluate whether psychological adaptation in the initial 12 months after the intervention mediates the effects of the intervention on long-term clinical disease outcomes. There is also a need to examine long-term effects of psychosocial intervention

on QOL and depressive symptoms, and whether psychological adaptation in the initial 12 months after the intervention may also be mediating this effect.

This study used information collected over the 12 month period from the previously completed study of the effects of CBSM in women with breast cancer (Antoni et al., 2006a, Antoni et al., 2006c) and linked this with clinical health and psychosocial outcome data collected over the subsequent period ranging from 8-15 years post diagnosis.

Importantly, the intervention in the present study is comparable to the cognitive-behavioral groups used by Andersen et al (2008) though shorter in duration. The sample is comprised of women with non-metastatic breast cancer ranging from stage 0-IIIb at diagnosis. Approximately 25% of the sample is Hispanic, allowing for enhanced generalizability of the findings beyond those of Andersen et al, which included largely non-Hispanic White sample. This work aimed to determine whether women who received CBSM intervention differed significantly from the control group on clinical disease endpoints and psychosocial outcomes, and whether changes in psychological adaptation over the initial 12 months of the study mediated these effects at the 8-15 year follow-up.

This 8-15 year follow-up time range is similar to that used by Andersen et al (2008) of 7-13 years with an 11-year median. It is common in the survival literature to have a wide follow-up range and is accounted for by the use of statistical methods estimating survival time (Goel, Khanna, Kishore, 2010). It is also important to take clinical practice guidelines into account when determining an appropriate time range to examine. Surveillance guidelines from the American Society of Clinical Oncology recommends follow-up visits every three to six months for three years, six to 12 months

at years four and five, and annually after year five (Smith, 2013). Observations of actual practice indicate that follow-ups become less frequent as the years progress and that most women do not always follow up annually after year 10, as this is the time period containing the most risk of recurrence (Smith, 2013; Schairer, Mink, Carroll, Devesa, 2004). Therefore, analyses were also conducted using a time frame of up to 10-years in order to narrow the window and examine the 10 years over which an event is most likely to occur.

Specific Study Aims

1. Examine whether women with breast cancer assigned to the 10 week CBSM group differ from those in the 1-day psychoeducational control group on clinical disease endpoints, including disease free survival, breast cancer specific survival, and overall survival at 8-15 years follow up and up to the 10-year follow-up.

2. Examine whether women with breast cancer assigned to the CBSM group differ from those in the 1-day psychoeducational control group on psychosocial outcomes, including multiple indicators of depressive symptoms and quality of life (QOL) at 8-15 years follow up.

3a. Examine whether change in affect over the initial 12-month study period (i.e., baseline to 1-year assessment) mediates the effect of the CBSM intervention on clinical disease endpoints (i.e., recurrence free interval, breast cancer specific survival, and overall survival) at 8-15 year and 10-year follow up.

3b. Examine whether change in affect over the initial 12-month study period (i.e., baseline to 1-year assessment) mediates the effect of the CBSM intervention on psychosocial outcomes (i.e., depressive symptoms and QOL).

Chapter 2: Methods

Participants

Two hundred and forty women with non-metastatic stage 0-IIIb breast cancer were enrolled in this study between 1998-2005. Ethical permission for the study was obtained and approved by the Human Subjects Research Office of the University of Miami Institutional Review Board in 1998. Women were recruited via physician referrals and community advertising. Potential participants received personalized letters from their breast surgical oncologist or from the American Cancer Society Reach to Recovery program via flyers referring them to the study as an opportunity to learn stress management techniques. A total of 502 potential participants were referred and screened for inclusion in this study. Exclusion criteria included prior cancer diagnosis and treatment, prior psychiatric treatment for serious mental disorder, and lack of fluency in English. Of the total women screened, 156 were not interested in participating and passively declined enrollment, 106 women did not meet inclusion criteria, and a total of 240 participants were enrolled. Baseline assessments were scheduled approximately 4-10 weeks post-surgery and prior to adjuvant treatment onset. Following the baseline assessment, women were randomized to either the 10-week group based Cognitive-Behavioral Stress Management intervention group (CBSM), or the 1-day Psychoeducational Seminar Control group (PE).

Intervention

The CBSM intervention was group-based and met for ten consecutive weeks at 2 hours per week. This manualized, structured psychosocial intervention (Antoni, 2003b) combines cognitive behavioral therapy (CBT) techniques with relaxation techniques.

Relaxation techniques include progressive muscle relaxation, guided visual imagery, and diaphragmatic breathing and meditation. CBT techniques include cognitive appraisal, cognitive reframing, coping skills training, interpersonal communication and assertiveness, and anger management skills. The intervention was targeted to decrease stress and negative mood states, replace cognitive distortions with accurate appraisals, enhance coping strategies and maintain/enhance social support networks. The intervention also aimed to decrease neuroendocrine markers of stress and modulate immune biomarkers in a way that could optimize health outcomes. The intervention components were tailored specifically to cancer diagnosis and treatment-related issues. Two interventionists were assigned per group. The first interventionist held a Ph.D. in Clinical Psychology, and the co-interventionists were students in the PhD program for Clinical Psychology at the University of Miami. They were trained in the protocol and ongoing supervision was provided. Sessions were videotaped and monitored for fidelity and standardization by two clinical psychologists.

Psychoeducation Seminar Control

Women in the control group participated in a 1-day psychoeducational seminar that was held in a classroom setting. The seminar took place over a weekend day that fell within the corresponding 10-week intervention period. The format of the seminar included general information related to breast cancer and cancer care. Women were also provided with a condensed version of stress management elements of the intervention. However, women in the control group were only provided with the written material and lacked the opportunity to practice or integrate any of the techniques presented. In addition, unlike the intervention group, they were not given at-home exercises to

facilitate mastery of the intervention strategies. This condition was designed to emulate a self-help type seminar.

Assessments

Initial assessments (T1) were conducted 2-10 weeks post-surgery in order to allow enough time for post-surgical pain and swelling to be resolved and for the assessment to be conducted before adjuvant treatment began. Data was collected relating to sociodemographic information. Self-report psychosocial and QOL questionnaires were administered. Women were followed post- intervention (T1.5) and assessed at 3 subsequent time points in the initial 12 months. The first subsequent time point took place 3 months post-intervention (T2), the second time point took place 6 months post the second assessment (T3) and the third time point (for the purposes of this dissertation) took place 5 years post study enrollment (T5). An additional assessment took place 6 months after T3 (T4) but was not used for the present analyses due to the extent of missing data. Assessments T1, T2 and T3 each consisted of blood samples and psychosocial questionnaires. The T5 assessment consisted of psychosocial questionnaires only, administered at approximately the 5yr follow-up. In addition, women were asked to report on the status of their breast cancer at T5. Specifically, women could indicate if they had a breast cancer recurrence, a new cancer occurrence, were unsure if their new cancer was a new primary or a recurrence, or had not had a second cancer diagnosis. If they had a recurrence or new cancer, they were asked to fill in the date of diagnosis. In the current study, women were assessed at an additional time point, T6. This time point took place 8-15 years post-study enrollment. The primary purpose of this follow-up assessment is to determine health status with respect to breast cancer and survival.

Specifically, this included: (a) incidence of death resulting from any cause and date of death, (b) incidence of death due to breast cancer and date of death, and (c) incidence of breast cancer recurrence and date of diagnosis. Various data collection methods were implemented in order to comprehensively collect information on these clinical outcomes. The details of the parent study are described in the original report (Antoni et al., 2006a).

Data Collection Procedures

Mortality data. Data on mortality, including date of death and cause of death, was collected through the Florida Cancer Data System (FCDS) of the Florida Department of Health (DOH). A linkage study was performed with the FCDS in which identifiable data (first name, last name, SSN, street address, race and gender) was linked to the registry to determine date and cause of death for any women who passed away since study enrollment. The FCDS is reported to be up to date as of December 2012.

In order to gain approval to access FCDS data, a multistep application process was initiated in March of 2012. First, an application was submitted to the Florida DOH Office of Vital Statistics on 3/5/2012 to request permission to obtain vital status, date of death, and cause of death (as required by FCDS prior to data release). While this application was reviewed, the study team prepared the data for the linkage study, by collecting identifiable information on all women in the study and arranging the record in FCDS mandated format. Approval was granted from Florida DOH Office of Vital Statistics on 5/4/2012 with instructions to initiate an application to the Florida DOH Bureau of Epidemiology in order to apply for a data use research agreement.

An application was subsequently submitted to the Florida DOH Bureau of Epidemiology on 6/5/2012. The study team received a review of the data use research

application from the Cancer Registry Review Committee (CRRC) on 8/8/2012. The study team then addressed the questions of the CRRC and re-submitted the application on 9/7/2012. The CRRC approved the data use research agreement on 10/9/2012 and instructed the study team to proceed to Florida DOH IRB submission.

The study team submitted an application to the Florida DOH IRB on 10/30/2012 to obtain final protocol approval. The Florida DOH IRB approved the protocol for the FCDS registry linkage on 4/9/13. The study team communicated the approval and sent appropriate documentation to the FCDS offices on 4/9/13, and the linkage process was initiated. The FCDS linkage was then completed on 5/24/13, and the data was delivered to the study team. The study team integrated this death data with the demographic, psychosocial, and biological data gathered from the prior assessments. Data was merged, cleaned, and prepared for analyses.

As women may have moved out of state since their last assessment, national registries were considered as well. The FCDS is not only current through 2012, but also routinely links with the National Death Index. The FCDS is therefore consistent with the National Death Index through the year 2011. All women were also searched on ancestry.com and archives.com using their first name, last name, date of birth, and social security number, to verify linkage data. Data on death status was obtained on all 240 women.

Recurrence data. Data related to disease recurrence was collected directly by study personnel via three approaches: chart review, self-report via questionnaire, and self-report via phone screen. At the time of initial study enrollment, women agreed to be followed over time with regard to their medical status. Women signed informed consent,

which included this clause, between the years of 1998-2005. However, many physician offices require a more recent medical release, within the past 6 to 12 months. Other physician offices required that women sign a release specific to their practice. Therefore, study personnel gained IRB approval to re-contact all study participants preemptively.

A protocol and related forms were created and submitted to the University of Miami (UM) IRB. The protocol allowed study personnel to re-contact study participants by phone and mail in order to obtain information regarding their current breast cancer status and permission to contact their current physician by obtaining an updated medical release. The protocol consisted of a scripted phone screen, including fields to update the participant's contact information, breast cancer status, and current physician/following oncologist. The packet to be mailed included a cover letter indicating the reason the participant was being contacted (see Appendix A for all forms including in this packet), a form for the participant to indicate their current breast cancer status, a generic or University specific authorization for release of medical information, and two brief psychosocial questionnaires (see Appendix B for questionnaires and scoring information). The protocol and all corresponding forms were submitted to the UM IRB on 9/15/12 and were approved on 10/3/12.

Study personnel re-contacted study participants during the months of October and November of 2012. Participants were called during both daytime and evening hours, and informed that they were being contacted by research associates on the Coping & Recovery Project, to follow-up on their health and cancer status. Study personnel gained participants' permission to proceed with questions. Self-report data was collected with regard to contact information, breast cancer status, and the name and contact information

of the current physician/oncologist. Women were informed that they would receive a packet in the mail asking them to sign a form that would allow study personnel to obtain their medical chart from the physician/oncologist they specified. Women were also reminded that they had agreed to have their medical status followed forward at the time they signed informed consent for the study, and that it was necessary to update this document in order to obtain access to their medical charts. Study personnel explained to participants that access to their medical chart was needed only to verify details about the original tumor pathology and treatment regimen, as well as new tumor pathology and treatment in the case of a breast cancer recurrence. Participants were reminded that their participation is voluntary should they wish not to provide this information. Study personnel left discrete voicemails for participants who were unreachable. Participants were called at different times of the day to maximize the chances of reaching them. Study personnel used Internet sources for looking up contact information for participants' whose phones lines were disconnected. Study personnel attempted to contact each participant up to five times over the course of two months. If there was no call back or no answer after the fifth try, the participant was considered "unreachable at T6 phone screen."

Once a participant agreed to provide an updated medical release, she was mailed the IRB-approved forms from the Coping & Recovery Project. All participants who were unreachable at phone screen were automatically sent a packet to the address on file after five unsuccessful attempts. Mailings were conducted during the months of October, November, and December of 2012. A pre-stamped and pre-addressed envelope was included in the packet for women to easily send back the completed forms. Information

obtained on the phone screen and in the returned forms was tracked in a database, as well as all efforts and attempts to re-contact participants.

Review of medical chart information was initiated in January 2013. Medical chart reviews were conducted on all participants in an effort to corroborate self-reported recurrence or disease free status and collect further information related to stage of recurrence and subsequent treatment. Study personnel contacted physician's office by phone and conducted in-person visits in order to complete chart reviews. The majority of offices preferred to receive the medical authorization by fax, and to subsequently send the requested medical chart back to study personnel by fax using a dedicated line in the office of the P.I. For participants who had provided a medical release, this updated release was faxed to the corresponding physician's office. For those participants who were unreachable by phone, or did not send back the updated release, study personnel faxed the original informed consent with the participant's signature to the physician's office. Study personnel did conduct in-office chart reviews at certain locations in which there were many participants from one doctor, or where the charts were kept electronically. As the Sylvester Cancer Center was a site of original study recruitment, study personnel obtained authorized permission to access electronic charts for participants who were recruited through this site. Study personnel searched for medical charts at both the women's original reported oncologist at study entry, and current oncologist as reported at follow-up T6 phone screen or completed packet. Through the months of January 2013 through June 2013, study personnel searched for medical charts of 240 participants.

Through the months of January 2013 through June 2013, study personnel conducted thorough chart reviews and collected information from available charts. All medical information was entered directly into a password protected secure database. The database was created in order to systematically obtain information on pre-determined factors including factors not collected at study entry and those related to recurrence. For instance, at the time of the original study, data regarding HER2-neu status was not routinely collected, as its clinical significance was not yet established. As it is now a known prognostic risk factor, study personnel reviewed all charts for HER2-neu status of the initial breast cancer diagnosis. Study personnel also verified all information related to pathology and treatment that had been initially collected at study entry.

Information verified by chart review included date of birth, patient contact information, stage of disease, surgery type (lumpectomy or mastectomy), surgery date, number of positive lymph nodes, estrogen receptor status, progesterone receptor status, chemotherapy treatment (yes/no), radiation treatment (yes/no), hormonal therapy (yes/no). New information collected included tumor size, HER2-neu status, Herceptin treatment (yes/no), chemotherapy duration, dosage and type, radiation duration and dosage, hormonal therapy duration and type, breast cancer recurrence (yes/no), and date of recurrence. For women who had a breast cancer recurrence, the same information was collected in regards to the breast cancer recurrence. Study personnel carefully verified whether the cancer diagnosis was in fact a breast cancer recurrence, or a new primary cancer. For women who did not have a recurrence, the date of their last progress note was documented in which they were said to be disease free.

During the months of June and July, study personnel entered the data into an SPSS data file. Data was quality controlled and double entered and checked by two study personnel. Data on recurrence was then merged with the existing dataset containing mortality and prior assessment data. The final dataset was cleaned and variables were created in order to conduct survival analyses. In August 2013, data cleaning and preparation was complete and study personnel began analyzing the data according to the proposed study aims. (see statistical procedures). Data analysis took place from late August 2013 to the beginning of October 2013. Recurrence status was available for 197 women at the 8-15 year follow-up.

Psychosocial data. The packet mentioned previously also contained two brief questionnaires measuring psychosocial well-being (i.e., depressive symptoms and quality of life) via the Center for Epidemiologic Studies - Depression Scale (CES-D; Radloff, 1977) and the Functional Assessment of Cancer Therapy – Breast Cancer (FACT-B; Brady et al., 1997) (see Appendices E,F,G, and H for measure and scoring information). Women were instructed to complete both questionnaires and to mail them back to the study personnel along with the authorization for release of medical information using the pre-paid, pre-addressed envelope provided in the packet.

Measures

Demographics. Information related to *demographics* (age, menopausal status, race/ethnicity), *socioeconomic* (education, income), *cancer diagnosis/treatment-related factors* (time since surgery, stage of disease, positive lymph nodes removed, hormone (ER/PR) receptor status, HER-2/neu receptor status, surgery type, chemotherapy, radiotherapy, hormonal therapies, psychiatric and pain medications), and *health behavior*

characteristics (physical activity, sleep, Body Mass Index (BMI)) was collected via self-report at the initial assessment prior to study randomization. As stated previously, data was verified via medical chart review. New information related to breast cancer recurrence treatment was also collected on these same variables (e.g., additional surgeries and treatments).

Depressive Symptoms. The Center for Epidemiologic Studies - Depression scale (CES-D) (Radloff, 1977) was used to assess participants' depressive symptomatology over the past week (see Appendix B). Participants were asked to rate 20 items related to depressive symptoms on a 4-point Likert type scale ranging from "Rarely or none of the time" to "Most or all of the time." Symptoms are expressed in statements such as "I felt hopeless about the future", and "I could not get going." A total score from 0-60 is computed by summing individual items scores. Higher scores are indicative of more depressive symptoms. Clinical cut-offs were established in the development and validation of the measure, and are as follows: 0-14 = Normal; 15-21 = Mild-Moderate Depression; >21 = Possibility of Major Depression (Radloff, 1977). In addition to the overall CES-D scale, two subscales were computed that were validated in the initial measure development (Radloff, 1997). These include Positive affect and Negative Affect subscales (Moskowitz, 2003; Ross & Mirowsky, 1984; Schroevers, Sanderman, Van Sonderen, & Ranchor, 2000; Sheehan, Fifield, Reisine & Tennen, 1995). Each subscale has been explored with regard to depressed individuals (Gupta & Yick, in press) and the negative and positive affect subscales have been used in the cancer literature specifically (Sanderman & Ranchor, 2000). Finally, a categorical score was created to indicate whether participants report depressive symptoms above or below the CES-D cutoff of 16.

Scores greater than 16 indicate moderate to severe depressive symptoms, while scores lower than 16 indicate mild to no depressive symptoms. The CES-D has been used specifically to measure depressive symptoms in a breast cancer population and has been shown to be a valid and reliable measure in this context (Hann, Winter & Jacobsen, 1999). The CES-D was found to have good reliability in the present sample of breast cancer survivors (α =.90). Chronbach's alphas for the positive and negative affect subscales in the current study were .86 and .81, respectively.

Quality of Life. The 44-item Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B; Brady et al., 1997) was used to assess participants' QOL in 5 separate domains (see Appendix B). Domains include Physical Well-Being, Functional Well-Being, Emotional Well-Being, Social/Family Well-Being, and Additional Concerns Related to Breast Cancer. Concerns specific to breast cancer include items such as "I feel sexually attractive" and "One or both of my arms are swollen or tender." Items are presented on 5-point Likert type scale ranging from "Not at all" to "Very Much." Subscales for each QOL domain are computed by averaging the individual items. A total FACT-B score can also be computed by averaging all scale items. Possible total scores range from 0-28, with higher scores being indicative of better QOL. The FACT was developed specifically for use with cancer patients, and the FACT-B was validated and normed for use in a breast cancer sample (Brady et al., 1997). The measure is used extensively in breast cancer research examining QOL and shown to be valid (Mandelblatt et al., 2011; Levine & Balk, 2012). The total FACT-B, Physical-Well Being, and Emotional-Well Being QOL subscales are of interest in the current study. In the present

study, the Chronbach's alphas for the FACT-B, physical and emotional well-being scale were .94, .84, and .79, respectively.

Psychological Adaptation. The Affect Balance Scale (ABS; Derogatis, 1975) was administered at baseline as a measure of psychological adaptation (see Appendix B). On this rating of affective mood states, 40 emotions are listed and participants rate how often they have experienced each emotion in the past 7 days. The ratings are on a 5-point Likert-type scale ranging from 1= never to 5 = always. A positive affect, negative affect, and composite affect balance score were computed from the 40- item scale. Positive emotion items were averaged to create a positive affect subscale score, as were negative emotion items. In order to create a positive affect balance score, the negative affect score was subtracted from the positive affect score. Higher scores are indicative of more positive affect. The ABS has been found to be a valid and reliable measure of affect in a breast cancer population (Carver & Antoni, 2004; Carver et al., 2005; Grabsch et al., 2006). The ABS positive affect, negative affect, and affect balance subscales were found to have good reliability in the present sample of breast cancer patients. The Chronbach's alphas in the current study were .78, .83, and .82, respectively.

Analytic Strategy

The survival data as well as recurrence data from the medical chart reviews was merged with sociodemographic and psychosocial data from T1-T3 and T5 in order to create a single database inclusive of time points T1-T3, T5 and T6. Data was screened for outliers and non-normality. Skewed data was log transformed. Time variables were created to compute the number of days, months, and years from study randomization to all-cause death, breast cancer-specific death, or breast cancer recurrence. Status variables

were created to indicate whether a participant had the event of interest or not (1=yes; 0 = no). Statistical Program for the Social Sciences (SPSS) version 19.0 was used for all analyses. Intent-to-treat analyses were conducted whereby all participants were included in the analyses regardless of whether they had actually participated in the study past the initial assessment and point of randomization. The sample size of N = 240 lends sufficient power to determine a real difference between the groups and avoid type II error. Previous research by Andersen et al. (2008) detected group differences in survival and recurrence with a sample of N = 227 (Andersen et al., 2008).

Aim 1. Time-to-event analyses. The purpose of the first aim was to examine whether women in the CBSM group differed from those in the psychoeducational control group on clinical disease endpoints, including disease free interval, breast cancer specific survival, and all-cause survival at 8-15 years follow up and 10-year follow-up. Unadjusted Kaplan-Meier Curves were plotted and log-rank and Breslow tests were evaluated at $p<0.05$ to determine whether group differences were observed on any of the clinical outcomes of interest. Values less than .05 indicate a significant difference between study groups. Log rank tests take into account the entire curve, while the Breslow test focuses on earlier parts of the curve (Kleinbaum & Klein, 2012). Cox Proportional Hazards Models were conducted to compare the CBSM and control groups on clinical endpoints over and above the effects of covariates in the model.

All-cause mortality was defined as the time from randomization to date of all-cause mortality. Breast cancer-specific mortality was defined as time from randomization to death due to breast cancer. Disease-free interval was defined as time from study randomization to a breast cancer recurrence. Time was measured in days. Time-to-event

(survival) analyses were conducted using unadjusted Kaplan-Meier curves to estimate the effect of the intervention (CBSM = 1; Control = 0) on all clinical disease outcomes. The time to the event of interest is termed an interval, and was graphed as a horizontal line. Intervals are defined by event occurrences (e.g., recurrence event, death event). Censored participants are indicated as tick marks on the Kaplan-Meier curve. The lengths of the horizontal lines along the X-axis of the serial times represent the survival duration for that interval. The Kaplan-Meier curve is not continuous, but rather step-wise estimates. Therefore interpretation focuses on the entirety of the curve, rather than at fixed periodic intervals.

Multivariate comparisons with Cox Proportional Hazards Ratio (Cox, 1972) were conducted to further investigate differences while including covariates in the models. The Proportionality Hazards Assumption was met for all regressions. Proportionality of hazards assumes that the effect of the predictor on the outcome is the same throughout the plotted curve. The proportionality assumption is met if the plotted cumulative hazard function for each group does not cross (Bewick, Cheek, & Ball, 2004**;** Clark, Bradburn, Love, & Altman, 2003). A hazard ratio (HR) is a relative event rate in each group. The Cox Proportional Hazards Models shows the increased rate of having an event in one curve versus the other. A hazard ratio of '1' indicates that the groups have equal risk of the event outcome. A ratio less than 1 indicates a lower risk, while a ratio greater than 1 indicates an increased risk of the event. Covariates were included in the models in order to examine the effects of the group assignment over and above the effect of baseline prognostic and treatment variables (see covariate section). Estimates for hazard ratios were interpreted at a two-tailed significance level of $p<0.05$. Confidence intervals (at

95%) were obtained for each estimate. Estimates whose lower and upper confidence interval limits do not contain the value of 1.0 (do not cross 1.0) are considered to be significant predictors of the outcome of interest. The smaller the sample size, the larger the confidence intervals will be.

Censoring. Data were censored for women who did not have an event at the time of the follow-up (alive and/or did not have a breast cancer recurrence), those who were lost to follow-up, had previously dropped out of the study, or whose cancer status could not be obtained from the medical chart. The censoring method is implemented when the total survival time for a given event cannot be determined, perhaps because a participant has not had an event prior to study completion (Rich, Neely, Paniello, Voelker, Nussenbaum & Wang, 2010). Data was right censored and met the assumption of non-informative censoring. The non-informative censoring assumes that the reasons participants drop out of the study are unrelated to the study, or study treatment. For example, informative censoring may occur if a study compares the effects of two cancer treatments on survival, and participants in the control group had more recurrences and were too sick to follow-up with the study. In this case, the survival rates would be based only on the patients who continued to follow-up, and would be overestimated for the control group (Ranganathan & Pramesh, 2012). Whether data meets this assumption is often determined by the study design. If patients were lost to follow-up for unforeseen circumstances or dropped out of the study for a variety of reasons, (as in the case of the present study) one can safely assume that censoring was non-informative. (Allison, 2010; Prinja, Gupta & Verma, 2010). Women who were alive were censored with the date they were last reported to be alive. Women who did not have a breast cancer recurrence or for

whom data was unavailable were censored with the last date they were known to be disease free.

Covariates. Two criteria were used to determine candidate confounders to be considered in the Cox Proportional Hazards Models as covariates. First, any variables that were significantly different between the CBSM and control group at baseline were considered as covariates in the predictor models. Second, prognostic risk factors and adjuvant treatments that are known to affect the clinical outcomes of interest were considered *a priori* as potential covariates (Babyak, 2004).

There is some concern to be noted with the consideration of covariates in a regression-type model. A model that is overly complex (i.e., has multiple candidate confounder variables), one that pretests candidate predictors and their relationship to the outcome, or uses an automated variable selection technique (such as backwards or stepwise elimination in regression) is at risk for being "overfitted." Overfitted models capitalize on "idiosyncrasies in the sample," in turn producing unstable estimates that often fail to replicate in future studies (Babyak, 2004). Backwards elimination procedures choose the "best" fitting covariates based on their relation to the outcome and level of significance, therefore maximizing type I error and producing problems such as biased parameter estimates, small standard errors, narrow confidence intervals, and issues with collinearity (Flom & Cassell, 2007; Harrell, 2001; Stefanek, Palmer, Thombs, & Coyne, 2009). As stated in Babyak, 2004, "The primary problem with automated selection is that under the most typical conditions we see in medical and psychological research, i.e., moderate-to-small sample sizes and many possible predictors, many of which are correlated to one another, the possibility of overfitting is far too great for the results to

have anything but the most tentative interpretation." Another common modality for covariate selection is to look at the univariate relationship between each variable and the outcome, and include only those that significantly affect the outcome in the regression analysis. This is also a problematic technique and is considered a variant of automated stepwise procedures (Babyak, 2004). First, this technique actually spends degrees of freedom in the univariate analyses that are not accounted for in the overall regression analysis stage. Furthermore, a predictor may behave differently in isolation than it does when evaluated simultaneously with other predictors. It is worthwhile to include independent variables despite a non-significant effect on the dependent variable, as they may affect the other parameters in the model. An effect may be meaningful even if it is non-significant (Flom & Cassell, 2007). Finally, the degree of correlation between candidate predictors is problematic and often not considered when selecting covariates (Babyak, 2004).

With these issues in mind, researchers have suggested guidelines for choosing covariates in regression-type models in order to avoid overfitting (Babyak, 2004; Harrell, 2001). Ideally, researchers should create an *a priori* list of covariates based on theory and empirical evidence and retain these covariates in the final model. However, when the number of predictors is too large, then the number of variables should be reduced in order to avoid overfitting the model. One suggested strategy is to examine the correlation between the predictors and eliminate closely correlated predictors (Babyak, 2004).

Given these suggestions, the current study selected an *a piori* list of covariates that either differed by group assignment at baseline, or were demographic, treatment and prognostic factors known to influence all-cause mortality, breast-cancer related mortality,

and breast cancer recurrence. These two criteria to establish covariates (i.e., consideration of variables that differ by groups at baseline and those that theoretically affect the outcome) were also used in the survival study by Anderson et al (2008) as potential covariates for time-to-event analyses. In the present study, the following demographic, prognostic, and treatment-related candidate confounders were considered apriori: age (Anders et al., 2008; Han et al., 2004), menopausal status (Carlson et al., 2009), time elapsed from surgery to baseline, stage of disease (Carlson et al., 2009; Galea, Blamey, Elston, & Ellis, 1992), tumor size (Soerjomataram, Louwman, Ribot, Roukema, & Coebergh, 2008), number of positive lymph nodes (Soerjomataram et al., 2008), procedure type (Carlson et al., 2009), estrogen receptor (ER) status (Allred et al., 2009), progesterone receptor (PR) status (Allred et al., 2009), HER2-neu receptor status (Carlson et al., 2006; Ross & Fletcher, 1998; Soerjomataram et al., 2008), chemotherapy received (Chia, Bryce, & Gelmon, 2005), radiation therapy received (Clark et al., 2005), hormonal therapy received (Chia, Bryce, & Gelmon, 2005), and Herceptin therapy received (Ross & Fletcher, 1998).

Next, as suggested by Babyak (2004), we narrowed down the number of covariates to be considered by conducting Pearson correlations to determine if there was high collinearity amongst any of these candidate confounder variables. For any predictor variables that were highly correlated ($r > 0.5$), a decision was made regarding which to retain in the final model. Variables that were highly correlated were the following: age with menopausal status, stage of disease with number of positive lymph nodes, procedure with radiation received, ER status with PR status, ER with hormonal therapy received, and PR with hormonal therapy received.

Next, chi-square tests and one-way ANOVAs were conducted to determine group differences at baseline among demographic, medical, treatment-related, and psychosocial variables. Candidate confounder variables that were significantly different between study groups at the baseline assessment (i.e., time since surgery and chemotherapy) were retained in the final model. Although surgical procedure type differed by group, it was also correlated with radiation treatment. Since we retained chemotherapy in the final model, we chose to retain radiation treatment, which therefore accounts for surgical procedure type as well.

The final covariates retained in the model were: age (accounts for menopausal status), time since surgery (differs by group), stage (accounts for nodes), tumor size (not accounted for by other covariates), HER2neu status (not accounted for by other covariates) radiation therapy (also accounts for procedure type which differed by group), chemotherapy received (differs by group), and hormonal therapy (accounts for ER and PR status).

Although Andersen et al (2008) used similar criterion to select candidate confounder variables (i.e., baseline group differences and prognostic and treatment factors known to affect the outcomes), this group seemingly did not examine the relationship among the predictors in order to narrow down or eliminate covariates. In addition, the method they used to choose which covariates would be retained in the final model was an automatic stepwise procedure called backwards elimination, which risks overfitting the model as described earlier (Babyak, 2004).

Instead, we used the “enter” method in SPSS for the Cox Proportional Hazards Models. The enter method ensures that each predictor entered will be retained in the final

model, regardless of whether the variable is a significant predictor of the outcome of interest. The variable indicating study arm was entered into the second block in an "enter" method as well. This method allows for the inclusion of an apriori list of covariates chosen with supported methods described above (i.e., age, stage of disease, time since surgery, tumor size, HER-2neu receptor status, chemotherapy, radiation, and hormonal therapy receipt) and is a preferred method over automated stepwise procedures such as backwards elimination methods (Babyak, 2004).

Aim 2. Regression analyses. The purpose of the second aim was to examine whether women in the CBSM group differ from those in the psychoeducational control group on psychosocial outcomes of depressive symptoms and QOL at 8-15 years follow up (T6).

Depressive symptoms. Linear regressions were conducted to test for these relationships, with scores on the CES-D at T6 regressed on group assignment as the independent variable. Individual subscales of the CES-D were also examined, including the positive affect and depressed affect subscales, and a categorical score indicating whether participants report depressive symptoms above or below the CES-D cutoff of 16. Then, theoretically supported covariates were included in the models to determine the effect of group assignment over and above the effect of the other predictors in the model. Criteria for determining these covariates were the same as for Aim 1: covariates retained in the model were those that are known to affect the outcome of interest and or that differed by group at baseline. Covariates tested when examining the effect of the intervention on depressive symptoms included depressive symptoms reported at baseline on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), as well as

sociodemographic characteristics and variables that have been shown to influence depressive symptoms. These included age (Cimprich, Ronis, & Martinez-Ramos, 2002), education (Costanzo et al., 2007), income (Mols, Vingerhoets, Coebergh, & van de Poll-Franse, 2005), race/ethnicity (Bowen et al., 2007), pain (So et al., 2009), and BMI (Howren, Lamkin, & Suls, 2009).

Quality of Life. These analyses were repeated with the FACT-B as the dependent variable regressed on group assignment. Individual subscales of the FACT-B were also examined as potential outcomes, including the Physical Well-Being and Emotional Well-Being QOL subscales. These analyses were conducted first without covariates. Theoretically supported covariates were included in the models. Criteria for determining these covariates were the same as Aim 1: covariates retained in the model were those that are known to affect the outcome of interest and or that differed by group at baseline. Potential covariates included reported QOL on the specific scale or subscale of interest at baseline, age (Cimprich, Ronis, & Martinez-Ramos, 2002), education (Costanzo et al., 2007), income (Mols, Vingerhoets, Coebergh, & van de Poll-Franse, 2005), race/ethnicity (Bowen et al., 2007), pain (So et al., 2009), and BMI (Howren, Lamkin, & Suls, 2009).

Unstandardized regression coefficients and corresponding effect sizes were evaluated to determine the significance of the relationships between study arm and depressive symptoms, positive affect, overall QOL and individual QOL domains. Measures of effect sizes were interpreted at the following levels: 0.20 = small; 0.50 = medium; 0.80 = large (Cohen, 1988).

Aim 3 mediation analyses. The purpose of the third aim was to determine what factors may mediate the effect of the study intervention on clinical disease outcomes

(survival and recurrence) and psychosocial outcomes (QOL and depressive symptoms) at the 8-15 year and 10-year follow-up (T6). Mediation tests using bootstrapping methods with an SPSS macros (Preacher & Hayes, 2004; Hayes, 2009; MacKinnon, Lockwood & Williams, 2004) were conducted to determine whether the effects of condition on (a) T6 clinical disease outcomes and (b) psychosocial outcomes were mediated by changes in psychological adaptation from 0-12 months.

These meditational tests build on the traditional Baron and Kenny (1986) approach to mediation, with a normal theory approach to estimate the indirect effect and a bootstrap approach to obtain confidence intervals of the indirect effect. Tests of mediation were interpreted by examining the direct effect of the independent variable on the mediator variable (path A), the direct effect of the mediator variable on the dependent variable controlling for the independent variable (path B), the total effect of the independent variable on the dependent variable (path C) and the direct effect of the independent variable on the dependent variable controlling for the mediator variable (path C'). The total effect is equal to the indirect effect plus the direct effect. A model which meets all Baron & Kenny (1986) criteria reveals significance of path A, path B, and a non-significant path C'. Next, the significance of the indirect effect is tested (path A x path B) with the Sobel test (Preacher & Hayes, 2004). The bootstrapped estimate of this indirect effect was interpreted based on the 95% confidence intervals. The confidence intervals indicate the likelihood that the true indirect effect will fall within the lower and upper limits of the interval. Therefore, if the value of zero lied within the 95% confidence interval, it was concluded that the indirect effect is not significant. If the value of zero did not lie within the 95% confidence interval, it was deduced that the indirect

effect is significant. A significant indirect effect implies that mediation does in fact exist, that the relationship between the independent variable to the dependent variable is mediated by the proposed mediator variable (Preacher & Hayes, 2004; Hayes, 2009; MacKinnon, Lockwood & Williams, 2004).

For aim 3a the condition (CBSM vs. PE Control) was the independent variable, with clinical disease outcomes at T6 as the dependent variables (recurrence free interval, and time to death interval). In the initial 12 months of the study, women in the CBSM group showed favorable changes in psychosocial adaptation as measured by the Affect Balance Scale (ABS). Therefore change scores from T1-T3 were computed to represent changes in psychological adaptation as measured by the negative affect score, positive affect score, and composite affect balance score. These psychological change scores served as mediators for these tests. Covariates from aim 1 were also included in these models (i.e., age, time since surgery, stage of disease, tumor size, HER2-neu, hormonal therapy, chemotherapy, and radiation therapy).

For aim 3b, bootstrapping methods were used to determine what factors may mediate the effect of the study intervention on psychosocial outcomes (QOL and depressive symptoms) at T6. For these tests of mediation, condition (CBSM vs. PE Control) was the independent variable, with psychosocial outcomes at T6 as the dependent variables. QOL at T6 was measured by the total, physical, and emotional well-being subscales of the FACT- Breast Cancer. Depressive symptoms at T6 were measured by the CES-D total score, the positive and depressed affect, and a categorical score indicating whether participants reported depressive symptoms above or below the CES-D cutoff of 16. As in aim 3a, change scores from T1-T3 were computed to represent

changes in psychological adaptation as measured by the negative affect score, positive affect score, and composite affect balance score. These psychological change scores served as mediators for these tests. Covariates from aim 2 were included in these models (i.e., age, income, education, race/ethnicity, pain, BMI, and T1 value for the psychosocial outcome of interest). For both aim 3a and 3b, unstandardized regression coefficients ($p < .05$) and the corresponding effect sizes were interpreted (Thompson, 2007).

Chapter 3: Results

Contacting Participants

Phone screens. Study personnel successfully contacted 107 (44.6%) participants at the T6 follow-up. Of the 107 study participants contacted, 107 agreed to answer study questions over the phone and complete the phone screen regarding the status of breast cancer recurrence. Of the 107 participants who completed the T6 phone questions, 99 (92.5%) agreed to release medical information from their physician or oncologist. A total of 8 (7.5%) participants did not agree to release medical information. Of the 133 women who were unreachable at the phone screen, reasons for incomplete phone screen include the following: Phone disconnected (16.7%), deceased (12.5%), did not return multiple voicemail messages (11.3%), requested no further contact at earlier time point (8.3%), unable to leave voicemail messages due continued ring on multiple call attempts (2.1%), unable to contact due to busy signal on multiple call attempts (1.3%), unable to leave message due to full voicemail box on multiple attempts (0.8%), phone number was transferred to a different person (0.8%), phone number not listed and not searchable (0.8%), family member informed study personnel that participant no longer lives in the U.S. and offered to forward the mailed packet (0.4%), phone number on file was an old work number (0.4%). Study personnel attempted to reach participants on every phone number on file from time of enrollment. Study personnel also searched online for participants' updated contact information (i.e., phone number and mailing addresses).

Study packet mailings. Out of the 107 participants who were successfully phone screened, all were asked for permission to be mailed a study packet asking them follow-up questions about their recurrence status. All but one participant agreed to have study

personnel mail them a packet with questions regarding their health status (i.e., recurrence status). Packets were mailed to participants who agreed by phone, as well as participants who were unreachable at the time of the phone screen for reasons described previously. A total of 100 study participants (41.7% of the initial 240) completed the study packets, including the psychosocial questionnaires, and mailed them back to study personnel. Reasons for incomplete study packets included the following: participant did not return packet (36.3%), participant deceased (12.5%), participant had requested no further contact at a previous time point (8.3%), address not available for participant (0.8%), participant refused packet at time of phone screen (0.4%). Of the 100 participants who completed and mailed back the packet, 81 (81.0%) completed the updated medical release. Of the 100 participants who completed the psychosocial questionnaires, 19 participants had been previously unreachable by phone. These participants were then contacted using updated contact information from the T6 packet they mailed back.

Medical Chart Reviews

Medical charts were searched for all participants at their respective oncologist/physician offices, using the updated medical release (N = 81). For women who had not completed an updated medical release (N = 159), the original informed consent was used as authorization for release of medical records. Certain offices (N = 91) accepted the original informed consent as authorization and released the medical records to study personnel. However, certain offices (N = 73) required an updated release, and would not release records unless this was available. In addition, many offices informed study personnel that medical charts were archived or destroyed after a number of years. Charts that were archived were requested to be recalled. Charts were searched for all 240

study participants, using the initial informed consent as well as the updated medical release in order to access the records. Medical records were reviewed for a total of 164 (68.3%) study participants. Reasons that a woman's chart was not reviewed include the following: Participant unreachable by phone and mail at T6 and no updated authorization available, medical chart searched for at original oncologist from study enrollment using original informed consent, however chart had been destroyed as the participant had not been back to oncologist in 3-5 years (14.2%), participant deceased and office required updated medical release and would not accept original informed consent (5.8%), participant returned T6 packet without updated medical authorization and office did not accept original informed consent (3.8%), participant previously requested no further contact and office did not accept original informed consent (3.8%), participant completed medical authorization only with original oncologist information and chart was not locatable at this office (3.3%), participant unreachable at T6 and original oncologist from study enrollment unknown (0.8%).

Participant Sample Characteristics

At the 8-15 year follow-up, women were an average of 60.41 (*SD*=9.47) years old. For additional descriptive information by group on demographics, medical, treatment-related, and psychosocial variables see Table 1. Study groups (i.e., CBSM, control) differed with regard to the time elapsed since surgery ($F(1,239) = 8.12$, $p = .005$), with women in the CBSM group averaging 34.47 (*SD*=19.69) days from the date of surgery to the date of randomization, and women in the control group averaging 44.81 (*SD*=25.34) days. Study groups differed marginally with regard to chemotherapy received ($\chi^2(1) = 3.49$, $p = 0.06$). In the CBSM group, 70 (58.3%) of women received

chemotherapy, while 44 (36.7%) did not. In the control group, 57 (47.5%) women received chemotherapy, while 59 (49.2%) did not. Study groups also differed marginally with regard to procedure type ($\chi^2(1) = 3.27$, $p = 0.07$. In the CBSM group, 54 (45.0%) women had a lumpectomy, while 66 (55.0%) underwent a mastectomy. In the control group, 68 (56.7%) women had a lumpectomy, while 52 (43.3%) underwent a mastectomy. The study groups did not differ on any other demographic, medical, treatment-related, psychosocial, or other study variables. For descriptives of study variables by group, see Table 2. When the range was restricted to the 10-year follow-up, a total of 187 women were included in the analyses.

Women who completed the psychosocial T6 questionnaire (N = 100) were mostly similar to women who did not complete the T6 psychosocial questionnaire (N = 140). Completers and non-completers were no different with regard to condition assignment (i.e., CBSM vs. control). They were also no different with regard to the time elapsed from surgery to baseline assessment, number of years of education, annual household income, employment status, menopausal status, BMI, stage of disease, tumor size, number of positive lymph nodes, ER status, PR status, HER-2/neu status, procedure type, use of pain, depression, anxiety, or sleep medication, chemotherapy treatment received, hormonal treatment received, or radiation treatment received. Completers and non-completers differed slightly with regard to age, with T6 psychosocial completers being older ($M = 52.00$, $SD = 8.89$) than non-completers ($M = 49.16$, $SD = 8.97$), $F(1,238) = 5.91$, $p = .016$. With regard to baseline psychosocial status, completers and non-completers were equivalent on measures of ABS-positive affect, ABS-negative affect, ABS-balance score, FACT- physical well-being, and FACT-emotional well-being at T1.

Women who completed the T6 psychosocial questionnaire had reported less depressive symptoms on the HRSD at baseline (M = 6.42, SD = 4.63) than women who did not complete the T6 questionnaire (M = 8.29, SD = 5.86), $F(1,229) = 6.70$, $p = .010$, and better overall QOL on the FACT-B total score at baseline (M = 101.46, SD = 18.56) than women who did not complete the T6 questionnaire (M = 94.10, SD = 16.70), $F(1,238) = 10.33$, $p = .001$.

A total of 47 women (19.6%) had a breast cancer recurrence. Caution was taken in determining whether the documented recurrence was indeed a breast cancer recurrence rather than a new primary cancer occurrence. Of the total sample (N=240), 30 (12.5%) women were deceased at T6 follow-up. Of these 30 deaths, 22 (9.2%) were a breast-cancer related mortality, and 8 were of non-breast cancer related causes. For these women whose death was not related to breast cancer (N=8), reason for death was reported as follows: Alzheimer's Disease, unspecified (N=1), Malignant neoplasm without specification of site (N=1), non-traumatic subarachnoid hemorrhage, unspecified (N=1), Ovarian cancer death (N=1), cause unknown (N=4). Average time to recurrence in days was 2,345.33 days (SD =1,430.73) and average time to recurrence in months was 76.55 months (SD= 46.97*)*. Average time to death in days was 2,962.66 days (SD=1,354.30), and average time to death in months was 96.85 months (SD=44.46). Women who did not have a breast cancer recurrence (80.4%) were censored using the date they were last documented to be disease free. Women who were still alive at the time of follow-up (87.5%) were censored using the last date they were documented to be alive.

Aim 1 Full Sample Unadjusted Kaplan-Meier Curves

All-cause mortality. Kaplan-Meier curves were plotted to test whether study group assignment significantly predicted time to all-cause mortality. This model was not adjusted for any covariates. Findings showed that study group was not a significant predictor of time to all-cause mortality (See Figure 2), with the control group having a mean survival time of 4,709.12 (*SE*=130.66*)* days and the CBSM group having a mean survival time of 4,794.88 (*SE*=120.04) days, Log Rank (*df*=1) =.002, *p* = .966; Breslow (*df* =1) =.02, *p* =.887). Examining only women in the 10-year follow-up window revealed similar results.

Breast cancer-specific mortality. Kaplan-Meier curves were plotted to test whether study group assignment significantly predicted time to breast cancer-specific mortality. This model was not adjusted for any covariates. Findings showed that study group was not a significant predictor of time to breast cancer-specific mortality (See Figure 3), with the control group having a mean survival time of 4,873.91 (*SE*=114.08*)* days and the CBSM group having a mean survival time of 4,877.79 (*SE*=113.67) days, Log Rank (*df*=1) =.17, *p* = .684; Breslow (*df* =1) =.02, *p* =.887). Examining only women in the 10-year follow-up window revealed similar results.

Disease-free interval. Kaplan-Meier curves were plotted to test whether study group assignment significantly predicted time to breast cancer recurrence. This model was not adjusted for any covariates. Findings showed that study group was not a significant predictor of time to breast cancer recurrence (See Figure 4), with the control group having a mean disease-free interval of 4,190.18 (*SE*=192.74*)* days and the CBSM group having a mean disease-free interval of 4,149.30 (*SE*=165.40) days, Log Rank (*df* =

1) =.01, p = .936; Breslow (df = 1) =.04, p =.840). Examining only women in the 10-year follow-up window revealed similar results.

Adjusted Cox Proportional Hazards Models (all covariates)

All-cause mortality. Cox proportional hazards models were conducted to determine group differences on time to all-cause mortality adjusting for age, time since surgery, stage, HER2neu, tumor size, hormonal therapy, chemotherapy, and radiation therapy. Stage of disease was categorized as early vs. advanced stage (stage 0 vs. stages I, II, III, and IV) (Lutgendorf et al., 2012). Of the retained covariates, age and hormone therapy receipt were the only significant predictors of all-cause mortality risk. Specifically, with every year increase in age at diagnosis, the hazard ratio decreased by .89 (p = .011). The older women were at diagnosis, the greater reduction in all-cause mortality risk. For hormone therapy, women who did not receive hormonal therapy were 5.89 times more likely to have an all-cause mortality event compared to those who did receive hormonal therapy (p = .024). Study condition significantly predicted time to all-cause mortality. Cox models showed that the all-cause mortality hazard for the CBSM group compared to the controls was .18, over and above the effect of the covariates (omnibus model $\chi^2(9) = 17.58$, p = .040, CBSM HR = 0.18 (95% CI [0.04, 0.80]; p = .025) (see Figure 5). Examining only women in the 10-year follow-up window also revealed significant results (omnibus model $\chi^2(9) = 23.84$, p = .005, CBSM HR = 0.07 (95% CI [0.01, 0.79]; p = .032).

Breast cancer-specific mortality. Cox proportional hazards models were conducted to determine group differences on time to breast cancer-specific mortality adjusting for age, time since surgery, stage, HER2neu, tumor size, hormonal therapy,

chemotherapy, and radiation therapy. Age significantly predicted time to breast cancer death, such that women who were diagnosed at older ages had a reduced risk of breast cancer-related death (HR = .89, p = .014). None of the other covariates in the model significantly predicted breast cancer-specific mortality. Study condition significantly predicted time to breast cancer-specific mortality. Cox models showed that the breast cancer-specific mortality hazard for the CBSM group compared to the controls was .21, over and above the effect of the covariates (omnibus model $\chi^2(9) = 16.29$, p = .061, CBSM HR = 0.21 (95% CI [0.05, 0.99]; p = .048) (see Figure 6). Examining only women in the 10-year follow-up window revealed marginally significant results (omnibus model $\chi^2(9) = 22.65$, p = .007, CBSM HR = 0.08 (95% CI [0.01, 1.08]; p = .057).

Disease-free interval. Cox proportional hazards models were conducted to determine group differences on time to disease-free interval adjusting for age, time since surgery, stage, HER2neu, tumor size, hormonal therapy, chemotherapy, and radiation therapy. Age significantly predicted time to breast cancer recurrence, such that women who were diagnosed at older ages had a reduced risk of breast cancer recurrence (HR = .94, p = .016). None of the other covariates in the model significantly predicted breast cancer recurrence. Study condition significantly predicted time to breast cancer recurrence. Cox models showed that the disease-free interval hazard for the CBSM group compared to the controls was .40, over and above the effect of the covariates (omnibus model $\chi^2(9) = 17.71$, p = .039, CBSM HR = 0.40 (95% CI [0.17, 0.98]; p = .044) (see Figure 7). Examining only women in the 10-year follow-up window similarly revealed significant results (omnibus model $\chi^2(9) = 27.46$, p = .001, CBSM HR = 0.12 (95% CI [0.03, 0.51]; p = .004).

Adjusted Cox Proportional Hazards Models (minimally controlled)

The covariate list described above was narrowed down in order to avoid over-fitting, or over-controlling the models, which is a main criticism of survival analyses (Stefanek, Palmer, Thombs, & Coyne, 2009) and regression models (Babyak, 2004). Of the final cancer-related covariates considered, those that are descriptive of tumor prognostic factors were included in the final models so that the smallest number of covariates are included. Covariates in the following models are: stage of disease, HER2neu, tumor size, hormonal treatment, age, and time since surgery. Age was included as it accounts for menopausal status. Time since surgery was included as it differed by condition at baseline. Cox proportional hazard regression results from this minimally controlled model are reported in Table 3.

All-cause mortality. Cox proportional hazards models were conducted to determine group differences on time to all-cause mortality adjusting for age, time since surgery, stage, HER2neu, tumor size, and hormonal therapy. Age and hormonal therapy received significantly predicted all-cause mortality. Specifically, with every year increase in age at diagnosis, the hazard ratio decreased by .90 (p = .015). The older women were at diagnosis, the greater reduction in all-cause mortality risk. For hormone therapy, women who did not receive hormonal therapy were 4.12 times more likely to have an all-cause mortality event compared to those who did receive hormonal therapy (p = .036). None of the other retained covariates were significant predictors of all-cause mortality (see Table 3). Study condition significantly predicted time to all-cause mortality. Cox models showed that the all-cause mortality hazard for the CBSM group compared to the controls was .21, over and above the effect of the covariates (omnibus model $\chi^2(7)$ =

15.66, p = .028, CBSM HR = 0.21 (95% CI [0.05, 0.91]; p = .037) (see Figure 8). Examining only women in the 10-year follow-up range similarly revealed significant results (omnibus model $\chi^2(7) = 20.13$ p = .005, CBSM HR = 0.15 (95% CI [0.03, 0.89]; p = .037).

Breast cancer-specific mortality. Cox proportional hazards models were conducted to determine group differences on time to breast cancer-specific mortality adjusting for age, time since surgery, stage, HER2neu, tumor size, and hormonal therapy. Age significantly predicted time to breast cancer death, such that women who were diagnosed at older ages had a reduced risk of breast cancer-related death (HR = .90, p = .014). None of the other covariates in the model significantly predicted breast cancer-specific mortality in this minimally controlled model (see Table 3). Study condition approached significance in the prediction of breast cancer-specific mortality. Cox models showed that the breast cancer-specific mortality hazard for the CBSM group as compared with the controls was .23, over and above the effect of the covariates (omnibus model $\chi^2(7) = 14.49$, p = .043, CBSM HR = 0.23 (95% CI [0.05, 1.08]; p = .063) (see Figure 9). Examining only women in the 10-year follow-up range similarly revealed marginally significant results (omnibus model $\chi^2(7) = 18.70$, p = .009, CBSM HR = 0.20 (95% CI [0.03, 1.29]; p = .091).

Disease-free interval. Cox proportional hazards models were conducted to determine group differences on disease-free interval adjusting for age, time since surgery, stage, HER2neu, tumor size, and hormonal therapy. Age significantly predicted time to breast cancer recurrence, such that women who were diagnosed at older ages had a reduced risk of breast cancer recurrence (HR = .94, p = .013). None of the other

covariates in the model significantly predicted breast cancer recurrence in this minimally controlled model (see Table 3). Study condition approached significance in the prediction of disease-free interval. Cox models showed that the disease-free interval hazard for the CBSM group as compared with the controls was .44, over and above the effect of the covariates (omnibus model $\chi^2(7) = 14.49$, $p = .043$, CBSM HR = 0.44 (95% CI [0.18, 1.04]; $p = .062$) (see Figure 10). Examining only women in the 10-year follow-up range revealed significant results (omnibus model $\chi^2(7) = 20.96$, $p = .004$, CBSM HR = 0.24 (95% CI [0.07, 0.80]; $p = .020$)

Aim 2 Intervention Effects on Psychosocial Outcomes

Quality of Life

FACT-Breast. Linear regressions were conducted in order to examine the effect of the intervention on QOL controlling for baseline QOL, unadjusted for other covariates. Intervention did not significantly predict FACT-B total at T6 controlling for FACT-B at T1. For regression results of intervention effects on QOL, refer to Table 4. To determine whether intervention condition predicted FACT-B total at T6 above and beyond the influence of sociodemographic and medical factors, control variables were included in the model using the "enter" method. Specifically, FACT-B scores at baseline and pain were significant predictors, such that higher baseline FACT-B QOL was predictive of higher FACT-B QOL at T6 ($p = .002$), and participants who reported more pain had lower FACT-B QOL at T6 ($p < .001$). When controlling for the influence of age, education, income, race/ethnicity, pain, BMI, and baseline FACT-B score, the effect of intervention condition on QOL on the FACT-B was significant. Women who were assigned to CBSM reported significantly better QOL ($M = 141.16$, $SE = 3.25$) compared

to women in the control group (M = 131.57, SE = 2.85), β = 9.59, SE = 4.56, p =.041, CI [0.42, 18.76] d = 0.62, a medium effect (see Figure 11). The model with all predictors explained a significant proportion of variance in the FACT-B, R^2= .55, F(10,48) = 8.21, p <.001. See Table 5 for the effects of all predictors in the model.

FACT-Physical Well-Being. Intervention condition did not significantly predict physical well-being at T6 when controlling only for baseline physical well-being on the FACT-B. Physical well-being scores on the FACT-B at baseline, income, and pain were significant predictors, such that higher baseline physical well-being QOL was predictive of higher physical well-being QOL at T6 (p = .007), women with higher income at baseline had better physical well-being at T6 (p = .043), and participants who reported more pain had lower physical well-being QOL at T6 (p < .001). When controlling for age, education, income, race/ethnicity, pain, BMI, and baseline physical well-being, the effect of intervention on physical well-being at T6 was significant above and beyond the effects of the other predictors in the model. Women who were assigned to CBSM reported significantly better physical well-being at T6 (M = 26.85, SE = 0.67) than women assigned to the control group (M = 23.85, SE = 0.58), β = 3.00, SE = 0.94, p =.002, 95% CI [1.11, 4.89], d = .89, a large effect (see Figure 12). The model with all predictors explained a significant proportion of variance in physical well-being at T6, R^2 =.65, F (10,48) = 8.88, p <.01. See Table 5 for the effects of all predictors in the model.

FACT-Emotional Well-Being. Intervention condition did not significantly predict emotional well-being at T6 when controlling only for baseline emotional well-being on the FACT-B. Emotional well-being scores on the FACT-B at baseline, being of Asian ethnicity, and pain were significant predictors, such that higher baseline emotional

well-being QOL was predictive of higher emotional well-being QOL at T6 (p = .006), women who self- identified as Asian had better emotional well-being at T6 (p = .028), and participants who reported more pain had lower emotional well-being QOL at T6 (p < .001). When controlling for age, education, income, race/ethnicity, pain, BMI, and baseline emotional well-being, the effect of intervention on emotional well-being at T6 was marginally significant, above and beyond the effects of other predictors in the model. Women who were assigned to CBSM reported significantly greater emotional well-being at T6 (M = 22.31, SE = 0.59) than women assigned to the control group (M = 20.49, SE = 0.51), β = 1.82, SE = 0.81, p =.030, 95% CI [0.19, 3.46], d = .61, a medium effect size (see Figure 13) The model with all predictors explained a significant proportion of variance in emotional well-being at T6, R^2 = .49, F (10,48) = 4.57, p <.001. See Table 5 for the effects of all predictors in the model.

Depressive Symptoms

CES-D Total. Linear regressions were conducted to determine whether intervention significantly influenced depressive symptoms at T6 controlling for baseline depressive symptoms on the HRSD. For all regression results of intervention effects on depressive symptoms, see Table 5. Intervention did not significantly predict depressive symptoms at T6 while controlling for baseline HRSD. Among the covariates included in adjusted analyses, self-reported pain was a significant predictor, such that participants who reported more pain had more depressive symptoms at T6 (p < .001).When controlling for age, education, income, race/ethnicity, pain, BMI, and baseline HRSD, there was a significant effect of intervention on depressive symptoms at T6 above and beyond the effects of the covariates. Women who were assigned to CBSM reported

significantly less depressive symptoms at T6 (M = 5.21, SE = 1.58) than women assigned to the control group (M = 9.66, SE = 1.43), β = -4.46, SE = 2.22, p =.051, 95% CI [-8.93, 0.01], d = .57, a medium effect size (see Figure 14). The model with all predictors explained a significant proportion of variance in depressive symptoms at T6, R^2 = .45, F (10,44) = 3.55, p <.01. See Table 5 for the effects of all predictors in the model.

CES-D Positive Affect. Intervention did not significantly predict positive affect on the CES-D at T6 when controlling for baseline depressive symptoms on the HRSD. Of the covariates in the adjusted model, being of Asian ethnicity and reported pain were significant predictors of positive affect, such that women who self-identified as Asian reported less positive affect (p = .004), and women who reported pain reported less positive affect (p = .030). While controlling for age, education, income, race/ethnicity, pain, BMI, and baseline HRSD, intervention was still not a significant predictor of T6 positive affect on the CES-D. Reported positive affect in the CBSM group (M = 10.14, SE = 0.66) was not significantly better than positive affect in women assigned to the control group (M = 8.85, SE = 0.60), β = 1.30, SE = 0.93, p =.169, 95% CI [-0.57, 3.17]. See table 5 for the effects of other predictors in the model.

CES-D Negative Affect. Intervention did not significantly predict negative affect on the CES-D at T6 when controlling for baseline depressive symptoms on the HRSD. Among the covariates used in the adjusted model, self-reported pain was a significant predictor, such that participants who reported more pain had more negative affect on the CES-D at T6 (p < .001). While controlling for age, education, income, race/ethnicity, pain, BMI, and baseline HRSD, there was a significant effect of intervention on negative affect at T6 above and beyond the effects of the covariates. Women who were assigned to

CBSM reported significantly less negative affect at T6 (M = 0.94, SE = .54) than women assigned to the control group (M = 2.52, SE = .49), β = -1.58, SE = 0.76, p =.044, 95% CI [-3.11, -0.04], d = .58, a medium to large effect size (see Figure 15). The model with all predictors explained a significant proportion of variance in negative affect at T6, R^2 = .47, F (10,44) = 3.96, p <.01. See Table 5 for the effects of all predictors in the model.

Aim 3 Mediation

Aim 3a Mediation Effects on Clinical Outcomes

A change score was computed with the ABS to represent change in mood from baseline to the 12-month assessment. The change score was calculated by subtracting the T1 baseline assessment score on the ABS from the T3 12-month assessment score. This was done for the ABS-positive affect, ABS-negative affect, and ABS-affect balance score. Regression analyses were used to test whether the change in mood on the ABS over the 12-month study period mediated the effects of intervention on clinical outcomes of all-cause mortality, breast cancer-related mortality, and disease free interval. First, traditional Baron and Kenny (1986) steps of mediation were estimated as described previously using covariates from the original model (8-covariates) and the minimally controlled model (6-covariates) in aim 1. Path A, the direct effect of the independent variable on the mediator (i.e. the effect of intervention on 12-month change in ABS-balance, ABS-positive affect, and ABS-negative affect) was not significant. In addition, path B, the direct effect of the mediator variable on the dependent variable controlling for the independent variable and previously used covariates, was not significant. Path B was not significant when examining ABS-balance score, ABS-positive affect, nor ABS-negative affect as a mediator. Therefore, mediation was not supported. Further tests of the

indirect effect and bootstrapped results of the indirect effect were not computed given the non-significant paths A and B. These steps were repeated using a restricted follow-up range of 10 years and results were similar showing no mediation.

Aim 3b Mediation Effects on Psychosocial Outcomes

The ABS-balance, ABS-positive affect, and ABS-negative affect 12-month change scores were then each tested as a mediator of the effect of intervention on psychosocial outcomes of QOL and depressive symptoms using covariates identical to those in aim 2. As in Aim3a, traditional Baron and Kenny (1986) steps of mediation were estimated first. Path B, the direct effect of the mediator (mood) variable on the dependent variable (QOL or depressive symptoms) controlling for the independent variable (intervention condition) and previously mentioned covariates, was not significant. Path B was not significant when examining ABS-balance score, ABS-positive affect, nor ABS-negative affect as a mediator. Therefore, mediation was not supported. Further tests of the indirect effect and bootstrapped results of the indirect effect were not computed given the non-significant path B.

Chapter 4: Discussion

The current study aimed to examine whether women with stage 0-IIIb breast cancer enrolled in a randomized controlled trial of CBSM post-surgery experienced physical or psychological benefits compared to women randomized to the control group at the 8-15 year follow-up (T6) and a restricted 10-year follow-up. Tests of the first aim evaluated whether women in the CBSM intervention condition showed improved survival, breast cancer specific survival, or disease free interval compared to the control group while adjusting for biomedical confounders. The objective of the second aim was to determine whether women in the CBSM intervention condition who were still alive at follow-up reported better psychosocial functioning on measures of QOL and depressive symptoms at 8-15 year follow-up as compared to the control group. The final aim examined whether changes in affect over the initial 12-month study period mediated the intervention effects on clinical and psychosocial outcomes at the 8-15 year and 10-year follow-ups.

Psychosocial Interventions, Survival, and Disease Progression in Breast Cancer

Kaplan-Meier tests of the first aim revealed that the effect of condition on clinical outcomes of all-cause mortality, breast cancer-specific mortality, and disease free interval were not significant when analyzing the data unadjusted for biomedical confounders. Findings were consistent when examining these effects in the 10-year follow-up window only. However, when theoretically supported covariates were included in the model (i.e., age, stage of disease, time elapsed from surgery to baseline, HER/2-neu receptor status, tumor size, chemotherapy receipt, radiation receipt, and hormonal therapy receipt), there was a significant protective of effect of being in the CBSM intervention condition over

and above the influence of the covariates. Specifically, women in the CBSM group had 82% reduced risk of all-cause mortality, 79% reduced risk of breast cancer-related mortality, and 60% reduced risk of breast cancer recurrence from study enrollment to the 8-15 year follow-up. When the follow-up range was restricted to the randomization through 10-year follow-up, results were similar for all-cause mortality risk and breast cancer recurrence risk. Specifically, in the 10-year follow-up window, women in the CBSM group had a significant 93% reduction in all-cause mortality risk, and an 88% reduced risk for breast cancer recurrence. While women in the CBSM group showed a 92% reduced risk of breast cancer-related mortality in this 10-year window, this hazard ratio did not reach significance (p=.057).

Analyses were repeated with fewer covariates (a minimally controlled model) in order to prevent over-fitting the model (Stefanek, Palmer, Thombs, & Coyne, 2009). When including age, stage of disease, time elapsed from surgery to baseline, HER/2-neu receptor status, tumor size, and hormonal treatment, findings held for all-cause mortality risk only. Specifically, women in the CBSM group showed a significant 79% risk reduction in all-cause mortality from study enrollment to 8-15 years follow-up. Women in the CBSM group had 77% reduced risk of breast cancer-related mortality and 56% risk reduction in breast cancer recurrence, although the hazard ratios for these two analyses did not reach significance (p = .063; p = .062, respectively). When examining the 10-year restricted follow-up range, results revealed that women in the CBSM group had a significant 85% reduced risk of all-cause mortality and a significant 76% reduced risk of breast cancer recurrence compared to controls, but no significant reductions in breast cancer-related mortality.

The findings are important given the controversial state of the literature regarding the influence of psychosocial interventions on disease outcomes (Spiegel et al., 1989; Goodwin et al., 2001; Spiegel et al., 2007; Andersen et al., 2008). While two seminal studies showed that a psychosocial intervention could improve survival in metastatic breast cancer patients (Spiegel et al., 1989) and patients with malignant melanoma (Fawzy et al., 1993), attempts to replicate these findings have not been successful (Boesen et al., 2007; Cunningham et al., 1998; Edelman, Lemon, Bell, & Kidman, 1999; Goodwin et al., 2001; Kissane et al., 2007; Spiegel et al., 2007). Spiegel et al (2007) did find a survival effect in a subsample of only women who had estrogen receptor (ER)-negative tumor types, but not in the overall sample. Fawzy, Canada, & Fawzy (2003) attempted to replicate the 5-6 year survival findings for patients with melanoma with a 10-year follow-up period. Results showed that the survival benefit was no longer significant at the 10-year follow-up, however, when controlling for other known prognostic risk factors, there was a protective effect of being in the intervention group (Fawzy et al., 2003).

Studies in other cancer populations have reported some noteworthy findings. A 10-year follow-up of an RCT for patients with gastrointestinal cancer found a significant difference in survival benefiting the psychotherapeutic support group compared to the usual care control (Küchler, Bestmann, Rappat, Henne-Bruns, & Wood-Dauphinee, 2007). However, serious methodological concerns have been pointed out regarding this study, including a failure to randomize adequately (participants were allowed to switch intervention groups upon request), and the fact that patients in the intervention group received twice as much chemotherapy treatment as those in the control (Kissane, 2009).

A 2-year follow-up of a home care intervention for post-surgical cancer patients (e.g., post-surgery for breast, colorectal, head/neck), administered by advanced practice nurses reported a survival advantage for those in the intervention group compared to the control group (McCorkle et al., 2000). However, when examining only breast cancer patients within this post-surgical sample, there was no significant finding for the effects of the home care intervention on survival.

Taking these studies into account, recent meta-analyses and systematic reviews have concluded that psychosocial interventions do not prolong survival in cancer patients (Chow, Tsao, & Harth, 2004), that there is insufficient evidence to state such claims (Edwards, Hulbert-Williams, & Neal, 2008), that the question is basically unresolved (Ross, Boesen, Dalton, Johansen, 2002), and that a definite conclusion is premature (Smedslund, & Ringdal, 2004). However, one recent Cochrane review reported that for women with metastatic breast cancer, psychological interventions seemed effective in improving survival at one-year post intervention, but were no longer effective at the longer term, 5-year follow-ups (Mustafa, Carson-Stevens, Gillespie, & Edwards, 2013). It is important to note that most reviews and meta-analyses examining the effects of psychosocial interventions on cancer survival are specific to a metastatic breast cancer sample. However, the current study sample was non-metastatic breast cancer patients, similar to that of Andersen et al (2008).

The study by Andersen et al (2008) provides the most similar comparison when evaluating the present findings in the context of previous research. In that study, women with early stage non-metastatic breast cancer (N=227) were randomized to either a psychologic intervention or a control group. The group-based psychologic intervention

was delivered over 4 months of weekly sessions and 8 monthly sessions (26 sessions total). The intervention aimed to reduce distress and improve QOL via stress management strategies including progressive muscle relaxation, problem solving, assertive communication, coping with treatment side effects, and maintaining adherence to treatment regimens (Andersen et al., 2008). At the 11-year median follow-up, researchers reported that women in the intervention group had a reduced risk of all-cause mortality (HR = 0.51), death from breast cancer (HR = 0.44), and breast cancer recurrence (HR = 0.55). The hazard ratios in the Andersen et al trial are adjusted for age, tumor classification, lymph node classification, hormone receptor status, histologic grade, histologic type, type of surgery, chemotherapy treatment, radiotherapy treatment, and variables that differed by group, specifically the baseline Karnofsky Performance Status, and The Profile of Mood States. The current study adjusted for some of the same covariates, including age, tumor size, hormone receptor status, chemotherapy, and radiation treatment. There are a few notable differences between the present study and that of Anderson et al (2008). First, their sample included only women with stage II through IIIB breast cancer, whereas the present study included women with stage 0-IIIB. In addition, while the psychologic intervention components that Anderson used do overlap to some extent with those of CBSM in the present study (i.e., progressive muscle relaxation, problem-solving, assertive communication), there are many intervention components that are different (i.e., improving dietary behaviors and adherence to medical treatment and follow-up). Furthermore, the present group-based CBSM intervention was delivered in weekly sessions for a total of consecutive 10 weeks, while the psychologic intervention in Anderson's study was delivered in 4 months of weekly sessions followed

by 8 monthly sessions. Despite these differences, the present study found similar results that contribute to the evidence showing favorable effects of psychosocial interventions on survival.

Long-term Effects on Psychosocial Outcomes

CBSM and QOL. Results of the second study aim showed that CBSM had long-term effects on psychosocial functioning for breast cancer survivors at the 8-15 year follow-up. Specifically, women in the CBSM group reported better overall QOL on the FACT-B. Women in the CBSM group also reported better physical well-being QOL than those in the control group when accounting for potential confounders, including age, education, income, race/ethnicity, pain, BMI, and baseline physical well-being scores on the FACT-B. Women in the CBSM group also reported greater emotional well-being QOL when controlling for age, education, income, race/ethnicity, pain, BMI, and baseline emotional well-being scores on the FACT-B.

The potential for CBSM to improve QOL was in line with expectations based on prior research and meta-analyses (Dirksen & Epstein, 2008). Psychosocial interventions based in cognitive-behavioral theory are most commonly used in clinical intervention research to improve QOL in cancer populations (Jassim, Whitford, & Grey, 2010; Moyer, Sohl, Knapp-Oliver, & Schneider, 2009). Meta-analyses of psychosocial interventions for breast cancer have found cognitive-behaviorally based therapy to be efficacious in improving QOL (Fors et al., 2011; Rhese & Pukrop, 2003, Tatrow & Montgomery, 2006). Previous research by our group found that women in the CBSM group show improved QOL up to 12-months after study randomization in women with non-metastatic breast cancer (Antoni et al., 2006a). The present finding builds on this finding in showing

that women who received the 10-week group-based CBSM intervention 2-10 weeks post-surgery appear to continue to benefit up to 15 years later. While many studies have reported on QOL following breast cancer treatment or soon thereafter, very few have examined QOL in breast cancer survivors this many years after treatment (Ganz et al., 2002; Gotay & Muraoka, 1998; Dorval et al., 1998). The longest follow-up to our knowledge was that of breast cancer survivors who had been disease free for 10 years (Mols, Vingerhoets, Coebergh, & van de Poll-Franse, 2009).

A systematic review of natural history studies with follow-ups of up to 5-8 years post-treatment have shown that breast cancer survivors often report good overall QOL, but score lower in the domains of physical and emotional/psychological well-being (Mols et al., 2005). Lower scores on physical QOL domains are attributed to ongoing pain, swelling, fatigue, and treatment-induced menopausal symptoms, while lower scores on emotional/psychological QOL domains are attributed to worries about the future and recurrence (Bloom, Petersen & Kang, 2007). A qualitative study which interviewed a multiethnic sample of African Americans, Asians, Latinas, and Caucasian breast cancer survivors reported that while overall health-related QOL was fairly good, all women reported moderate physical concerns and persistent concerns about recurrence, their children, and burdening their families (Tam Ashing-Giwa et al., 2004). A population-based multiethnic, multicenter, prospective study of survivors of stages 0-IIIa breast cancer reported lower physical function QOL than population norms up to 40.6 months post-diagnosis (Bowen et al., 2007). Having received systemic adjuvant treatment is associated with declined functioning in certain domains of QOL, such as physical well-being, 5-10 years post-diagnosis (Ganz et al., 2002). A recent systematic review revealed

that long-term survivors (i.e., > 5 years after initial treatment) between 5-23 years post-treatment reported lower physical, psychological, and overall QOL than healthy controls (Mols et al., 2005).

A study by Holzner and colleagues (2001) examined QOL on the FACT-B in breast cancer survivors at different follow-up times post-initial treatment (i.e., 1-2 years, 2-5 years, and >5 years). For women who were more than 5-years post-initial treatment (n = 29), the reported mean on the FACT-B physical well-being subscale was 24.3 (SD = 5.6), which is similar to the 8 – 15 year follow-up value of women in the present study who were randomized to the control group (M = 23.85). The reported FACT-B emotional well-being score in the Holzner et al. (2001) study was 18.0 (SD = 4.3), which is also similar to the reported mean of the control group in the present study (M = 20.49). In contrast, women in the CBSM intervention condition in the present study reported a physical well-being mean score of 26.85, and an emotional well-being score of 22.31 at 8 – 15 year follow-up. In summary, QOL scores in the control group at follow-up in the present study were similar to those reported in the Holzner et al (2001) study, and both the Holzer et al (2001) QOL mean scores and our control group mean scores were lower than those achieved by women in the CBSM intervention condition. This is further evidence that CBSM can provide a buffering effect to prevent deterioration in QOL, or help to maintain good QOL throughout survivorship.

CBSM and depressive symptoms. Women in the CBSM group reported less depressive symptoms than those in the control group at the 8-15 year follow-up on the CES-D when controlling for potential confounders, including age, education, income, race/ethnicity, pain, BMI, and baseline depressive symptoms on the HRSD. Women in

the CBSM group also reported less negative affect when controlling for age, education, income, race/ethnicity, pain, BMI, and baseline depressive symptoms on the HRSD. Previous research by our group has shown that women in the CBSM group showed reduced prevalence of moderate depression, less depressive symptoms on the CES-D, and negative affect during the first 12-months of the study (Antoni et al., 2001; Antoni et al., 2006a; Antoni et al., 2006c, Stagl et al., 2013). However, up until now the long-term benefits of CBSM on depressive symptoms were largely unknown.

A meta-analysis of cognitive-behavioral interventions concluded that CBT is efficacious for short-term effects on depression in adult cancer survivors, but more research is needed to investigate the long-term effects (Osborn, Demoncada, & Feuerstein, 2006). One study found that long-term breast cancer survivors reported higher prevalence of symptoms of mild to moderate depression compared to healthy controls, and that depression scores predicted lower QOL approximately 5-8 years post-treatment (Mols et al., 2005).

Depression definitely continues to be a concern during survivorship, although evidence suggests that prevalence of depression does decrease as women move farther in time from primary treatment. For instance, an observational study of breast cancer survivors reported that at diagnosis, the prevalence of depression was 33%, while it dropped to 15% at 5-years post-diagnosis (Burgess et al., 2005). Another study showed that 16% of a sample of 240 breast cancer survivors who were 6-13 years post-treatment was categorized as depressed. In addition, depression in this sample of breast cancer survivors was associated with poorer QOL (Reyes-Gibby et al., 2012). A study that compared depressive symptoms on the CES-D by cancer sites found that 22% of the

breast cancer survivor sample reported depressive symptoms. The follow-up time was at least 1 year or more post-treatment. This study reported that breast cancer survivors scored a mean of 10.5 (*SD* = 8.3) on the CES-D total, compared to healthy controls (*M* = 8.3, *SD* = 6.4) (Van Wilgen, Dijkstra, Stewart, Ranchor, & Roodenburg, 2006).

In the present study, women in the CBSM group scored a 5.01 on the CES-D, compared to the control group mean of 9.75. The control group mean of 9.75 is comparable to the mean CES-D score of the breast cancer survivors reported in the study by Van Wilgen et al (2006), while the CBSM group score of 5.01 is significantly lower than these survivors. On the negative affect/depressed affect subscale, breast cancer survivors in the Van Wilgen et al (2006) study reported a mean of 1.9 (*SD* = 2.6), compared to healthy controls (*M* = 0.9, *SD* = 1.7). Women in the CBSM group in the present study reported a mean negative affect score of 0.94, which is comparable to the healthy controls in the Van Wilgen analysis. The control group in the present study averaged 2.52, a score nearly identical to that of the breast cancer survivor sample in the Van Wilgen et al (2006) study. Ultimately, studies have shorter follow-up times when examining the effects of a psychosocial intervention on depression or depressive symptoms. The current study adds to this gap in the literature by suggesting that CBSM may have long-term benefits for depressive symptom reduction in breast cancer survivors at 8-15 year follow-up.

Long-term Effects of Psychosocial Interventions

As this is the first study to date examining the long term effects of CBSM at 8-15 years post-randomization, it is difficult to compare these findings with that of previous research. One study examined the long-term effects of two RCT's of Cognitive-

Behavioral Therapy (CBT) for generalized anxiety disorder 8-14 years after original treatment. Results showed that the CBT conditions reported lower severity of symptomatology in the long-term compared to the non-CBT conditions (Durham, Chambers, MacDonald, Power, & Major, 2003). Another study examined the effects of CBT for fatigued cancer survivors at a mean follow-up for 1.9 years with a 1-4 year range. The CBT was found to reduce functional impairment and fatigue in these survivors up to 2 years post-intervention (Gielissen, Verhagen, & Bleijenberg, 2007). A study by Helgeson and colleagues (2001) evaluated the long-term effects of an 8-week educational intervention that was previously shown to improve QOL 6 months post-intervention for women with early stage breast cancer. Researchers found that the women in the educational intervention group continued to show benefits up to 3-years post-intervention. Effects in the long-term follow-up were not as strong as those found in the 6-month follow-up (Helgeson, Cohen, Schulz, & Yasko, 2001).

Previous research by the our group showed that women who were randomized to the CBSM intervention showed significantly less depressive symptoms on the CES-D at the 5-year follow-up than women in the control group (Stagl et al., 2013). The study by Andersen et al. (2007) showed that reduced distress after a 4-month psychologic intervention for 227 women with early stage breast cancer mediated the intervention effects on health outcomes at 12-months post illness onset. However, Andersen et al (2007) did not report on psychological outcomes at this 12-month follow-up. A later follow-up study of this cohort showed that of women who experienced a breast cancer recurrence, those in both the intervention and control groups reported similar psychological distress. However, up to 12-months post-recurrence, women who had

received the psychologic intervention improved with regard to distress whereas women in the control group did not (Andersen et al., 2010). In general there is a lack of research examining the long-term effects of psychosocial interventions delivered during acute early phases of breast cancer treatment (Ganz et al., 2002). The present study with an extended follow-up period contributes to the literature by showing that a group-based CBSM intervention delivered during active adjuvant treatment has potential psychological benefits for breast cancer survivors up to 15 years post-study enrollment.

Mechanisms of Psychosocial Interventions

Tests of mediation showed that change in affect over the initial 12-month study period was not a mediator of intervention effects on clinical outcomes at the 10-year or 8-15 year follow-up. Furthermore, 12-month affect changes did not mediate the intervention effects on psychosocial outcomes of QOL and depressive symptoms at the 8-15 year follow-up. There is much to be done in the way of elucidating potential psychosocial mechanisms responsible for the clinical and psychological benefits seen here and in other studies (Andersen et al., 2008; Stanton, Luecken, MacKinnon, & Thompson, 2013).

Relaxation training components of CBSM aim to increase confidence in stress management skills, and have been shown to be effective in doing so (Antoni et al., 2006b; Phillips et al., 2012). It is possible that women who feel confident in their ability to engage in relaxation techniques continue to use relaxation as a coping modality post-treatment, in turn lowering distress. For instance, a study showed that women with increased confidence in stress management techniques prior to chemotherapy reported better mood and QOL later in treatment (Faul, Jim, Williams, Loftus, & Jacobsen, 2010).

Women often experience intrusive thoughts related to disease progression, recurrence, death, and disability that persist post-treatment (Herschbach et al., 2004; Tatrow & Montgomery, 2006). These cognitions contribute to ongoing emotional distress and are associated with greater depressive symptoms in breast cancer survivors (Cordova, Cunningham, Lauren, Carlson, & Andrykowski, 2001). Cognitive-behaviorally based aspects of the CBSM intervention address cancer-specific distress around fears of recurrence and disease progression by teaching women cognitive restructuring and adaptive coping. It is possible that women continue to use these skills after treatment cessation and through survivorship in order to cope with ongoing fears of recurrence and uncertainty of the future. Fewer cognitive intrusions, in turn, may lessen depressive symptoms. While maladaptive avoidance coping and appraisals of harm and loss are shown to contribute to depressive symptoms and QOL in breast cancer patient and survivors (Bigatti, Steiner, & Miller, 2012), women who received the CBSM intervention were taught adaptive coping techniques and re-appraisal. The timing of the intervention, close to diagnosis and post-surgery, may be key in buffering effects of stress. For instance, research shows that cancer-related traumatic stress symptoms at the time of diagnosis predict later QOL (Golden-Kruetz et al., 2005).

It is possible that the psychological improvements from the CBSM intervention mediated the effects on survival. Strong evidence exists for the association between depression and breast cancer survival (Hjerl et al., 2003; Kissane, 2009). Even depression in the first year of treatment is associated with shorter breast cancer survival (Giese-Davis et al., 2011). Studies have shown that women with early stage breast cancer who have higher levels of depression have an increased risk of death at a 5-year (Watson,

Haviland, Greer, Davidson, & Bliss, 1999) and 10-year follow-up (Watson, Homewood, Haviland, & Bliss, 2005). Depression is an established risk factor for noncompliance with medical treatment (Bower, 2008; Colleoni et al., 2000; DiMatteo, Lepper, Croghan, 2000). Treatment noncompliance with long-term regimes such as hormonal therapy, and noncompliance with follow-up visits, in turn, may explain poorer clinical outcomes for depressed breast cancer patients (Somerset et al., 2004; Giese-Davis et al., 2011; Hjerl et al., 2003).

Changes in immune and neuroendocrine function may partially explain the reduced survival and recurrence in the CBSM intervention group. Stress response pathways and bio-behavioral factors have been shown to alter metastatic processes and tumor biology (Antoni et al., 2006b; Lutgendorf et al., 2010). Flatter cortisol slopes are predictive of cancer-related mortality (Sephton et al., 2000). Previous research from the current study has shown that women in the CBSM group had lower T-cell production of Th1 vs. Th2 cytokines than the control group (Blomberg et al., 2009). In addition, women in the 10-week group-based CBSM intervention condition showed reduced serum cortisol (Phillips et al., 2008), an effect that was mediated by changes in perceived relaxation and CBT skills following the intervention (Phillips et al., 2011). Finally, women in the CBSM group displayed downregulation of pro-inflammatory and metastases-related genes and upregulation of type I interferon response genes compared to the control group (Antoni et al., 2012). Results from the Andersen et al (2008) survival study showed that the significant reduction in distress observed in the women who received the psychologic intervention predicted positive improvements in health at the 12-month assessment. Stress-mediated changes in immune, neuroendocrine, and leukocyte genomic expression

are possible pathways by which CBSM led to improved survival and recurrence outcomes in the present study.

Strengths and Limitations

Strengths. This study is the first randomized controlled trial that we know of to date examining the long-term effects of a CBSM intervention on clinical health and psychosocial outcomes in women with early stage breast cancer. Strengths of the study include the homogenous and adequately large sample of 240 women with non-metastatic breast cancer. The study employs a structured, manualized CBSM intervention (Antoni, 2003), which increases feasibility and ease for future replication. An intention-to-treat approach was employed in all statistical tests, including all participants in the analyses. Despite ethnic disparities in QOL (e.g., women of ethnic minority often experience poorer QOL), breast cancer intervention studies historically enroll predominantly white middle class women (Giedzinska, Meyerowitz, Ganz, & Rowland, 2004). Approximately one third (36.3%) of the current sample was of a racial or ethnic minority (i.e., Black, African American, Hispanic, Asian) thereby increasing the generalizability of the findings to women of various ethnic backgrounds. The window of time during which women were enrolled and received CBSM (i.e., 2-10 weeks post-surgery) is a unique period of time to intervene and teach stress management skills to enhance psychosocial adaptation. Learning stress management skills during this time specifically may set women up for better coping and adaptation as they move through cancer treatment, which may partially explain long term survival advantages seen in the CBSM intervention condition. During follow-up phone calls with study participants, women were consistently appreciative that this research team was interested in their physical and psychological well-being as a breast cancer survivor. Many

women noted that they had benefited greatly from the intervention materials and were grateful to have had the opportunity to participate in such a study. Noted limitations of RCT's evaluating the effectiveness of psychosocial interventions for breast cancer patients include small sample sizes, short follow-ups, or the lack of a non-intervention control group (Fors et al., 2011). The current study therefore contributes to the body of literature by overcoming these limitations, especially by involving longer follow-ups.

Limitations. As the study was conducted in a university-based setting, women in the present sample may be more highly motivated to participate in research than most women who may be seen at a community clinic or hospital. This should be noted when considering intervention effectiveness and feasibility in real-world settings. Women in the current study had been diagnosed with stage 0-IIIb breast cancer, while women with stage IV, advanced metastatic disease were excluded. This exclusionary criterion was established in order to maintain a homogenous sample of early stage breast cancer. Ductal Carcinoma In-Situ (DCIS), stage 0 cancers, are generally non-life threatening and women with DCIS have an overall favorable prognosis. Even so, 7% of women originally diagnosed with DCIS will experience a breast cancer recurrence within 10 years of their original diagnosis (Sue, Killelea, Horowitz, Lannin, & Chagpar, 2012). In addition, women with stage 0 DCIS report no less psychological distress when compared to women with later stage disease (Lauzier et al., 2010; Kennedy, Harcourt, & Rumsey, 2008). Given that a subset of women with DCIS will recur and evidence that women with DCIS experience similar psychological distress, we chose to conduct our analyses on the original full sample of 240 women, including those with stage 0 DCIS. This should be noted when interpreting the results, and future research could examine intervention effects on clinical outcomes in only women with invasive tumors.

All demographic and psychosocial measures were self-report, which may give way to women over- or under-estimating symptoms and psychosocial functioning. Medical and treatment information was verified by medical chart review, which increases the reliability of the biomedical confounder variables used in the analyses. Women in the current study had given consent to be re-contacted in the future and to have their health and medical progress followed over time. However, women had not been told that they would be re-contacted 8-15 years after study enrollment, as this was not a planned assessment time point in the original study. As a result, many women (N = 140) were lost to follow-up at the T6 psychosocial assessment. However, the fact that 100 women were reachable and agreeable is still notable, given that women were not aware they would be given the option to participate in another assessment time point. Given that women were not aware of this additional assessment time point, it is difficult to compare this participation rate to the retention rates in other studies, where regular follow-up visits were part of the study protocol. Recurrence data was available at the T6 follow-up for 197 women out of 240 participants (82.08%). This is slightly lower than the available recurrence data of the total sample (93.39%) in the study by Andersen et al (2008). However, women in this study were assessed every 6 months and were aware that they would be re-contacted at these biannual intervals. Long-term follow-up research should focus on maintaining relationships with women throughout follow-up periods in an effort to reduce attrition and maximize participation in follow-up assessment time points.

Another limitation is that in some cases it was difficult to obtain medical charts in order to obtain information about recurrence and verify treatment and prognostic tumor factors. Physician offices often destroy or discard medical charts after the woman has not returned for a visit for a certain number of years (variable upon office). It is not uncommon for women to

discontinue seeing their oncologist after treatment cessation, and maintain follow-up visits with their primary care physician. For those women who do continue to see their oncologist, it is not uncommon for them to discontinue routine follow-up visits after 10 years. Therefore, it was difficult to obtain charts for women who were 10 or more years past their original breast cancer diagnosis. Furthermore, some physician offices required updated medical releases, and would not accept original study consent from the years of 1998-2005 as authorization for release of medical information. Although every attempt was made to reach these women in order to obtain an updated medical release, this was not possible in certain cases if the woman was lost to follow-up. Most women who were reached however did provide us with an updated consent and were willing to release medical information to study personnel.

Critiques of the state of the evidence regarding whether psychotherapy can influence survival in cancer raise a number of methodological issues that should be considered when interpreting the results. Survival and recurrence were not primary endpoints in this study. Furthermore, effects were only found to be significant when adjusting for biomedical confounders known to be prognostic risk factors (Coyne, Stefanek, & Palmer, 2007).

Clinical Implications

The present study contributes unique findings showing that psychosocial services early on in the cancer trajectory may provide a buffering effect up to 15 years later. Distress is considered to be the 6th vital sign in cancer care, and experts suggest that psychological therapy should be part of the cancer treatment plan, alongside adjuvant medical treatments (Cunningham, 2000). Studies that have found reduced QOL in breast cancer survivors during long-term post-treatment survival highlight the need for ongoing psycho-oncological support (Holzner et al., 2001).

The CBSM intervention used in the present study is a manualized, structured intervention that can eventually be administered by oncology social workers. This enhances the feasibility and cost-effectiveness of implementing such a therapy in clinical oncology settings. In addition, the current and previous findings show that CBSM is efficacious when administered in a group setting, which contributes to the overall cost-effectiveness. Group therapy is no less effective than individual therapy (Carlson & Bultz, 2004).

Continued assessment of psychosocial functioning into long-term survivorship is highly relevant given that the majority of women diagnosed with breast cancer will survive and live for many years (Mols et al., 2005; Dorval et al., 1998). Women face different issues during survivorship phases than during active treatment. It is important to understand the psychosocial challenges produced by long-term and late onset effects in order to provide targeted follow-up care (Mehnert & Koch, 2008). Survivorship care plans are a hot topic as of late. Researchers are focusing on how to create clinically meaningful survivorship care plans that help women transition from treatment to post-treatment phases of cancer care. Many women note continued symptom burden, side effects, yet have much less contact with their health care providers after treatment cessation. Continuity of care is important for breast cancer survivors, as is psychosocial functioning and gaining a sense of new normalcy (Singh-Carlson, Wong, Martin, & Nguyen, 2013).

Future Research

Given that the current sample includes women with stage 0 breast cancer who have a more favorable prognostic outlook, future research could examine the effects of

CBSM for only women who have more advanced breast cancer (i.e., > than stage 0). In addition, recent work has suggested a relationship between depression and survival, such that women with breast cancer who report greater depressive symptoms show higher all-cause mortality hazards than their depression-free counterparts (Giese-Davis et al., 2011). Given that the current study assessed depression at baseline and subsequent study time points, future work could explore whether this depression-survival relationship is observed in the present sample, and whether it is moderated by receipt of CBSM. Future work could also examine potential physiological indicators of stress and biological markers of immune and inflammatory processes as mediators of intervention effects on clinical outcomes (Stanton et al., 2013). As much as possible, trials should plan follow-up assessments at the beginning of the study and outline these for study participants in order to minimize loss. Study coordinators could maintain contact with participants by sending postcards asking women to update their contact information every so often.

Criticism of studies examining whether psychological interventions can improve survival for cancer patients call for large-scale studies in which patients are screened in advanced for distress (Ross et al., 2002). It is possible that the inconclusive evidence is in part due to diluted effects when a full sample of both distressed and non-distressed patients are included in survival analyses. In addition, interventions should be standardized in order to feasibly replicate them and determine whether certain intervention components are driving the effects (Ross et al., 2002). Given evidence of stress-related biological changes following the CBSM intervention groups (Antoni et al., 2012; Blomberg et al., 2009; Phillips et al., 2008), questions of whether intervention-

related immune and neuroendocrine changes are mediating changes in survival should be addressed in future research (Thaker & Sood, 2008; Kissane, 2009).

There are many biomedical confounds to consider when examining the effects of a psychosocial intervention on clinical outcomes. Although study personnel attempted to gather information on as many medical and treatment characteristics as possible, future data collection in survival studies should attempt to collect information related to histological grade, whether the invasive breast carcinoma is of lobular or ductal origin, and adherence to hormonal therapy. Research shows that when estimating survival and recurrence rates, histological grade (morphological subdivisions describing the tumor growth pattern and degree of differentiation) is important to consider in conjunction with other prognostic tumor factors such as TNM (tumor, node, metastasis) staging and hormone receptor status (Rakha et al., 2010).

Evidence suggests that the incidence of regional lymph node metastases does not differ significantly between invasive ductal and invasive lobular breast carcinomas. However, there have been noted significant differences in incidence of metastases to the gastrointestinal system, gynecologic organs, peritoneum-retroperitoneum, with lobular carcinomas being more likely to metastasize to these regions (Borst & Ingold, 1993). More recent research shows that patients with lobular carcinomas have significantly worse survival (Korhonen et al., 2013).

Finally, while women who are ER or PR positive are prescribed anti-hormonal therapy for up to 5-years post-treatment (e.g., tamoxifen, arimidex), not all women adhere to this treatment regimen (Murphy, Bartholomew, Carpentier, Bluethmann, & Vernon, 2012). One study of 8,769 women with breast cancer who filled a prescription

for a hormonal therapy found that 31% of this sample discontinued treatment and 28% were non-adherent. Furthermore, non-adherence and discontinuation of hormonal therapy were significantly associated with increased risk of mortality (Hershman et al., 2010). While this data was not available in the current study, it would be important to account for hormonal therapy adherence in future studies examining outcomes such as breast cancer survival and recurrence.

Conclusion

Women with early stage breast cancers who receive Cognitive-Behavioral Stress Management 2-10 weeks post-surgery show significantly reduced risk of all-cause mortality compared to women in the 1-day group psychoeducational seminar control condition at an 11-year median follow-up. Risk of breast cancer-related mortality and breast cancer recurrence was marginally, but not significantly, reduced for women in the CBSM group. Women in the CBSM group also reported greater physical and emotional well-being and less depressive symptoms and negative affect at this 11-year median follow-up. This study contributes to the ongoing research regarding the physical and psychological benefits of psychosocial interventions, and has clinical implications for the use of these interventions in clinical oncology settings.

References

Allison, P. D. (2010). Survival analysis. In G.R. Hancock & R.O. Mueller (Eds.), *The reviewer's guide to quantitative methods in the social sciences* (pp. 413-425). New York, NY: Routledge.

Allred, D. C., Carlson, R. W., Berry, D. A., Burstein, H. J., Edge, S. B., Goldstein, L. J., ... & Wolff, A. C. (2009). NCCN Task Force Report: estrogen receptor and progesterone receptor testing in breast cancer by immunohistochemistry. *Journal of the National Comprehensive Cancer Network*, *7*(Suppl 6), S1-S21. PMID: 19755043

Anders, C. K., Hsu, D. S., Broadwater, G., Acharya, C. R., Foekens, J. A., Zhang, Y., ... & Blackwell, K. L. (2008). Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *Journal of Clinical Oncology*, *26*(20), 3324-3330. doi:10.1200/JCO.2007.14.2471

Andersen, B. L., Farrar, W. B., Golden-Kreutz, D., Emery, C. F., Glaser, R., Crespin, T., & Carson III, W. E. (2007). Distress reduction from a psychological intervention contributes to improved health for cancer patients. *Brain, Behavior, and Immunity*, *21*(7), 953-961. doi: 10.1016/j.bbi.2007.03.005

Andersen, B. L., Farrar, W. B., Golden-Kreutz, D., Kutz, L. A., MacCallum, R., Courtney, M. E., & Glaser, R. (1998). Stress and immune responses after surgical treatment for regional breast cancer. *Journal of the National Cancer Institute, 90*(1), 30-36. doi:10.1093/jnci/90.1.30

Andersen, B. L., Thornton, L. M., Shapiro, C. L., Farrar, W. B., Mundy, B. L., Yang, H., & Carson, 3.,William E. (2010). Biobehavioral, immune, and health benefits following recurrence for psychological intervention participants. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research, 16*(12), 3270-3278. doi:10.1158/1078-0432.CCR-10-0278

Andersen, B. L., Yang, H., Farrar, W. B., Golden-Kreutz, D. M., Emery, C. F., Thornton, L. M., . . . Carson, 3.,William E. (2008). Psychologic intervention improves survival for breast cancer patients: A randomized clinical trial. *Cancer, 113*(12), 3450-3458. doi:10.1002/cncr.23969

Antoni, M. H. (2003a). Psychoneuroendocrinology and psychoneuroimmunology of cancer: Plausible mechanisms worth pursuing? *Brain, Behavior, and Immunity, 17*(S), 84-91.

Antoni, M. H. (2003b). Stress management for women with breast cancer. In M. H. Antoni (Ed.), *Stress management intervention for women with breast cancer.* (pp. 7-50). Washington, DC US: American Psychological Association. doi:10.1037/10488-001

Antoni, M. H. (2013). Psychosocial intervention effects on adaptation, disease course and biobehavioral processes in cancer. *Brain, Behavior, and Immunity, 30 Suppl*, S88. doi:10.1016/j.bbi.2012.05.009

Antoni, M. H., Lechner, S. C., Kazi, A., Wimberly, S. R., Sifre, T., Urcuyo, K. R., . . . Carver, C. S. (2006a). How stress management improves quality of life after treatment for breast cancer. *Journal of Consulting and Clinical Psychology, 74*(6), 1143-1152. doi:10.1037/0022-006X.74.6.1143

Antoni, M. H., Lechner, S., Diaz, A., Vargas, S., Holley, H., Phillips, K., . . . Blomberg, B. (2009). Cognitive behavioral stress management effects on psychosocial and physiological adaptation in women undergoing treatment for breast cancer. *Brain Behavior and Immunity, 23*(5), 580-591. doi:10.1016/j.bbi.2008.09.005

Antoni, M. H., & Lutgendorf, S. (2007). Psychosocial factors and disease progression in cancer. *Current Directions in Psychological Science*, *16*(1), 42-46.

Antoni, M. H., Lutgendorf, S. K., Blomberg, B., Carver, C. S., Lechner, S., Diaz, A., . . . Cole, S. W. (2012). Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. *Biological Psychiatry, 71*(4), 366-372. doi:10.1016/j.biopsych.2011.10.007

Antoni, M. H., Lutgendorf, S. K., Cole, S. W., Dhabhar, F. S., Sephton, S. E., McDonald, P. G., . . . Sood, A. K. (2006b). The influence of bio-behavioural factors on tumour biology: Pathways and mechanisms. *Nature Reviews Cancer, 6*(3), 240-248.

Antoni, M. H., Wimberly, S. R., Lechner, S. C., Kazi, A., Sifre, T., Urcuyo, K. R., . . . Carver, C. S. (2006c). Reduction of cancer-specific thought intrusions and anxiety symptoms with a stress management intervention among women undergoing treatment for breast cancer. *The American Journal of Psychiatry, 163*(10), 1791-1797. doi:10.1176/appi.ajp.163.10.1791

Ashing-Giwa, K. T., Padilla, G., Tejero, J., Kraemer, J., Wright, K., Coscarelli, A., ... & Hills, D. (2004). Understanding the breast cancer experience of women: a qualitative study of African American, Asian American, Latina and Caucasian cancer survivors. *Psycho-Oncology*, *13*(6), 408-428. doi: 10.1002/pon.750

Babyak, M. A. (2004). What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosomatic Medicine*, *66*(3), 411-421. doi: 10.1097/01.psy.0000127692.23278.a9

Badger, T. A., Braden, C. J., Mishel, M. H., & Longman, A. (2004). Depression burden, psychological adjustment, and quality of life in women with breast cancer: Patterns over time. *Research in Nursing & Health, 27*(1), 19-28. doi:10.1002/nur.20002

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51*(6), 1173-1182. doi:10.1037/0022-3514.51.6.1173

Ben-Eliyahu, S., Page, G. G., Yirmiya, R., & Shakhar, G. (1999). Evidence that stress and surgical interventions promote tumor development by suppressing natural killer cell activity. *International Journal of Cancer, 80*(6), 880-888. doi:10.1002/(SICI)1097-0215(19990315)80:6<880::AID-IJC14>3.0.CO;2-Y

Ben-Eliyahu, S., Yirmiya, R., Liebeskind, J. C., Taylor, A. N., & Gale, R. P. (1991). Stress increases metastatic spread of a mammary tumor in rats: Evidence for mediation by the immune system. *Brain, Behavior, and Immunity, 5*(2), 193-205. doi:10.1016/0889-1591(91)90016-4

Berry, D. A., Feuer, E. J., Cronin, K. A., Plevritis, S. K., Fryback, D. G., Clarke, L., . . . Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators. (2005). Effect of screening and adjuvant therapy on mortality from breast cancer. *The New England Journal of Medicine, 353*(17), 1784-1792. doi:10.1056/NEJMoa050518

Berry, D. A., Inoue, L., Shen, Y., Venier, J., Cohen, D., Bondy, M., . . . Munsell, M. F. (2006). Modeling the impact of treatment and screening on U.S. breast cancer mortality: A bayesian approach. *Journal of the National Cancer Institute.Monographs,* (36), 30.

Bewick, V., Cheek, L., & Ball, J. (2004). Statistics review 12: Survival analysis. *Critical Care London*, *8*, 389-394.s

Bigatti, S. M., Steiner, J. L., & Miller, K. D. (2012). Cognitive appraisals, coping and depressive symptoms in breast cancer patients. *Stress and Health*, *28*(5), 355-361. doi: 10.1002/smi.2444

Blomberg, B. B., Alvarez, J. P., Diaz, A., Romero, M. G., Lechner, S. C., Carver, C. S., . . . Antoni, M. H. (2009). Psychosocial adaptation and cellular immunity in breast cancer patients in the weeks after surgery: An exploratory study. *Journal of Psychosomatic Research, 67*(5), 369-376. doi:10.1016/j.jpsychores.2009.05.016

Bloom, J. R., Petersen, D. M., & Kang, S. H. (2007). Multi-dimensional quality of life among long-term (5+ years) adult cancer survivors. *Psycho-Oncology*,*16*(8), 691-706. doi: 10.1002/pon.1208

Boesen, E. H., Boesen, S. H., Frederiksen, K., Ross, L., Dahlstrøm, K., Schmidt, G., ... & Johansen, C. (2007). Survival after a psychoeducational intervention for patients with cutaneous malignant melanoma: a replication study. *Journal of Clinical Oncology*, *25*(36), 5698-5703. doi: 10.1200/JCO.2007.10.8894

Borst, M. J., & Ingold, J. A. (1993). Metastatic patterns of invasive lobular versus invasive ductal carcinoma of the breast. *Surgery*, *114*(4), 637. PMID: 8211676.

Bowen, D. J., Alfano, C. M., McGregor, B. A., Kuniyuki, A., Bernstein, L., Meeske, K., ... & Barbash, R. B. (2007). Possible socioeconomic and ethnic disparities in quality of life in a cohort of breast cancer survivors. *Breast Cancer Research and Treatment*, *106*(1), 85-95. doi: 10.1007/s10549-006-9479-2

Bower, J. E. (2008). Behavioral symptoms in patients with breast cancer and survivors. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 26*(5), 768-777. doi:10.1200/JCO.2007.14.3248

Brady, M. J., Cella, D. F., Mo, F., Bonomi, A. E., Tulsky, D. S., Lloyd, S. R., . . . Shiomoto, G. (1997). Reliability and validity of the functional assessment of cancer therapy-breast quality-of-life instrument. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 15*(3), 974-986.

Bunt, S. K., Yang, L., Sinha, P., Clements, V. K., Leips, J., & Ostrand-Rosenberg, S. (2007). Reduced inflammation in the tumor microenvironment delays the accumulation of myeloid-derived suppressor cells and limits tumor progression. *Cancer Research, 67*(20), 10019-10026. doi:10.1158/0008-5472.CAN-07-2354

Burgess, C., Cornelius, V., Love, S., Graham, J., Richards, M., & Ramirez, A. (2005). Depression and anxiety in women with early breast cancer: Five year observational cohort study. *BMJ (Clinical Research Ed.), 330*(7493), 702-705. doi:10.1136/bmj.38343.670868.D3

Carlson, L. E., & Bultz, B. D. (2004). Efficacy and medical cost offset of psychosocial interventions in cancer care: making the case for economic analyses. *Psycho-Oncology*, *13*(12), 837-849. doi: 10.1002/pon.832

Carlson, R. W., Allred, D. C., Anderson, B. O., Burstein, H. J., Carter, W. B., Edge, S. B., ... & Wolff, A. C. (2009). Breast cancer. *Journal of the National Comprehensive Cancer Network*, *7*(2), 122-192.

Carlson, R. W., Moench, S. J., Hammond, M. E. H., Perez, E. A., Burstein, H. J., Allred, D. C., ... & Winer, E. P. (2006). HER2 testing in breast cancer: NCCN Task Force report and recommendations. *Journal of the National Comprehensive Cancer Network*, *4*(3), S1-S22. PMID: 16813731

Carver, C. S., & Antoni, M. H. (2004). Finding benefit in breast cancer during the year after diagnosis predicts better adjustment 5 to 8 years after diagnosis. *Health Psychology, 23*(6), 595-598. doi: 10.1037/0278-6133.23.6.595

Carver, C. S., Smith, R. G., Antoni, M. H., Petronis, V. M., Weiss, S., & Derhagopian, R. P. (2005). Optimistic personality and psychosocial well-being during treatment predict psychosocial well-being among long-term survivors of breast cancer. *Health Psychology, 24*(5), 508-516. doi:10.1037/0278-6133.24.5.508

Casso, D., Buist, D. S. M., & Taplin, S. (2004). Quality of life of 5-10 year breast cancer survivors diagnosed between age 40 and 49. *Health and Quality of Life Outcomes, 2*(1), 25-25. doi:10.1186/1477-7525-2-25

Cella, D. F., & Cherin, E. A. (1988). Quality of life during and after cancer treatment. *Comprehensive Therapy, 14*(5), 69-75. PMID: 3292140

Cella, D. F., & Tulsky, D. S. (1990). Measuring quality of life today: Methodological aspects. *Oncology, 4*(5), 29-38. PMID: 2143408

Chia, S., Bryce, C., & Gelmon, K. (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Commentary. *Lancet*, *365*(9472), 1687-1717. doi: 10.1016/S0140-6736(05)66544-0

Chida, Y., Hamer, M., Wardle, J., & Steptoe, A. (2008). Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nature Reviews Clinical Oncology, 5*(8), 466-475. doi:10.1038/ncponc1134

Chow, E., Tsao, M. N., & Harth, T. (2004). Does psychosocial intervention improve survival in cancer? A meta-analysis. *Palliative Medicine*, *18*(1), 25-31. doi: 10.1191/0269216304pm842oa

Cimprich, B., Ronis, D. L., & Martinez-Ramos, G. (2002). Age at diagnosis and quality of life in breast cancer survivors. *Cancer Practice*, *10*(2), 85-93. doi: 10.1046/j.1523-5394.2002.102006.x

Clark, T. G., Bradburn, M. J., Love, S. B., & Altman, D. G. (2003). Survival analysis part IV: Further concepts and methods in survival analysis. *British Journal of Cancer, 89*(5), 781-786. doi:10.1038/sj.bjc.6601117

Clarke, M., Collins, R., Darby, S., Davies, C., Elphinstone, P., Evans, E., ... & Tennvall-Nittby, L. (2005). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, *366*(9503), 2087-2106. doi: 10.1016/S0140-6736(05)67887-7

Cleeland, C. S., Bennett, G. J., Dantzer, R., Dougherty, P. M., Dunn, A. J., Meyers, C. A., . . . Lee, B. (2003). Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer, 97*(11), 2919-2925. doi: 10.1002/cncr.11382

Cohen, L., Cole, S. W., Sood, A. K., Prinsloo, S., Kirschbaum, C., Arevalo, J. M., ... & Pisters, L. (2012). Depressive symptoms and cortisol rhythmicity predict survival in patients with renal cell carcinoma: role of inflammatory signaling. *PloS one*, *7*(8), e42324. doi: 10.1371/journal.pone.0042324

Cole, S. W. (2009). Social regulation of human gene expression. *Current Directions in Psychological Science, 18*(3), 132. doi:10.1111/j.1467-8721.2009.01623.x

Cole, S. W., Hawkley, L. C., Arevalo, J. M., Sung, C. Y., Rose, R. M., & Cacioppo, J. T. (2007). Social regulation of gene expression in human leukocytes. *Genome Biol*, *8*(9), R189.

Colleoni, M., Mandala, M., Peruzzotti, G., Robertson, C., Bredart, A., & Goldhirsch, A. (2000). Depression and degree of acceptance of adjuvant cytotoxic drugs. *Lancet, 356*(9238), 1326-1327. doi:10.1016/S0140-6736(00)02821-X

Cordova, M. J., Cunningham, L. L., Carlson, C. R., & Andrykowski, M. A. (2001). Posttraumatic growth following breast cancer: a controlled comparison study. *Health Psychology*, *20*(3), 176. doi: 10.1037/0278-6133.20.3.176

Costanzo, E. S., Lutgendorf, S. K., Mattes, M. L., Trehan, S., Robinson, C. B., Tewfik, F., & Roman, S. L. (2007). Adjusting to life after treatment: distress and quality of life following treatment for breast cancer. *British Journal of Cancer*, *97*(12), 1625-1631. doi:10.1038/sj.bjc.6604091

Cox, D. R. (1972). Regression models and life-tables. *Journal of the Royal Statistical Society.Series B (Methodological), 34*(2), 187-220.

Coyne, J. C., Stefanek, M., & Palmer, S. C. (2007). Psychotherapy and survival in cancer: The conflict between hope and evidence. *Psychological Bulletin, 133*(3), 367-394. doi:10.1037/0033-2909.133.3.367

Creed, F., & Dickens, C. (2007). Depression in the medically ill. In A. Steptoe (Ed.), (pp. 3-18). New York, NY US: Cambridge University Press.

Cunningham, A. J. (2000). Adjuvant psychological therapy for cancer patients: putting it on the same footing as adjunctive medical therapies. *Psycho-Oncology*, *9*(5), 367-371. doi: 10.1002/1099-1611(200009/10)

Cunningham, A. J., Edmonds, C. V. I., Jenkins, G. P., Pollack, H., Lockwood, G. A., & Warr, D. (1998). A randomized controlled trial of the effects of group psychological therapy on survival in women with metastatic breast cancer. *Psycho-Oncology*, *7*(6), 508-517. doi: 10.1002/(SICI)1099-1611(199811/12)7:6<508::AID-PON376>3.0.CO;2-7

Derogatis, L.R. & Rutigliano, P.J. (1996). Derogatis affect balance scale (DABS). In B. Spilker (Ed.) Quality of Life and Pharmacoeconomics In Clinical Trials, 2nd Ed. Philadelphia, PA: Lippincott-Raven.

DeSantis, C., Siegel, R., Bandi, P., & Jemal, A. (2011). Breast cancer statistics, 2011. *CA: A Cancer Journal for Clinicians, 61*(6), 409-418. doi:10.3322/caac.20134

Deshields, T., Tibbs, T., Fan, M., & Taylor, M. (2006). Differences in patterns of depression after treatment for breast cancer. *Psycho−oncology, 15*(5), 398-406. doi:10.1002/pon.962

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine*, *160*(14), 2101-2107. doi:10.1001/archinte.160.14.2101.

Dirksen, S. R., & Epstein, D. R. (2008). Efficacy of an insomnia intervention on fatigue, mood and quality of life in breast cancer survivors. *Journal of Advanced Nursing*, *61*(6), 664-675. doi: 10.1111/j.1365-2648.2007.04560.x

Dorval, M., Maunsell, E., Deschênes, L., Brisson, J., & Mâsse, B. (1998). Long-term quality of life after breast cancer: Comparison of 8-year survivors with population controls. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 16*(2), 487.

Duijts, S. F. A., Zeegers, M. P. A., & Borne, B. V. (2003). The association between stressful life events and breast cancer risk: A meta-analysis. *International Journal of Cancer. 107*(6), 1023-1029. doi:10.1002/ijc.11504

Durham, R.C, Chamber, J.A., MacDonald, R.R., Power, K.G., Major, K. (2003). Does cognitive- behavioural therapy influence the long-term outcome of generalized anxiety disorder? An 8-14 year follow-up of two clinical trials. *Psychological Medicine, 33*, 499-509. doi: 10.1017/S0033291702007079

Edelman, S., Lemon, J., Bell, D. R., & Kidman, A. D. (1999). Effects of group CBT on the survival time of patients with metastatic breast cancer. *Psycho‐Oncology*, *8*(6), 474-481. doi: 10.1002/(SICI)1099-1611(199911/12)8:6<474::AID-PON427>3.0.CO;2-A

Edwards, A. G., Hulbert-Williams, N., & Neal, R. D. (2008). Psychological interventions for women with metastatic breast cancer. *Cochrane Database Systematic Review*, *3*. doi: 10.1002/14651858.CD004253.pub3

Faul, L. A., Jim, H. S., Williams, C., Loftus, L., & Jacobsen, P. B. (2010). Relationship of stress management skill to psychological distress and quality of life in adults with cancer. *Psycho-Oncology*, *19*(1), 102-109. doi: 10.1002/pon.1547

Fawzy, F. I., Canada, A.L., Fawzy, N. W. (2003). Malignant melanoma: effects of a brief, structured psychiatric intervention on survival and recurrence at 10-year follow-up. *Archives of General Psychiatry*, *60*(1), 100-103. doi:10.1001/archpsyc.60.1.100.

Fawzy, F. I., Fawzy, N. W., Hyun, C. S., Elashoff, R., Guthrie, D., Fahey, J. L., & Morton, D. L. (1993). Malignant melanoma: effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. *Archives of General Psychiatry*, *50*(9), 681. doi:10.1001/archpsyc.1993.01820210015002

Fidler, I. J. (2003). Timeline: The pathogenesis of cancer metastasis: The 'seed and soil' hypothesis revisited. *Nature Reviews Cancer, 3*(6), 453-458. doi:10.1038/nrc1098

Flom, P. L., & Cassell, D. L. (2007). Stopping stepwise: Why stepwise and similar selection methods are bad, and what you should use. In *NorthEast SAS Users Group Inc 20th Annual Conference: 11-14th November 2007; Baltimore, Maryland*.

Fors, E. A., Bertheussen, G. F., Thune, I., Juvet, L. K., Elvsaas, I. K. Ø., Oldervoll, L., . . . Leivseth, G. (2011). Psychosocial interventions as part of breast cancer rehabilitation programs? Results from a systematic review. *Psycho-Oncology*, *20*(9), 909-918. doi:10.1002/pon.1844

Friedman, L. C., Baer, P. E., Nelson, D. V., Lane, M., Smith, F. E., & Dworkin, R. J. (1988). Women with breast cancer: Perception of family functioning and adjustment to illness. *Psychosomatic Medicine, 50*(5), 529.

Galea, M. H., Blamey, R. W., Elston, C. E., & Ellis, I. O. (1992). The Nottingham Prognostic Index in primary breast cancer. *Breast Cancer Research and Treatment*, *22*(3), 207-219. doi: 10.1007/BF01840834

Ganz, P. A., Rowland, J. H., Desmond, K., Meyerowitz, B. E., & Wyatt, G. E. (1998). Life after breast cancer: Understanding women's health-related quality of life and sexual functioning. *Journal of Clinical Oncology, 16*(2), 501.

Ganz, P. A., Desmond, K. A., Leedham, B., Rowland, J. H., Meyerowitz, B. E., & Belin, T. R. (2002). Quality of life in long-term, disease-free survivors of breast cancer: A follow-up study. *Journal of the National Cancer Institute, 94*(1), 39-49. doi:10.1093/jnci/94.1.39

Giedzinska, A. S., Meyerowitz, B. E., Ganz, P. A., & Rowland, J. H. (2004). Health-related quality of life in a multiethnic sample of breast cancer survivors. *Annals of Behavioral Medicine*, *28*(1), 39-51. doi:10.1207/s15324796abm2801_6

Gielissen, M. F. M., Verhagen, C. A. H. H. V. M., & Bleijenberg, G. (2007). Cognitive behaviour therapy for fatigued cancer survivors: long-term follow-up. *British Journal of Cancer*, *97*(5), 612-618. doi:10.1038/sj.bjc.6603899

Giese-Davis, J., Collie, K., Rancourt, K. M. S., Neri, E., Kraemer, H. C., & Spiegel, D. (2011). Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: A secondary analysis. *Journal of Clinical Oncology, 29*(4), 413-420. doi:10.1200/JCO.2010.28.4455

Goel, M. K., Khanna, P., & Kishore, J. (2010). Understanding survival analysis: Kaplan-meier estimate. *International Journal of Ayurveda Research, 1*(4), 274-278. doi:10.4103/0974-7788.76794

Golden-Kreutz, D. M., Thornton, L. M., Wells-Di Gregorio, S., Frierson, G. M., Jim, H. S., Carpenter, K. M., . . . Andersen, B. L. (2005). Traumatic stress, perceived global stress, and life events: Prospectively predicting quality of life in breast cancer patients. *Health Psychology*, *24*(3), 288. doi:10.1037/0278-6133.24.3.288

Goodwin, J. S., Hunt, W. C., Key, C. R., & Samet, J. M. (1987). The effect of marital status on stage, treatment, and survival of cancer patients. *JAMA: The Journal of the American Medical Association, 258*(21), 3125-3130. doi:10.1001/jama.1987.03400210067027

Goodwin, P. J., Navarro, M., Speca, M., Hunter, J., Leszcz, M., Ennis, M., . . . Chochinov, H. M. (2001). The effect of group psychosocial support on survival in metastatic breast cancer. *The New England Journal of Medicine, 345*(24), 1719-1726. doi:10.1056/NEJMoa011871

Gotay, C. C., & Muraoka, M. Y. (1998). Quality of life in long-term survivors of adult-onset cancers. *Journal of the National Cancer Institute*, *90*(9), 656-667.

Grabsch, B., Clarke, D. M., Love, A., McKenzie, D. P., Snyder, R. D., Bloch, S., . . . Kissane, D. W. (2006). Psychological morbidity and quality of life in women with advanced breast cancer: A cross-sectional survey. *Palliative & Supportive Care, 4*(1), 47-56.

Greenfeld, K., Avraham, R., Benish, M., Goldfarb, Y., Rosenne, E., Shapira, Y., . . . Ben-Eliyahu, S. (2007). Immune suppression while awaiting surgery and following it: Dissociations between plasma cytokine levels, their induced production, and NK cell cytotoxicity. *Brain Behavior and Immunity, 21*(4), 503-513. doi:10.1016/j.bbi.2006.12.006

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry, 23,* 56-62.

Han, W., Kim, S. W., Park, I. A., Kang, D., Kim, S. W., Youn, Y. K., ... & Noh, D. Y. (2004). Young age: an independent risk factor for disease-free survival in women with operable breast cancer. *BMC cancer*, *4*(1), 82. doi:10.1186/1471-2407-4-82

Hann, D., Winter, K., & Jacobsen, P. (1999). Measurement of depressive symptoms in cancer patients: Evaluation of the center for epidemiological studies depression scale (CES-D). *Journal of Psychosomatic Research, 46*(5), 437-443. doi:10.1016/S0022-3999(99)00004-5

Harrell, F. E. (2001). *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*. New York, NY: Springer.

Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical mediation analysis in the new millennium. *Communication Monographs, 76*(4), 408-420. doi:10.1080/03637750903310360

Helgeson, V. S., Cohen, S., Schulz, R., & Yasko, J. (2001). Long-term effects of educational and peer discussion group interventions on adjustment to breast cancer. *Health Psychology*, *20*(5), 387-392. doi: 10.1037/0278-6133.20.5.387

Herschbach, P., Keller, M., Knight, L., Brandl, T., Huber, B., Henrich, G., & Marten-Mittag, B. (2004). Psychological problems of cancer patients: A cancer distress screening with a cancer-specific questionnaire. *British Journal of Cancer*, *91*(3), 504-511. doi:10.1038/sj.bjc.6601986

Hershman, D. L., Kushi, L. H., Shao, T., Buono, D., Kershenbaum, A., Tsai, W. Y., ... & Neugut, A. I. (2010). Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *Journal of Clinical Oncology*, *28*(27), 4120-4128. doi:10.1007/s10549-010-1132-4

Hewitt, M. E., Herdman, R., Holland, J. C., Institute of Medicine (U.S.), National Cancer Policy Board (U.S.), & National Research Council (U.S.). (2004). *Meeting psychosocial needs of women with breast cancer*. Washington, D.C: National Academies Press.

Holzner, B., Kemmler, G., Kopp, M., Moschen, R., Rd Schweigkofler, H., Du Nser, M., ... & Sperner-Unterweger, B. (2001). Quality of life in breast cancer patients—not enough attention for long-term survivors? *Psychosomatics*, *42*(2), 117-123. doi:10.1176/appi.psy.42.2.117

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic medicine*, *71*(2), 171-186.

Hjerl, K., Andersen, E. W., Keiding, N., Mouridsen, H. T., Mortensen, P. B., & Jorgensen, T. (2003). Depression as a prognostic factor for breast cancer mortality. *Psychosomatics*, *44*(1), 24-30. Doi: 10.1176/appi.psy.44.1.24

Irwin, M. (2002). Psychoneuroimmunology of depression: Clinical implications. *Brain, Behavior, and Immunity, 16*(1), 1-1. doi:10.1006/brbi.2001.0654

Jassim, G. A., Whitford, D. L., & Grey, I. M. (2010). Psychological interventions for women with non-metastatic breast cancer. *The Cochrane Library*. doi:10.1002/14651858.CD008729

Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. *CA: A Cancer Journal for Clinicians, 61*(2), 69-90. doi:10.3322/caac.20107

Kalager, M., Haldorsen, T., Bretthauer, M., Hoff, G., Thoresen, S. O., & Adami, H. (2009). Improved breast cancer survival following introduction of an organized mammography screening program among both screened and unscreened women: A population-based cohort study. *Breast Cancer Research, 11*(4), R44.

Kennedy, F., Harcourt, D., & Rumsey, N. (2008). The challenge of being diagnosed and treated for ductal carcinoma in situ (DCIS). *European Journal of Oncology Nursing*, *12*(2), 103-111. doi: 10.1016/j.ejon.2007.09.007

Kennedy, S., Kiecolt-Glaser, J., & Glaser, R. (1988). Immunological consequences of acute and chronic stressors: Mediating role of interpersonal relationships. *The British Journal of Medical Psychology, 61 (Pt 1)*, 77-85.

Kiecolt-Glaser, J. K., Fisher, L. D., Ogrocki, P., Stout, J. C., Speicher, C. E., & Glaser, R. (1987). Marital quality, marital disruption, and immune function. *Psychosomatic Medicine, 49*(1), 13.

Kissane, D. (2009). Beyond the psychotherapy and survival debate: the challenge of social disparity, depression and treatment adherence in psychosocial cancer care. *Psycho‐Oncology*, *18*(1), 1-5. DOI: 10.1002/pon.1493

Kissane D.W, Grabsch B, Love A, Clarke D.M, Bloch S, & Smith G.C. (2004). Psychiatric disorder in women with early stage and advanced breast cancer: A comparative analysis. *Australian and New Zealand Journal of Psychiatry, 38*(5), 320-320. doi:10.1111/j.1440-1614.2004.01358.x

Kissane, D. W., Grabsch, B., Clarke, D. M., Smith, G. C., Love, A. W., Bloch, S., . . . Li, Y. (2007). Supportive−expressive group therapy for women with metastatic breast cancer: Survival and psychosocial outcome from a randomized controlled trial. *Psycho−oncology, 16*(4), 277-286. doi:10.1002/pon.1185

Kleinbaum, D. G., & Klein, M. (2012). *Survival analysis*. Springer.

Knight, R. G., Williams, S., McGee, R., & Olaman, S. (1997). Psychometric properties of the centre for epidemiologic studies depression scale (CES-D) in a sample of women in middle life. *Behaviour Research and Therapy, 35*(4), 373-380. doi:10.1016/S0005-7967(96)00107-6

Korhonen, T., Kuukasjärvi, T., Huhtala, H., Alarmo, E. L., Holli, K., Kallioniemi, A., & Pylkkänen, L. (2013). The impact of lobular and ductal breast cancer histology on the metastatic behavior and long term survival of breast cancer patients. *The Breast*, *22*(6), 1119-1124. doi: 10.1016/j.breast.2013.06.001

Kreitler, S., Chaitchik, S., Rapoport, Y., & Algor, R. (1995). Psychosocial effects of level of information and severity of disease on head-and-neck cancer patients. *Journal of Cancer Education, 10*(3), 144-154.

Küchler, T., Bestmann, B., Rappat, S., Henne-Bruns, D., & Wood-Dauphinee, S. (2007). Impact of psychotherapeutic support for patients with gastrointestinal cancer undergoing surgery: 10-year survival results of a randomized trial. *Journal of Clinical Oncology*, *25*(19), 2702-2708. doi: 10.1200/JCO.2006.08.2883

Lauzier, S., Maunsell, E., Levesque, P., Mondor, M., Robert, J., Robidoux, A., & Provencher, L. (2010). Psychological distress and physical health in the year after diagnosis of DCIS or invasive breast cancer. *Breast cancer research and treatment*, *120*(3), 685-691. doi: 10.1007/s10549-009-0477-z

Levine, A., S., & Balk, J., L. (2012). Pilot study of yoga for breast cancer survivors with poor quality of life. *Complementary Therapies in Clinical Practice, 18*(4), 241-245. doi:10.1016/j.ctcp.2012.06.007

Lutgendorf, S. K., Sood, A. K., & Antoni, M. H. (2010). Host factors and cancer progression: Biobehavioral signaling pathways and interventions. *Journal of Clinical Oncology, 28*(26), 4094-4099. doi:10.1200/JCO.2009.26.9357

Lutgendorf, S. K., Sood, A. K., Cole, S. W., DeGeest, K., Sung, C. Y., Arevalo, J. M., . . . Farley, D. M. (2009). Depression, social support, and beta-adrenergic transcription control in human ovarian cancer. *Brain Behavior and Immunity, 23*(2), 176-183. doi:10.1016/j.bbi.2008.04.155

MacKinnon, D. P., Lockwood, C. M., & Williams, J. (2004). Confidence limits for the indirect effect: Distribution of the product and resampling methods. *Multivariate Behavioral Research, 39*(1), 99-128. doi:10.1207/s15327906mbr3901_4

Mandelblatt, J. S., Luta, G., Kwan, M. L., Makgoeng, S. B., Ergas, I. J., Roh, J. M., . . . Kushi, L. H. (2011). Associations of physical activity with quality of life and functional ability in breast cancer patients during active adjuvant treatment: The pathways study. *Breast Cancer Research and Treatment, 129*(2), 521-529. doi:10.1007/s10549-011-1483-5

McCorkle, R., Strumpf, N. E., Nuamah, I. F., Adler, D. C., Cooley, M. E., Jepson, C., ... & Torosian, M. (2000). A specialized home care intervention improves survival among older post-surgical cancer patients. *Journal of the American Geriatrics Society*, *48*(12), 1707. PMID:11129765

McDaniel, J. S., Musselman, D. L., Porter, M. R., & Reed, D. A. (1995). Depression in patients with cancer: Diagnosis, biology, and treatment. *Archives of General Psychiatry, 52*(2), 89-99. doi:10.1001/archpsyc.1995.03950140007002

McGregor, B. A., Antoni, M. H., Boyers, A., Alferi, S. M., Blomberg, B. B., & Carver, C. S. (2004). Cognitive-behavioral stress management increases benefit finding and immune function among women with early-stage breast cancer. *Journal of Psychosomatic Research, 56*(1), 1-8. doi:10.1016/S0022-3999(03)00036-9

Mehnert, A., & Koch, U. (2008). Psychological comorbidity and health-related quality of life and its association with awareness, utilization, and need for psychosocial support in a cancer register-based sample of long-term breast cancer survivors. *Journal of psychosomatic research*, *64*(4), 383-391. doi:10.1016/j.jpsychores.2007.12.005

Miller, G., Chen, E., & Cole, S. W. (2009). Health psychology: Developing biologically plausible models linking the social world and physical health. *Annual Review of Psychology, 60*(1), 501-524. doi:10.1146/annurev.psych.60.110707.163551

Miovic, M., & Block, S. (2007). Psychiatric disorders in advanced cancer. *Cancer, 110*(8), 1665-1676. doi:10.1002/cncr.22980

Mols, F., Vingerhoets, A. J., Coebergh, J. W., & van de Poll-Franse, L. V. (2005). Quality of life among long-term breast cancer survivors: a systematic review. *European Journal of Cancer*, *41*(17), 2613-2619. doi:10.1016/j.ejca.2005.05.017.

Mols, F., Vingerhoets, A. J., Coebergh, J. W. W., & van de Poll-Franse, L. V. (2009). Well-being, posttraumatic growth and benefit finding in long-term breast cancer survivors. *Psychology and Health*, *24*(5), 583-595.

Montazeri, A. (2008). Health-related quality of life in breast cancer patients: A bibliographic review of the literature from 1974 to 2007. *Journal of Experimental & Clinical Cancer Research: CR, 27*, 32-32.

Moyer, A., Sohl, S. J., Knapp-Oliver, S. K., & Schneider, S. (2009). Characteristics and methodological quality of 25 years of research investigating psychosocial interventions for cancer patients. *Cancer Treatment Reviews*, *35*(5), 475-484. doi:10.1016/j.ctrv.2009.02.003

Murphy, C. C., Bartholomew, L. K., Carpentier, M. Y., Bluethmann, S. M., & Vernon, S. W. (2012). Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Research and Treatment*, *134*(2), 459-478. doi: 10.1007/s10549-012-2114-5

Mustafa, M., Carson-Stevens, A., Gillespie, D., & Edwards, A. G. (2013). Psychological interventions for women with metastatic breast cancer. *Cochrane Database Systematic Review*, *6*. doi: 10.1002/14651858.CD004253.pub4

Naaman, S. C., Radwan, K., Fergusson, D., & Johnson, S. (2009). Status of psychological trials in breast cancer patients: A report of three meta-analyses. *Psychiatry, 72*(1), 50-69.

National Cancer Institute (U.S.). (2008). *Psychological stress and cancer: Questions and answers*. Bethesda, MD.: National Cancer Institute.

Okamura, H., Watanabe, T., Narabayashi, M., Katsumata, N., Ando, M., Adachi, I., . . . Uchitomi, Y. (2000). Psychological distress following first recurrence of disease in patients with breast cancer: Prevalence and risk factors. *Breast Cancer Research and Treatment, 61*(2), 131-137. doi:10.1023/A:1006483214678

Osborn, R. L., Demoncada, A. C., & Feuerstein, M. (2006). Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses. *The International Journal of Psychiatry in Medicine*, *36*(1), 13-34. doi: 10.2190/EUFN-RV1K-Y3TR-FK0L

Palesh, O., Butler, L. D., Koopman, C., Giese-Davis, J., Carlson, R., & Spiegel, D. (2007). Stress history and breast cancer recurrence. *Journal of Psychosomatic Research, 63*(3), 233.

Patrick, D. L., Ferketich, S. L., Frame, P. S., Harris, J. J., Hendricks, C. B., Levin, B., . . . Vernon, S. W. (2003). National institutes of health state-of-the-science conference statement: Symptom management in cancer: Pain, depression, and fatigue, July 15-17, 2002. *Journal of the National Cancer Institute, 95*(15), 1110-1117.

Phillips, K. M., Antoni, M. H., Lechner, S. C., Blomberg, B. B., Llabre, M. M., Avisar, E., ... & Carver, C. S. (2008). Stress management intervention reduces serum cortisol and increases relaxation during treatment for nonmetastatic breast cancer. *Psychosomatic Medicine*, *70*(9), 1044-1049. doi:10.1097/PSY.0b013e318186fb27

Phillips, K. M., Jim, H. S., Small, B. J., Tanvetyanon, T., Roberts, W. S., & Jacobsen, P. B. (2012). Effects of Self-directed Stress Management Training and Home-based Exercise on Stress Management Skills in Cancer Patients Receiving Chemotherapy. *Stress and Health*, *28*(5), 368-375. doi: 10.1002/smi.2450

Prinja, S., Gupta, N., & Verma, R. (2010). Censoring in clinical trials: Review of survival analysis techniques. *Indian Journal of Community Medicine*, *35*(2), 217-221. doi: 10.4103/0970-0218.66859

Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, & Computers: A Journal of the Psychonomic Society, Inc, 36*(4), 717-731. doi:10.3758/BF03206553

Quinten, C., & EORTC Clinical Groups. (2009). Baseline quality of life as a prognostic indicator of survival: A meta-analysis of individual patient data from EORTC clinical trials. *Lancet Oncology, 10*(9), 865-871. doi:10.1016/S1470-2045(09)70200-1

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385-401. doi:10.1177/014662167700100306

Rakha, E. A., Reis-Filho, J. S., Baehner, F., Dabbs, D. J., Decker, T., Eusebi, V., ... & Ellis, I. O. (2010). Breast cancer prognostic classification in the molecular era: the role of histological grade. *Breast Cancer Research*, *12*(4), 207. doi: doi:10.1186/bcr2607

Ranganathan, P., & Pramesh, C. S. (2012). Censoring in survival analysis: Potential for bias. *Perspectives in Clinical Research*, *3*(1), 40-42. doi: 10.4103/2229-3485.92307

Reddick, B. K., Nanda, J. P., Campbell, L., Ryman, D. G., & Gaston-Johansson, F. (2005). Examining the influence of coping with pain on depression, anxiety, and fatigue among women with breast cancer. *Journal of Psychosocial Oncology, 23*(2), 137-157.

Reich, M., Lesur, A., & Perdrizet-Chevallier, C. (2008). Depression, quality of life and breast cancer: A review of the literature. *Breast Cancer Research and Treatment, 110*(1), 9-17. doi:10.1007/s10549-007-9706-5

Reyes-Gibby, C., Anderson, K., O., Morrow, P., Kanh, Shete, S., & Hassan, S. (2012). Depressive symptoms and health-related quality of life in breast cancer survivors. *Journal of Women's Health, 21*(3), 311-318. doi:10.1089/jwh.2011.2852

Rehse, B., & Pukrop, R. (2003). Effects of psychosocial interventions on quality of life in adult cancer patients: meta-analysis of 37 published controlled outcome studies. *Patient Education and Counseling*, *50*(2), 179-186. doi:10.1016/S0738-3991(02)00149-0

Rich, J. T., Neely, J. G., Paniello, R. C., Voelker, C. C. J., Nussenbaum, B., & Wang, E. W. (2010). A practical guide to understanding kaplan-meier curves. *Otolaryngology--Head and Neck Surgery, 143*(3), 331-336. doi:10.1016/j.otohns.2010.05.007

Ross, L., Boesen, E. H., Dalton, S. O., & Johansen, C. (2002). Mind and cancer: does psychosocial intervention improve survival and psychological well-being? *European Journal of Cancer*, *38*(11), 1447-1457. doi: 10.1016/S0959-8049(02)00126-0

Ross, J. S., & Fletcher, J. A. (1998). The HER−2/neu oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. *Stem Cells*, *16*(6), 413-428. doi: 10.1002/stem.160413

Sanderman, R., & Ranchor, A. V. (2000). The evaluation of the center for epidemiologic studies depression (CES-D) scale: Depressed and positive affect in cancer patients and healthy reference subjects. *Quality of Life Research, 9*(9), 1015-1029. doi:10.1023/A:1016673003237

Satin, J. R., Linden, W., & Phillips, M. J. (2009). Depression as a predictor of disease progression and mortality in cancer patients. *Cancer, 115*(22), 5349-5361. doi:10.1002/cncr.24561

Saul, A. N., Dhabhar, F. S., Oberyszyn, T. M., Daugherty, C., Kusewitt, D., Jones, S., . . . Lemeshow, S. (2005). Chronic stress and susceptibility to skin cancer. *Journal of the National Cancer Institute, 97*(23), 1760-1767. doi:10.1093/jnci/dji401

Schairer, C., Mink, P. J., Carroll, L., & Devesa, S. S. (2004). Probabilities of death from breast cancer and other causes among female breast cancer patients. *Journal of the National Cancer Institute, 96*(17), 1311-1321. doi:10.1093/jnci/djh253

Schroevers, M. J., Sanderman, R., Van Sonderen, E., & Ranchor, A. V. (2000). The evaluation of the Center for Epidemiologic Studies Depression (CES-D) scale: Depressed and Positive Affect in cancer patients and healthy reference subjects. *Quality of Life Research*, *9*(9), 1015-1029. doi: 10.1023/A:1016673003237

Segerstrom, S. C., & Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin, 130*(4), 601-630. doi:10.1037/0033-2909.130.4.601

Sephton, S. E., Sapolsky, R. M., Kraemer, H. C., & Spiegel, D. (2000). Diurnal cortisol rhythm as a predictor of breast cancer survival. *Journal of the National Cancer Institute, 92*(12), 994-1000.

Sephton, S., & Spiegel, D. (2003). Circadian disruption in cancer: A neuroendocrine-immune pathway from stress to disease? *Brain Behavior and Immunity, 17*(5), 321-328. doi:10.1016/S0889-1591(03)00078-3

Siegel, R., Naishadham, D., & Jemal, A. (2012). Cancer statistics, 2012. *CA: A Cancer Journal for Clinicians, 62*(1), 10-29. doi:10.3322/caac.20138

Singh–Carlson, S., Wong, F., Martin, L., & Nguyen, S. K. A. (2013). Breast cancer survivorship and South Asian women: understanding about the follow-up care plan and perspectives and preferences for information post treatment. *Current Oncology*, *20*(2), e63-e79. doi:10.3747/co.20.1066

Slavich, G. M., & Cole, S. W. (2013). The emerging field of human social genomics. *Clinical Psychological Science, 1(3)*, 331-338. doi:10.1177/2167702613478594

Smedslund, G., & Ringdal, G. I. (2004). Meta-analysis of the effects of psychosocial interventions on survival time in cancer patients. *Journal of Psychosomatic Research*, *57*(2), 123-131. doi:10.1016/S0022-3999(03)00575-0

Smith, T. J. (2013). Breast cancer surveillance guidelines. *Journal of Oncology Practice / American Society of Clinical Oncology, 9*(1), 65-67. doi:10.1200/JOP.2012.000787

So, W. K., Marsh, G., Ling, W. M., Leung, F. Y., Lo, J. C., Yeung, M., & Li, G. K. (2009). The symptom cluster of fatigue, pain, anxiety, and depression and the effect on the quality of life of women receiving treatment for breast cancer: a multicenter study. *Oncology Nursing Forum* 3*6(*4). E205-E214. doi: 10.1188/09.ONF.E205-E214

Soerjomataram, I., Louwman, M. W., Ribot, J. G., Roukema, J. A., & Coebergh, J. W. W. (2008). An overview of prognostic factors for long-term survivors of breast cancer. *Breast Cancer Research and Treatment*, *107*(3), 309-330. doi: 10.1007/s10549-007-9556-1

Somerset, W., Stout, S. C., Miller, A. H., & Musselman, D. (2004). Breast cancer and depression. *Oncology, 18*(8), 1021-1048. PMID:15328896

Spiegel, D. (1997). Psychosocial aspects of breast cancer treatment. *Seminars in Oncology, 24*(1), S1-36; S1-47.

Spiegel, D., Bloom, J. R., Kraemer, H. C., & Gottheil, E. (1989). Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet, 2*(8668), 888-891. doi:10.1016/S0140-6736(89)91551-1

Spiegel, D. (2002). Effects of psychotherapy on cancer survival. *Nature Reviews Cancer, 2*(5), 383-388. doi:10.1038/nrc800

Spiegel, D., & Giese-Davis, J. (2003). Depression and cancer: Mechanisms and disease progression. *Biological Psychiatry, 54*(3), 269-282. doi:10.1016/S0006-3223(03)00566-3

Spiegel, D., Butler, L. D., Giese‐Davis, J., Koopman, C., Miller, E., DiMiceli, S., ... & Kraemer, H. C. (2007). Effects of supportive‐expressive group therapy on survival of patients with metastatic breast cancer. *Cancer*, *110*(5), 1130-1138. doi: 10.1002/cncr.22890

Stagl, J.M., Antoni, M.H., Lechner, S., Gudenkauf, L.M., Jutagir, D.R., Glück, S., Blomberg, B., Carver, C.S. (2013, March) Cognitive-behavioral stress management and depression in a 5-year follow-up study of breast cancer survivors. Presented at the Annual Meeting and Scientific Sessions of the Society of Behavioral Medicine, San Francisco, CA.

Steel, J. L., Geller, D. A., Gamblin, T. C., Olek, M. C., & Carr, B. I. (2007). Depression, immunity, and survival in patients with hepatobiliary carcinoma. *Journal of Clinical Oncology, 25*(17), 2397-2405.

Stefanek, M. E., Palmer, S. C., Thombs, B. D., & Coyne, J. C. (2009). Finding what is not there. *Cancer*, *115*(24), 5612-5616.

Sue, G. R., Killelea, B., Horowitz, N. R., Lannin, D. R., & Chagpar, A. B. (2012). Recurrence in patients diagnosed with ductal carcinoma in situ: predictors and prognostic significance. *Cancer Research*, *72*(24 Supplement 3). doi:10.1158/0008-5472.SABCS12-P3-14-05

Tabar, L., Yen, M., Vitak, B., Chen, H. T., Smith, R. A., Duffy, S. W., . . . Radiologi. (2003). Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. *The Lancet, 361*(9367), 1405-1410. doi:10.1016/S0140-6736(03)13143-1

Tatrow, K., & Montgomery, G. H. (2006). Cognitive behavioral therapy techniques for distress and pain in breast cancer patients: A meta-analysis. *Journal of Behavioral Medicine*, *29*(1), 17-27. doi:10.1007/s10865-005-9036-1

Thornton, L. M., Andersen, B. L., & Blakely, W. P. (2010). The pain, depression, and fatigue symptom cluster in advanced breast cancer: Covariation with the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system. *Health Psychology, 29*(3), 333-337. doi:10.1037/a0018836

Thaker, P. H., & Sood, A. K. (2008). Neuroendocrine influences on cancer biology. *Seminars in Cancer Biology*, *18*(3), 164-170. doi:10.1016/j.semcancer.2007.12.005

Thornton, L. M., Andersen, B. L., Crespin, T. R., & Carson, W. E. (2007). Individual trajectories in stress covary with immunity during recovery from cancer diagnosis and treatments. *Brain Behavior and Immunity, 21*(2), 185-194. doi:10.1016/j.bbi.2006.06.007

Toriola, A. T., & Colditz, G. A. (2013). Trends in breast cancer incidence and mortality in the United States: implications for prevention. *Breast Cancer Research and Treatment*, *138*(3), 665-673. doi: 10.1007/s10549-013-2500-7.

Van Wilgen, C. P., Dijkstra, P. U., Stewart, R. E., Ranchor, A. V., & Roodenburg, J. L. N. (2006). Measuring somatic symptoms with the CES–D to assess depression in cancer patients after treatment: comparison among patients with oral/oropharyngeal, gynecological, colorectal, and breast cancer. *Psychosomatics*, *47*(6), 465-470. doi: 10.1176/appi.psy.47.6.465

Watson, M., Haviland, J. S., Greer, S., Davidson, J., & Bliss, J. M. (1999). Influence of psychological response on survival in breast cancer: a population-based cohort study. *The Lancet*, *354*(9187), 1331-1336. doi: 10.1016/S0140-6736(98)11392-2

Watson, M., Homewood, J., Haviland, J., & Bliss, J. M. (2005). Influence of psychological response on breast cancer survival: 10-year follow-up of a population-based cohort. *European Journal of Cancer*, *41*(12), 1710-1714. doi: 10.1016/j.ejca.2005.01.012

Webster, K., Cella, D., & Yost, K. (2003). The functional assessment of chronic illness therapy (FACIT) measurement system: Properties, applications, and interpretation. *Health and Quality of Life Outcomes, 1*(1), 79-79. doi:10.1186/1477-7525-1-79

Williams, J. B., Pang, D., Delgado, B., Kocherginsky, M., Tretiakova, M., Krausz, T., . . . Conzen, S. D. (2009). A model of gene-environment interaction reveals altered mammary gland gene expression and increased tumor growth following social isolation. *Cancer Prevention Research , 2*(10), 850-861. doi:10.1158/1940-6207.CAPR-08-0238

Zorrilla, E. P., Luborsky, L., McKay, J. R., Rosenthal, R., Houldin, A., Tax, A., . . . Schmidt, K. (2001). The relationship of depression and stressors to immunological assays: A meta-analytic review. United States: Academic Press. doi:10.1006/brbi.2000.0597

Tables

Table 1

Means, Standard Deviations, and Frequencies of All Study Covariates by Group

Variable	Control	Intervention	Statistic	*p*
Age at baseline (years)	50.99 (9.06)	49.69 (8.98)	$F(1,238) = 1.25$	.265
Age at T6 (years)	61.07 (9.19)	59.75 (9.73)	$F(1,238) = 1.16$	.282
Menopausal Status			$\chi^2(1) = 0$ .02	.897
Premenopausal	53 (44.2%)	54 (45.0%)		
Postmenopasual	67 (55.8%)	66 (55.0%)		
Race/Ethnicity			$\chi^2(3) = 1.97$	.580
White non-Hispanic	74 (61.7%)	78 (65.0%)		
Hispanic	31 (25.8%)	30 (25.0%)		
African American	10 (8.3%)	11 (9.2%)		
Asian	4 (3.3%)	1 (.8%)		
Employment Status			$\chi^2(1) = 0.78$	.376
Not Employed	28 (23.3%)	34 (28.3%)		
Employed	92 (76.7%)	86 (71.7%)		
Education (years)	15.47 (2.26)	15.69 (2.5)	$F(1,238) = 0.53$	.466
Income (thousands of dollars)	79.22 (68.47)	80.45 (66.11)	$F(1,210) = 0.01$	.895
Partnered Status			$\chi^2(1) = 0.00$	1.00
Not partnered	45 (37.5%)	45 (37.5%)		
Partnered	75 (62.5%)	75 (62.5%)		
Stage			$\chi^2(4) = 4.06$	.398
0	24 (20%)	18 (15%)		
I	44 (36.7%)	39 (32.5%)		
II	43 (35.8%)	47 (39.2%)		
III	9 (7.5%)	13 (10.8%)		
IV	0 (0%)	2 (1.7%)		
Invasive vs. Non-Invasive			$\chi^2(1) = 0.686$	.407
0	23 (19.2%)	18 (15.0%)		
I, II, III, IV	97 (80.8%)	101 (84.2%)		
Positive Lymph Nodes	1.56 (3.60)	1.45 (2.97)	$F(1,237) = 0.07$	.791
Size of Tumor	1.65 (1.14)	3.76 (12.93)	$F(1,121) = 1.74$	.189
ER Status			$\chi^2(1) = 1.88$	.170
Positive	78 (65%)	78 (65%)		
Negative	16 (13.3%)	26 (21.7%)		
PR Status			$\chi^2(1) = 0.11$	.746
Positive	55 (45.8%)	58 (48.3%)		
Negative	30 (25%)	35 (29.2%)		

HER2/neu Status			$\chi^2(1) = 1.41$	.236
Positive	10 (8.3%)	16 (13.3%)		
Negative	48 (40%)	45 (37.5%)		
Procedure Type			$\chi^2(1) = 3.27$	.071
Lumpectomy	68 (56.7%)	54 (45.0%)		
Mastectomy	52 (43.3%)	66 (55.0%)		
Time Since Surgery	44.80 (25.34)	36.47 (23.03)	$F(1, 238) = 8.12$	.005**
Received chemotherapy			$\chi^2(1) = 3.49$	.061
Yes	57 (47.5%)	70 (58.3%)		
No	59 (49.2%)	44 (36.7%)		
Received radiation therapy			$\chi^2(1) = 0.29$	.588
Yes	69 (57.5%)	65 (54.2%)		
No	44 (36.7%)	48 (40%)		
Received hormonal therapy			$X^2(1) = 0$ .87	.351
Yes	78 (65%)	83 (69.2%)		
No	37 (30.8%)	30 (25.0%)		
Body Mass Index	26.60 (6.16)	26.63 (5.26)	$F(1,132) < 0.01$	.971
Body Mass Categories			$\chi^2(3) = 3.5$	.318
Underweight	0 (0.0%)	1 (0.8%)		
Normal	33 (27.5%)	30 (25.0%)		
Overweight	28 (23.3%)	16 (13.3%)		
Obese	12 (10.0%)	14 (11.7%)		
HRSD-T1	7.30 (5.10)	7.73 (5.80)	$F(1,229) = 0.37$	.544
Pain in Body T6	0.96 (1.32)	1.10 (1.25)	$F(1,98) = 0.29$	.591
FACT-Breast Total T1	98.83 (17.87)	95.50 (17.71)	$F(1,238) = 2.11$	.148
FACT-Physical WB T1	20.98 (5.45)	20.70 (5.98)	$F(1,238) = 0.15$	.700
FACT-Emotional WB T1	18.14 (3.90)	17.60 (3.94)	$F(1,238) = 1.14$	.288

Note. ER = Estrogen Receptor; PR = Progesterone Receptor; HER2/neu = Human Epidermal Growth Factor Receptor ; HRSD = Hamilton Rating Scale for Depression; FACT = Functional Assessment of Cancer Therapy; WB = Well-Being; T1 = Baseline assessment; T6 = 8-15 year follow-up assessment

Table 2

Means, Standard Deviations, and Frequencies of All Study Variables by Group

Variable	Control	Intervention	Statistic	*p*
Time to Death	2,948.28 (1354.45)	2,977.04 (1359.67)	$F(1, 238)=0.03$	.870
Time to Recurrence	2,307.51 (1443.59)	2,383.15 (1422.85)	$F(1, 238)=0.17$	.683
All-Cause Mortality			$\chi^2(1)=0.00$	1.00
Yes	15 (12.5%)	15 (12.5%)		
No	105 (87.5%)	105 (87.5%)		
Breast Cancer Mortality			$\chi^2(1 =0.20$	.655
Yes	10 (8.3%)	12 (10.0%)		
No	110 (91.7%)	108 (90.0%)		
Breast Cancer Recurrence			$\chi^2(1)=0.03$	.871
Yes	23 (19.2%)	24 (20.0%)		
No	97 (80.8%)	96 (80.0%)		
CES-D Total T6	8.67 (9.89)	8.06 (8.43)	$F(1,97)=0.11$	.742
CES-D Positive T6	9.02 (3.85)	9.82 (2.53)	$F(1,97)=1.52$	.220
CES-D Negative T6	2.00 (3.43)	2.16 (3.64)	$F(1,97)=0.05$	.826
FACT-Breast Total T6	136.14 (24.01)	132.88 (16.69)	$F(1,98)=0.63$	.431
FACT-Physical WB T6	24.94 (5.29)	25.73 (2.49)	$F(1,98)=0.92$	.341
FACT-Emotional WB T6	21.00 (3.99)	20.98 (2.80)	$F(1,98)<0.01$	.977
ABS-Balance 12-mo Δ	5.11 (17.94)	11.41 (18.02)	$F(1,187)=5.82$	.017
ABS-Negative 12-mo Δ	-2.42 (11.11)	-5.70 (9.09)	$F(1,187)=4.94$	.027
ABS-Positive 12-mo Δ	2.68 (9.7)	5.58 (11.63)	$F(1,89)=3.50$	.063

Note. CES-D = Center for Epidemiologic Studies-Depression; FACT = Functional Assessment of Cancer Therapy; WB = Well-Being; ABS = Affect Balance Scale; Δ = change; T1 = Baseline assessment; T6 = 8-15 year follow-up assessment

Table 3

Intervention Effects on Clinical Outcomes at 8-15 Year Follow-Up Cox Proportional Hazards Regressions

Outcome	*β*	*SE*	*p*	*Exp (B)*	Lower 95% CI	Upper 95% CI
Age at diagnosis	-0.10	0.04	*.015	0.90	0.83	0.98
Her2/neu (negative)	-0.87	0.74	.237	0.42	0.98	1.78
Tumor size	0.64	0.46	.163	1.90	0.77	4.69
Hormonal Therapy (no)	1.42	0.67	*.036	4.12	1.10	15.39
Stage (early)	0.63	1.27	.619	1.88	0.16	22.38
Time since surgery	0.02	0.01	.220	1.02	0.99	1.05
CBSM	-1.57	0.75	*.037	0.21	0.05	0.91
All-Cause Mortality; $N = 102$; $\chi^2(7) = 15.66$, p = .028*						
Age at diagnosis	-0.11	0.04	*.014	0.90	0.82	0.98
Her2/neu (negative)	-0.81	0.78	.295	0.44	0.10	2.03
Tumor size	0.57	0.48	.232	1.77	0.70	4.51
Hormonal Therapy (no)	1.15	0.73	.115	3.17	0.75	13.31
Stage (early)	-12.91	896.37	.989	0.00	0.00	.
Time since surgery	0.02	0.01	.151	1.02	0.99	1.05
CBSM	-1.45	0.78	∞ .063	0.23	0.05	1.08
Breast Cancer-Specific Mortality; N = 102; $\chi^2(7) = 14.49$, p = .043*						
Age at diagnosis	-0.07	0.03	*.013	0.94	0.89	0.99
Her2/neu (negative)	-0.51	0.50	.308	0.60	0.23	1.60
Tumor size	0.36	0.24	.137	1.44	0.89	2.31
Hormonal Therapy (no)	0.89	0.48	∞ .067	2.43	0.94	6.26
Stage (early)	-0.31	1.09	.775	0.73	0.09	6.23
Time since surgery	0.002	0.01	.880	1.00	0.98	1.02
CBSM	-0.83	0.44	∞ .062	0.44	0.18	1.04
Disease Free Interval; N = 101; $\chi^2(7) = 14.49$, p = .043						

Notes: β = Unstandardized Coefficient; SE = Standard Error; CI = Confidence Interval; HER2/neu = Human Epidermal Growth Receptor; CBSM = Cognitive Behavioral Stress Management

∞ p<.10; *p < .05; **p<.01; ***p<.001;

Table 4

Intervention Effects on Quality of Life at 8-15 Year Follow-Up Regression Table

Outcome	*β*	*SE*	*t*	*p*	Lower 95% CI	Upper 95% CI
FACT-B T1	0.49	0.15	3.31	**.002	0.19	0.78
Age T6	0.27	0.25	1.09	.28	-0.23	0.78
Income	0.05	0.03	1.57	.122	-0.01	0.10
Education	-0.04	0.89	-0.05	.962	-1.84	1.75
Race: Black	-10.01	9.89	-1.01	.317	-29.89	9.88
Race: Hispanic	2.70	4.82	0.56	.577	-6.98	12.39
Race: Asian	30.55	17.80	1.72	∞.093	-5.24	66.34
Pain T6	-11.01	1.92	-5.73	***<.001	-14.87	-7.15
BMI	0.79	0.41	1.91	∞.062	-0.04	1.63
CBSM	9.59	4.56	2.10	*.041	0.423	18.76
FACT-Breast Total T6; $N = 59$, $R2 = .55$, $F(10,48) = 8.21$, $p < .001$***						
FACT-PWB T1	0.32	0.11	2.84	**.007	0.09	0.54
Age T6	0.08	0.05	1.51	.137	-0.03	0.18
Income	0.01	0.01	2.08	.043	0.00	0.02
Education	-0.02	0.19	-0.10	.918	-0.35	0.35
Race: Black	-0.04	2.01	-0.02	.984	-4.09	4.01
Race: Hispanic	0.61	0.99	0.62	.541	-1.38	2.59
Race: Asian	4.93	3.42	1.44	.156	-1.94	11.81
Pain T6	-2.46	0.39	-6.27	***<.001	-3.24	-1.67
BMI	0.10	0.09	1.19	.240	-0.07	0.27
CBSM	3.00	0.94	3.19	**.002	1.11	4.89
FACT-Physical Well-Being T6; $N = 59$, $R2 = .65$, $F(10,48) = 8.88$ $p < .001$***						
FACT-EWB T1	0.32	0.11	2.87	**.006	0.10	0.54
Age T6	0.06	0.05	1.18	.243	-0.04	0.15
Income	0.01	0.01	1.30	.200	-0.01	0.02
Education	0.05	0.16	0.32	.752	-0.27	0.37
Race: Black	1.04	1.77	0.59	.559	-2.52	4.60
Race: Hispanic	0.54	0.88	0.62	.540	-1.22	2.31
Race: Asian	7.50	3.32	2.26	*.028	0.84	14.17
Pain T6	-1.39	0.33	-4.24	***<.001	-2.05	-0.73
BMI	0.07	0.08	0.97	.335	-0.08	0.23
CBSM	1.82	0.81	2.24	*.030	0.19	3.46
FACT-Emotional Well-Being T6; $N = 59$, $R2 = .49$, $F(10,48) = 4.57$, $p < .001$***						

Notes: β = Unstandardized Coefficient; SE = Standard Error; CI = Confidence Interval; FACT-B = Functional Assessment of Cancer Therapy- Breast; PWB = Physical Well-Being; EWB = Emotional Well-Being; BMI = Body Mass Index; CBSM = Cognitive Behavioral Stress Management

∞ p<.10; *p < .05; **p<.01; ***p<.001;

Table 5

Intervention Effects on Depressive Symptoms at 8-15 Year Follow-Up Regression Table

Outcome	*β*	*SE*	*t*	*p*	Lower 95% CI	Upper 95% CI
HRSD T1	0.44	0.27	1.63	.110	-0.10	0.99
Age T6	-0.14	0.13	-1.06	.293	-0.40	0.12
Income	-0.03	0.01	-1.67	.102	-0.05	0.01
Education	-0.26	0.43	-0.60	.554	-1.12	0.61
Race: Black	1.74	4.94	0.35	.727	-9.22	1170
Race: Hispanic	-0.79	2.36	-0.33	.741	-5.54	3.97
Race: Asian	6.08	7.90	0.77	.445	-9.84	22.00
Pain T6	4.15	0.97	4.27	***<.001	2.19	6.12
BMI	-0.25	0.21	-1.22	.229	-0.64	0.16
CBSM	-4.46	2.22	-2.01	.051	-8.93	0.01
CES-D Total T6; $N = 55$, $R2 = .45$, $F(10,44) = 3.55$, $p = .001$***						
HRSD T1	0.04	0.11	0.35	.729	-0.19	0.27
Age T6	-0.01	0.06	-0.21	.84	-0.12	0.10
Income	0.01	0.01	1.55	.127	-0.003	0.02
Education	0.07	0.18	0.37	.713	-0.29	0.43
Race: Black	-3.17	2.07	-1.53	.133	-7.33	0.10
Race: Hispanic	-1.31	0.99	-1.33	.192	-3.30	0.68
Race: Asian	-9.98	3.30	-3.02	.004	-16.64	-3.32
Pain T6	-0.91	.41	-2.25	.030	-1.73	-0.10
BMI	0.15	0.09	1.71	∞.095	-0.03	0.32
CBSM	1.30	0.93	1.40	.169	-0.57	3.17
CES-D Positive Affect T6; $N = 55$, $R2 = .34$, $F(10,44) = 2.24$, $p = .032$*						
HRSD T1	0.18	0.09	1.95	∞ .057	-0.01	0.37
Age T6	-0.08	0.05	-1.67	.102	-0.02	0.02
Income	-0.01	0.01	-1.26	.215	-0.02	0.00
Education	-0.07	0.15	-0.50	.620	-0.37	0.22
Race: Black	-1.13	1.70	-0.67	.508	-4.56	2.29
Race: Hispanic	-0.93	0.81	-1.14	.260	-2.56	0.71
Race: Asian	-1.98	2.71	-0.73	.469	-7.54	3.49
Pain T6	1.40	0.33	4.19	***<.001	0.73	2.07
BMI	-0.01	0.07	-0.10	.921	-0.15	0.14
CBSM	-1.58	0.76	-2.07	*.044	-3.11	-0.04
CES-D Negative Affect T6; $N = 55$, $R2 = .47$, $F(10,44) = 3.96$, $p < .001$***						

Notes: β = Unstandardized Coefficient; SE = Standard Error; CI = Confidence Interval; CES-D = Center for Epidemiologic Studies; HRSD = Hamilton Rating Scale for Depression; BMI = Body Mass Index; CBSM = Cognitive Behavioral Stress Management

∞ p<.10; *p < .05; **p<.01; ***p<.001;

Figures

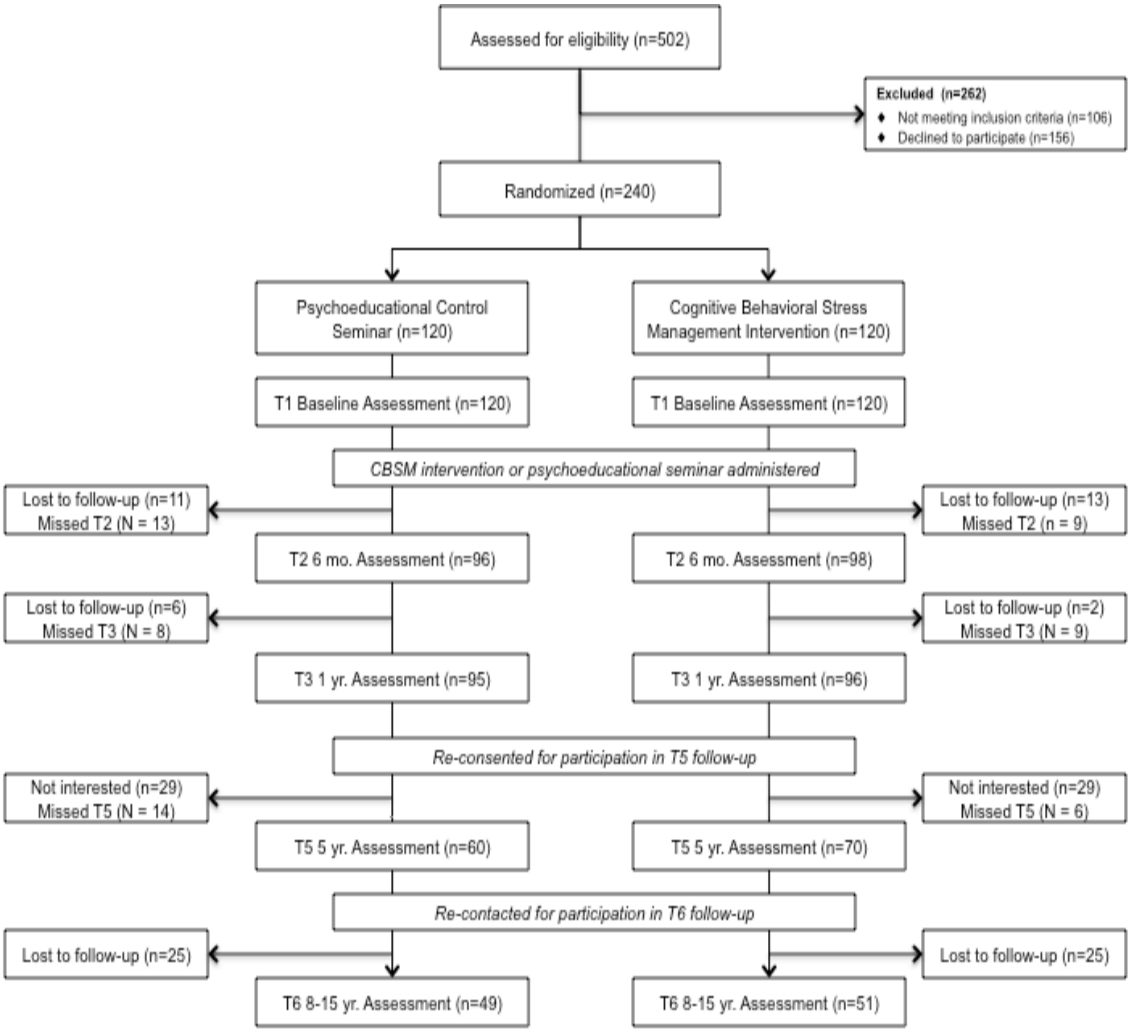

Figure 1. CONSORT Flow Diagram

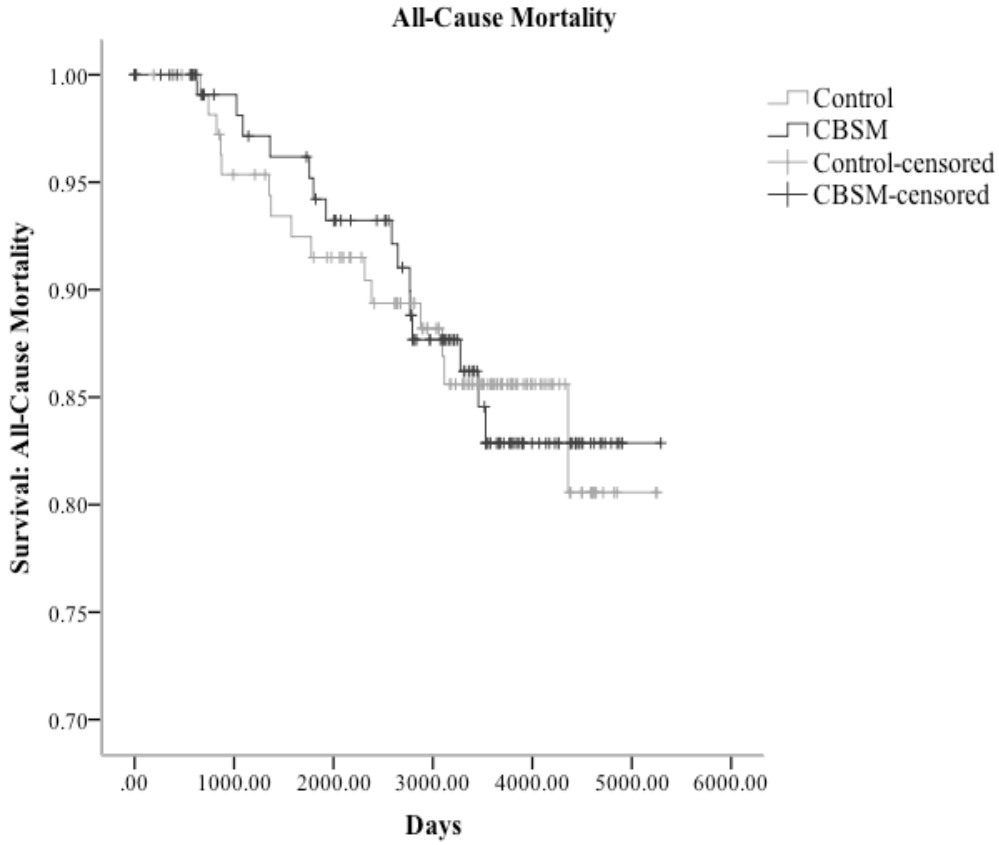

Figure 2. Unadjusted Kaplan-Meier Survival Curves predicting time to all-cause mortality. No significant difference was found between study groups. Note: y-axis does not begin at 0.

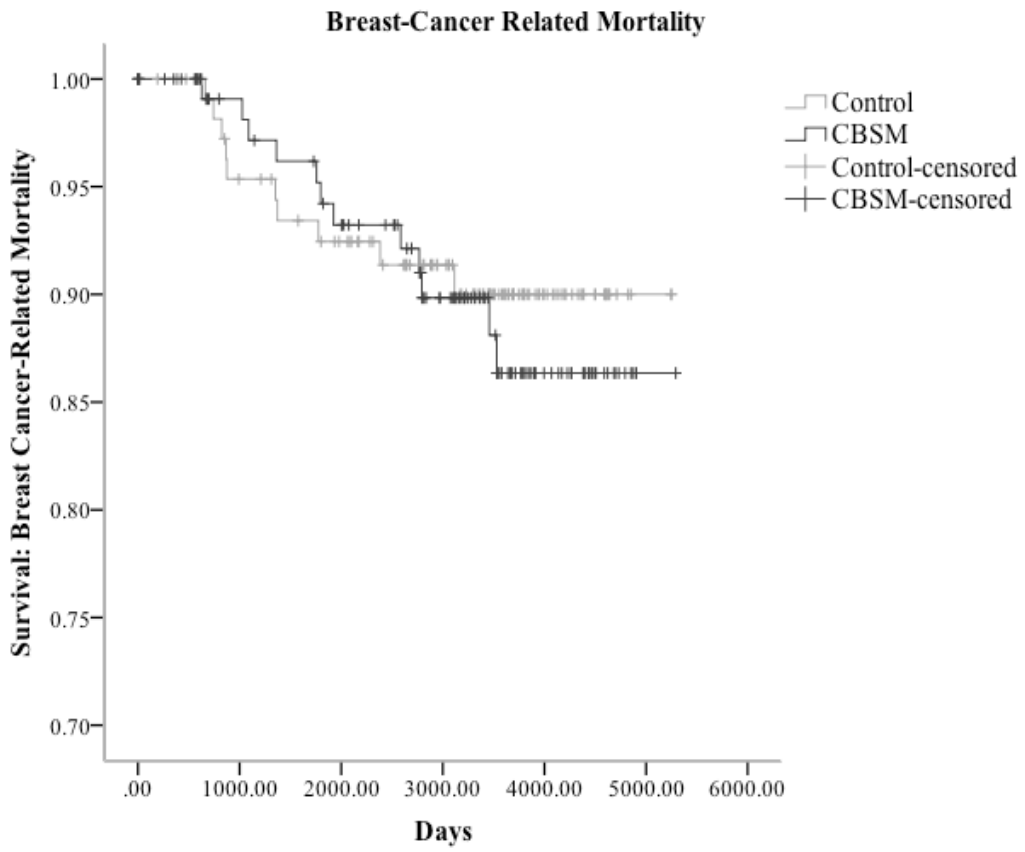

Figure 3. Unadjusted Kaplan-Meier Survival Curves predicting time to breast cancer-related mortality. No significant difference was found between study groups. Note: y-axis does not begin at 0.

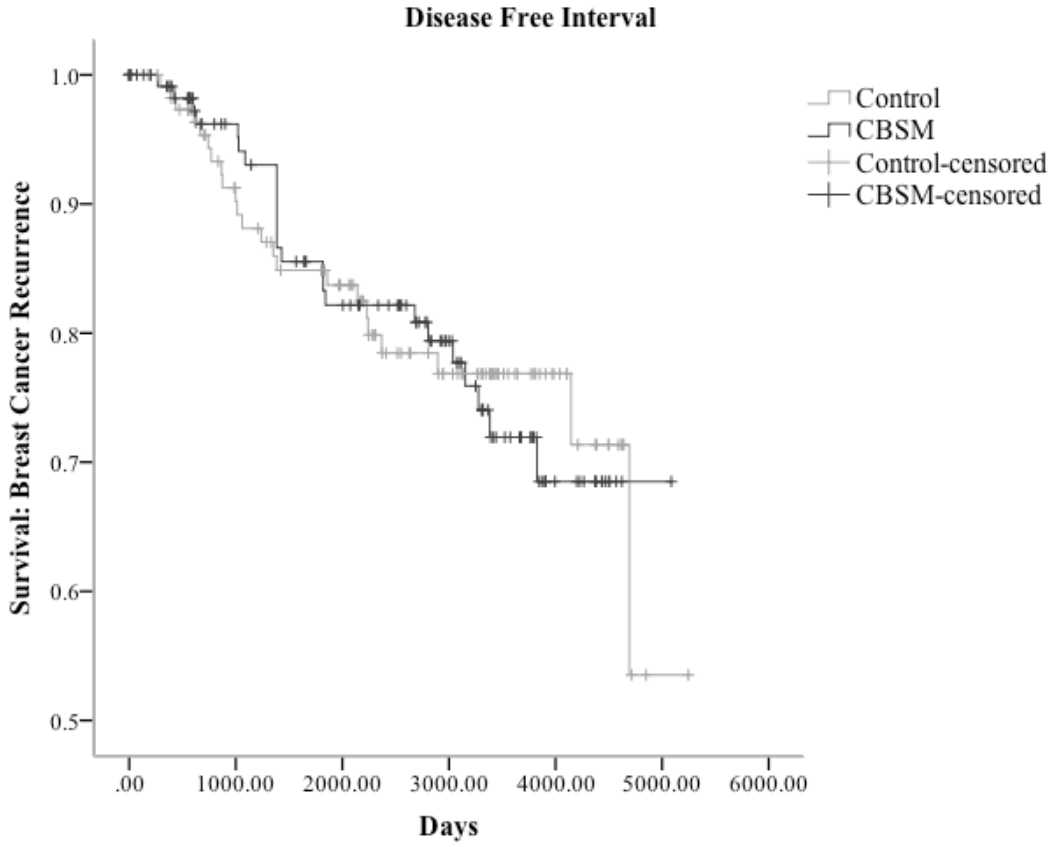

Figure 4. Unadjusted Kaplan-Meier Survival Curves predicting time to breast cancer recurrence. No significant difference was found between study groups. Note: y-axis does not begin at 0.

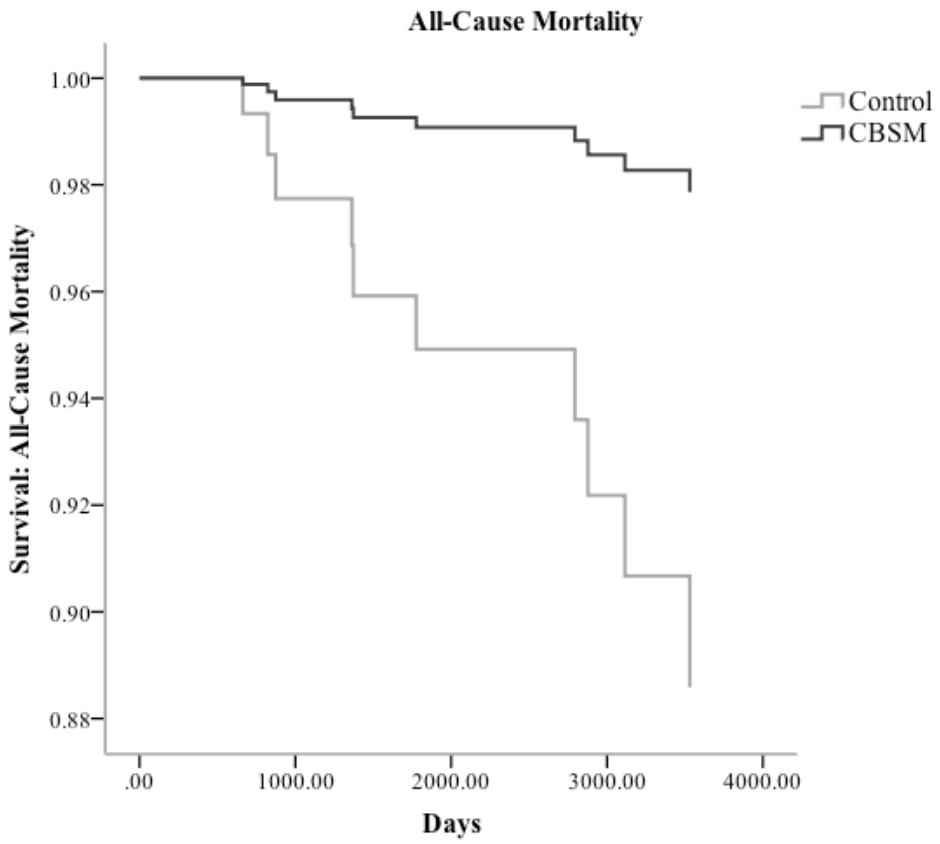

Figure 5. Cox Proportional Hazards Models showing intervention effects on all-cause mortality adjusted for age, time since surgery, stage, HER2neu, tumor size, hormonal therapy, chemotherapy, and radiation therapy. CBSM HR = 0.18 (95% CI [0.04, 0.80]; *p* = .025). Note: y-axis does not begin at 0.

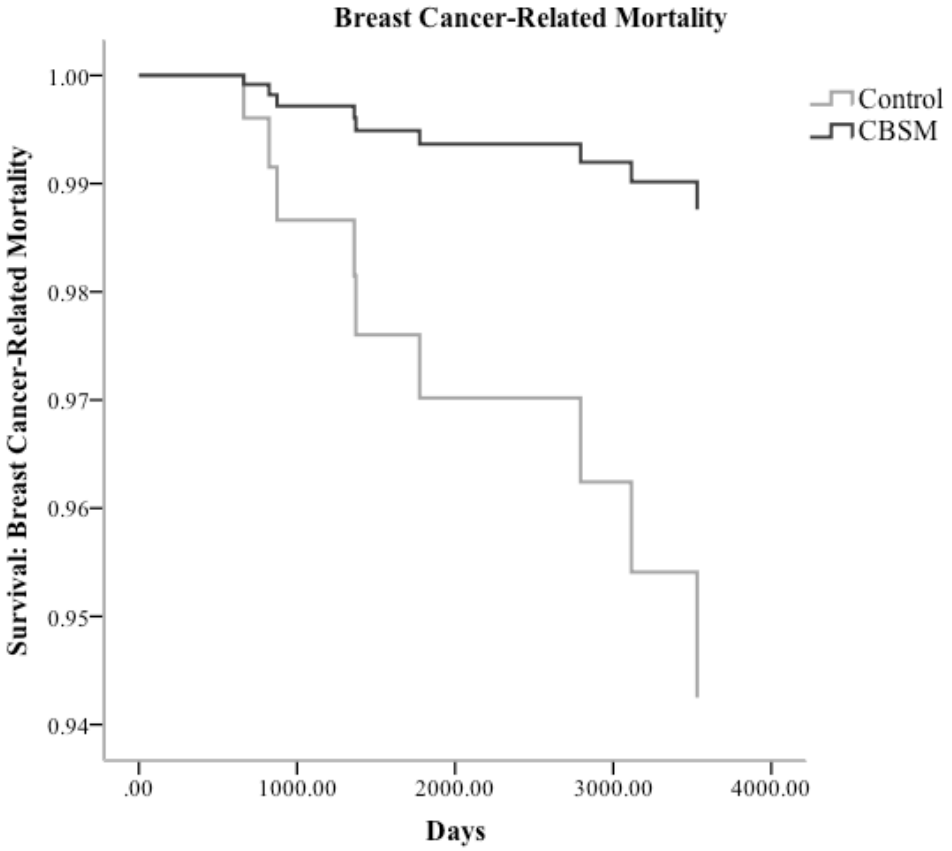

Figure 6. Cox Proportional Hazards Models showing intervention effects on breast cancer-related mortality adjusted for age, time since surgery, stage, HER2neu, tumor size, hormonal therapy, chemotherapy, and radiation therapy. CBSM HR = 0.21 (95% CI [0.05, 0.99]; p = .048). Note: y-axis does not begin at 0.

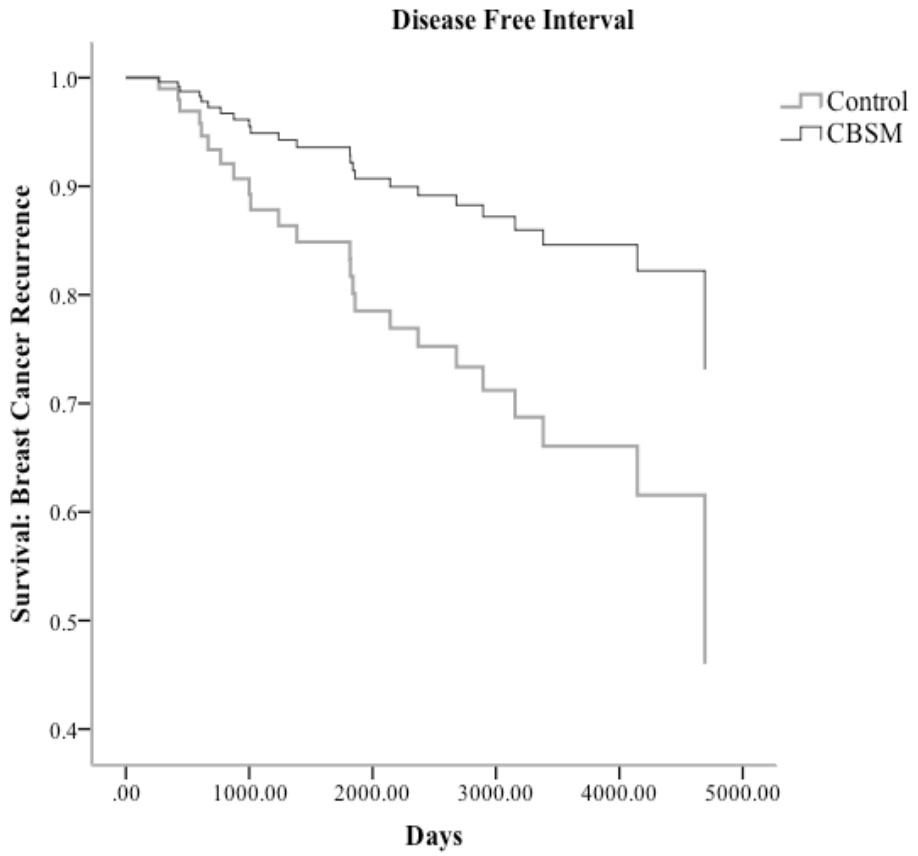

Figure 7. Cox Proportional Hazards Models showing intervention effects on disease-free interval adjusted for age, time since surgery, stage, HER2neu, tumor size, hormonal therapy, chemotherapy, and radiation therapy. CBSM HR = 0.40 (95% CI [0.17, 0.98]; *p* = .044). Note: y-axis does not begin at 0.

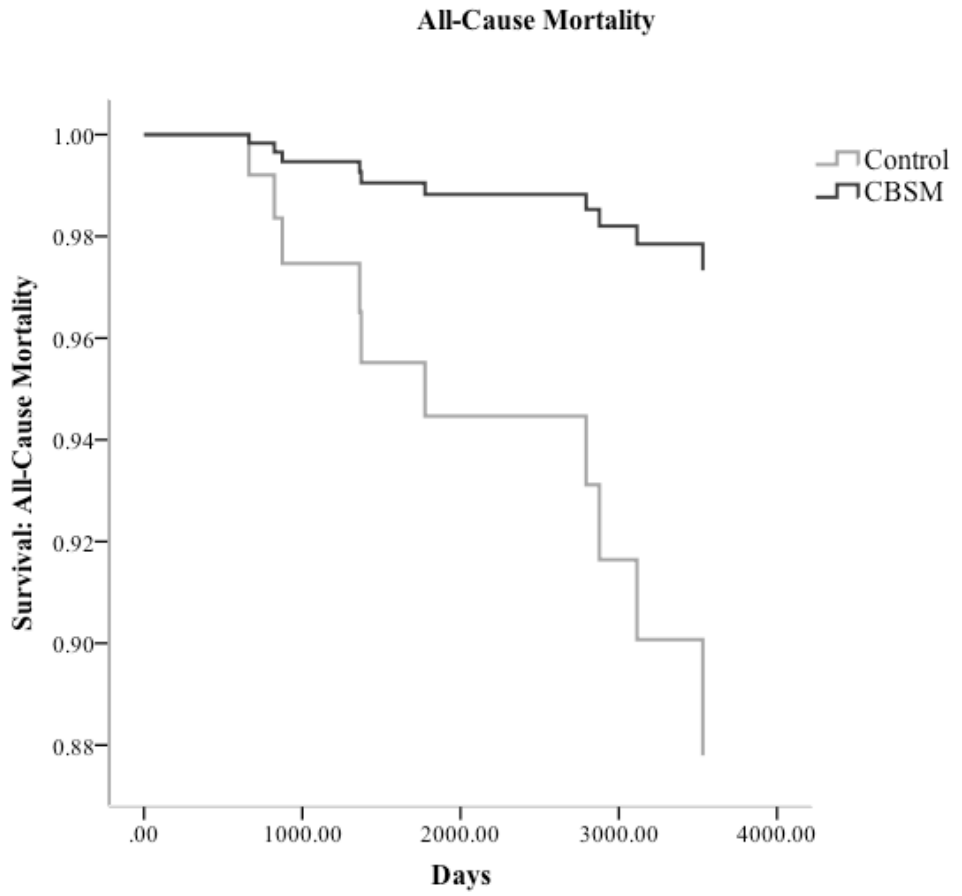

Figure 8. Cox Proportional Hazards Models showing intervention effects on all-cause mortality adjusted for age, time since surgery, stage of disease, HER2neu, tumor size, and hormonal therapy. CBSM HR = 0.21 (95% CI [0.05, 0.91]; p = .037). Note: y-axis does not begin at 0.

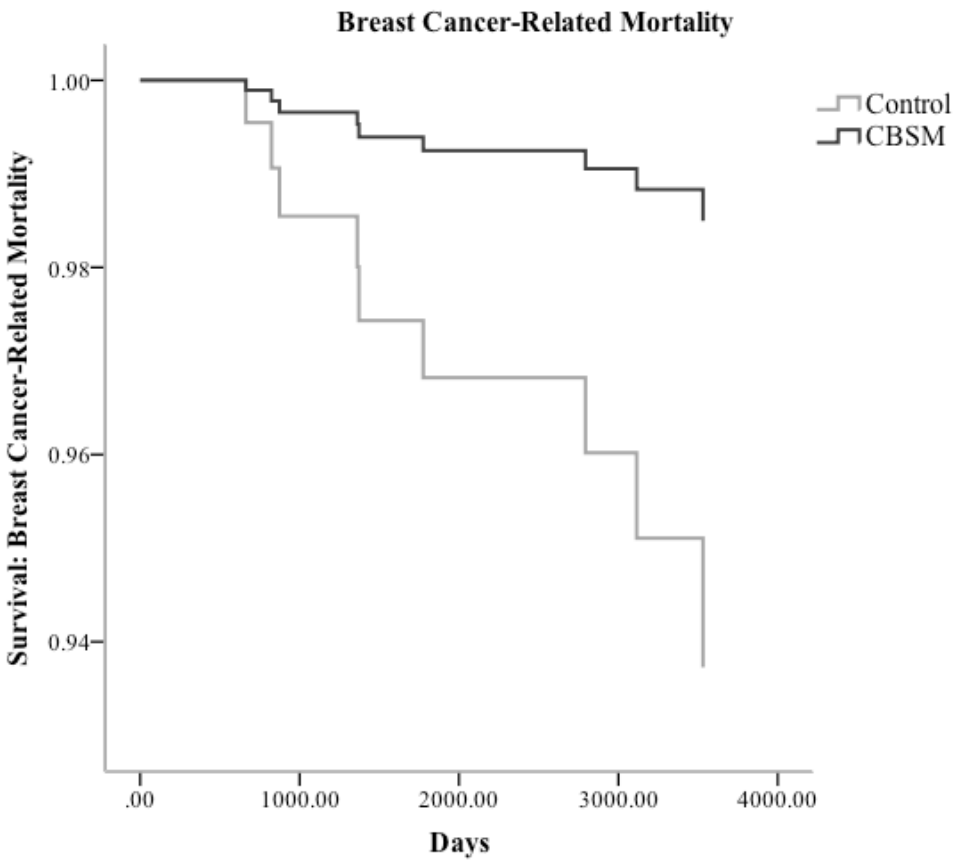

Figure 9. Cox Proportional Hazards Models showing intervention effects on breast cancer-related mortality adjusted for age, time since surgery, stage of disease, HER2neu, tumor size, and hormonal therapy. CBSM HR = 0.23 (95% CI [0.05, 1.08]; p = .063). Note: y-axis does not begin at 0.

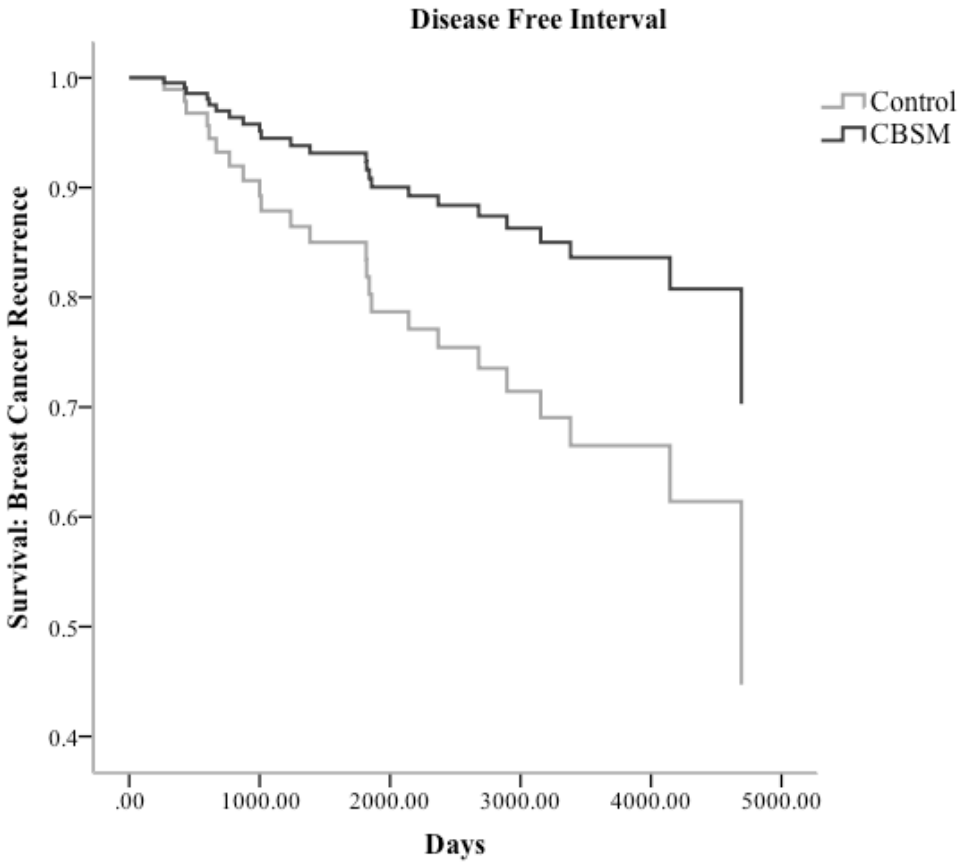

Figure 10. Cox Proportional Hazards Models showing intervention effects on disease-free interval adjusted for age, time since surgery, stage of disease, HER2neu, tumor size, and hormonal therapy. CBSM HR = 0.44 (95% CI [0.18, 1.04]; p = .062). Note: y-axis does not begin at 0.

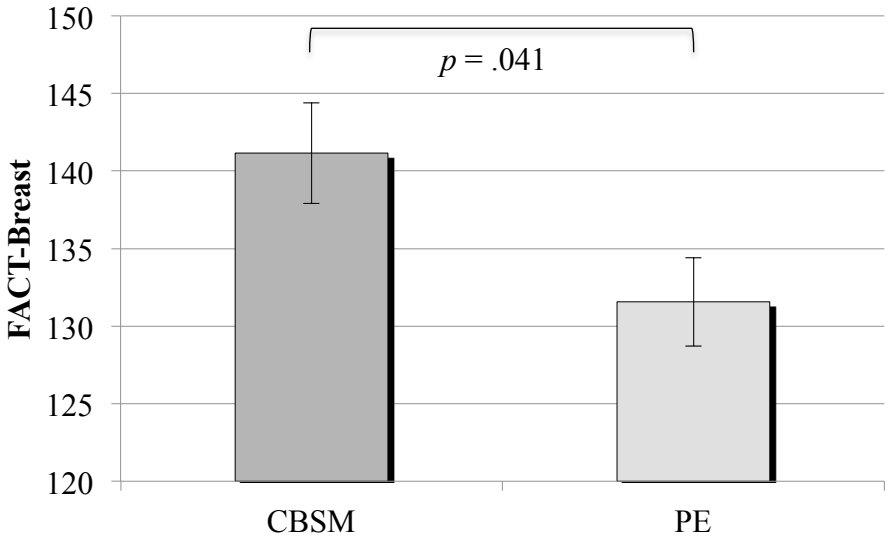

Figure 11. Group differences on FACT-Breast at 8-15 year follow-up in cognitive behavioral stress management (CBSM) vs psychoeducation control (PE). Covariates in the model: age, education, income, race/ethnicity, pain, BMI, and baseline FACT-B score. Error bars reflect the standard error.

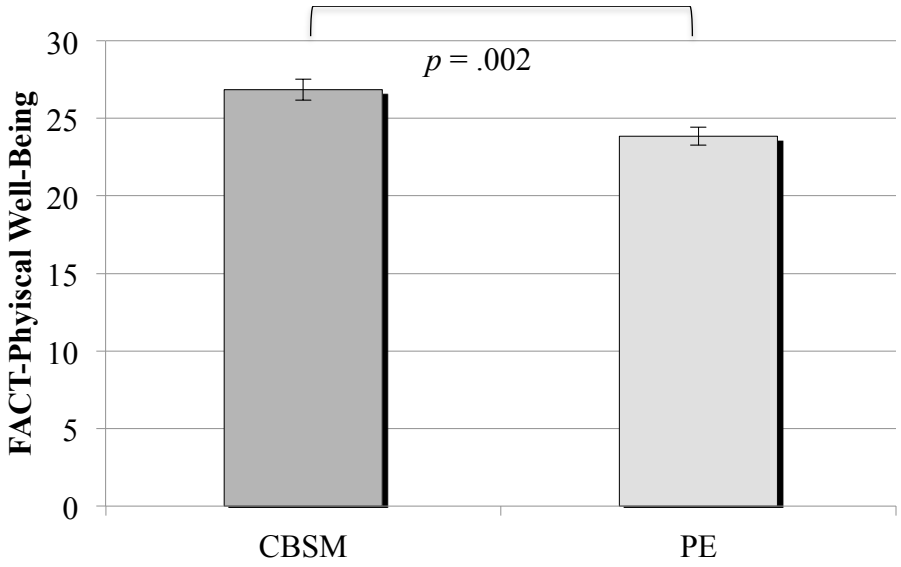

Figure 12. Group differences on FACT-Physical Well-Being at 8-15 year follow-up in cognitive behavioral stress management (CBSM) vs psychoeducation control (PE). Covariates in the model: age, education, income, race/ethnicity, pain, BMI, and baseline FACT-Physical Well-Being score. Error bars reflect the standard error.

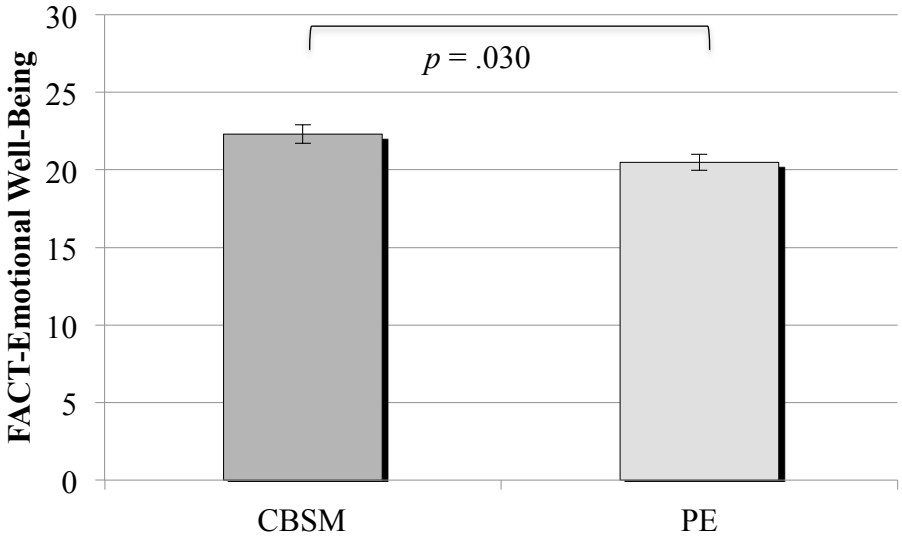

Figure 13. Group differences on FACT-Emotional Well-Being at 8-15 year follow-up in cognitive behavioral stress management (CBSM) vs psychoeducation control (PE). Covariates in the model: age, education, income, race/ethnicity, pain, BMI, and baseline FACT-Emotional Well-Being score. Error bars reflect the standard error.

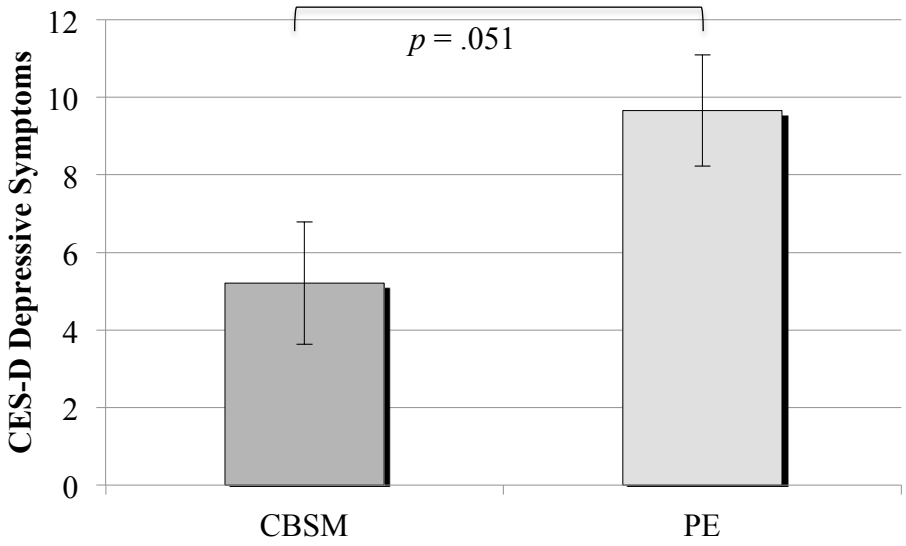

Figure 14. Group differences on CES-D Depressive Symptoms at 8-15 year follow-up in cognitive behavioral stress management (CBSM) vs psychoeducation control (PE). Covariates in the model: age, education, income, race/ethnicity, pain, BMI, and baseline FACT-B score. Error bars reflect the standard error.

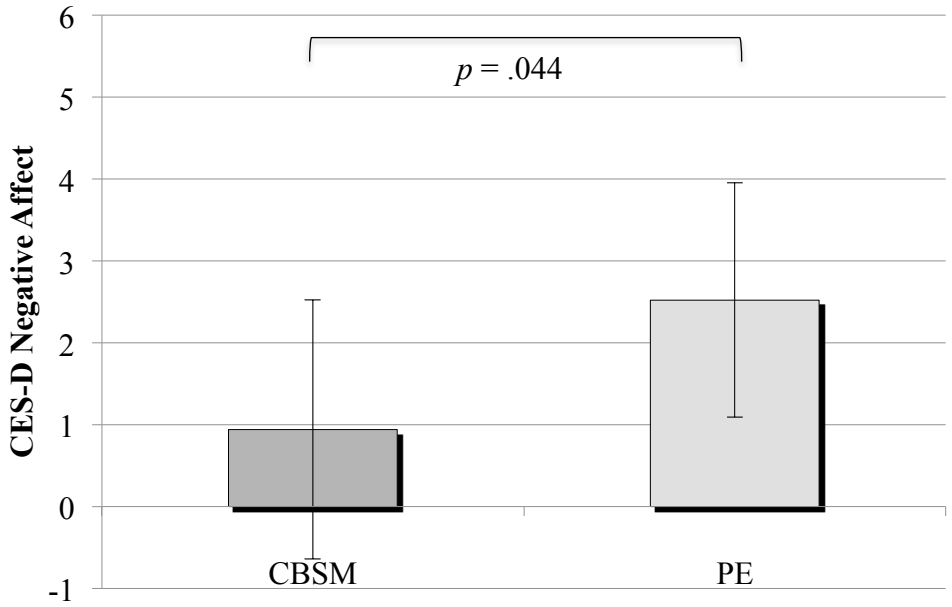

Figure 15. Group differences on CES-D Negative Affect at 8-15 year follow-up in cognitive behavioral stress management (CBSM) vs psychoeducation control (PE). Covariates in the model: age, education, income, race/ethnicity, pain, BMI, and baseline HRSD score. Error bars reflect the standard error.

APPENDIX A

FORMS MAILED IN PACKET

Date

Name
Address
City, FL Zip

Dear Ms. (Name):

A few years ago you were in a project called *Coping and Recovery*, which studied how women adjust after surgery for breast cancer. That study was conducted by the Department of Psychology at the University of Miami. At the time you joined the study, you indicated that you would be willing to let us follow your progress over time. The research team is committed to learning how women have been doing since they competed the initial phase of this study. For that reason we are contacting all of the women who participated to ask about your health status in the years after you completed treatment. We will use this information to help us understand how your initial experiences relate to your present status. After this portion of the study is completed, we would be very happy to send you a complete report about the findings that emerged from the *Coping and Recovery* studies.

If you are willing to continue your involvement in this study, we would like to obtain information about your current health status, in two ways. We kindly ask that you please complete the attached questionnaires, telling us about your health status and mood since your initial treatment. This will take about 10 minutes to complete. We also ask that you give us the name and contact number for your current oncologist. If you are willing to do that, please also complete the authorization form for release of medical information by the oncologist, and send these forms back in the enclosed postage-paid envelope. As always, this information will be used solely for the purposes of research and will be kept completely confidential.

No risks and/or direct benefits are anticipated for your participation. Information will be maintained confidential. If you have any questions about this, please feel free to email us at copingandrecovery@psy.miami.edu, or call us at 305-284-2220, and leave a message. When you call, say that you are calling about the *Coping and Recovery* ***Follow-up*** project. You can also call the *Coping and Recovery* number if you simply want to get more information about the project. Calling in does not obligate you to participate in this portion of the study and you are free to choose to not participate at any point.

We would very much like to hear from you in the coming week!
The Coping and Recovery Project.

Michael H. Antoni, Ph.D.
Principal Investigator
Program Leader in Biobehavioral Oncology
Sylvester Comprehensive Cancer Center

If you have any questions about your rights as a research subject, please contact the University of Miami Human Subjects Research Office at 305-243-3195.

Below are some questions related to your health status. Please mail this form (along with the form on the other page) in the enclosed postage-paid envelope. If you have any questions, please email copingandrecovery@psy.miami.edu or call Jamie Stagl or Laura Bouchard at 305-284-2220.

Your Name: _____

Your Address: _____

_____

Your Phone #: _____

1. In the years since your initial breast cancer diagnosis, have you been diagnosed with breast cancer a second time (had a breast cancer recurrence)?

No ____Yes ____, If yes, where was the recurrence?_____
(ex: breast, lungs, bone)

2. In the years since your initial breast cancer diagnosis, have you been diagnosed with another type of cancer?

No ____Yes ____, If yes, where was the other cancer?_____
(ex: colon, thyroid, ovarian)

3. The oncologist who is following me at this time is:

Physician name: _____

Physician phone number: _____

___ I prefer to answer these questions over the phone and can be reached at:

Day (_____) _____ _____

Evening (_____) _____ _____

Best time to call __a.m. ___p.m.

___I would like more information.

___I am not able or willing to answer questions at this time.

Please don't forget to complete the next form and send both back in the envelope. Thank you!

Authorization to release Medical Information relevant to the research study

I authorize the use or disclosure of health information about me as described below:

1. Person(s) or class of persons authorized to use or disclose the information
Physician (Oncologist) Name and phone number:

_____

2. Person(s) or class of persons authorized to receive the information:
Dr. Michael H. Antoni and authorized research staff

3. Description of information that may be used or disclosed:
Medical information related to breast cancer treatment and diagnosis and current health status

4. The information will be used or disclosed for the following purposes:
At the request of the patient; the information will be used for the purposes of research at the University of Miami.

5. I understand that I may refuse to sign this authorization and that my refusal to sign will not affect my ability to obtain treatment or payment, enrollment, or my eligibility for benefits.

6. I understand that I may revoke this authorization (except to the extent that action has been taken in reliance on it) at any time by sending a written request to:
University of Miami
Coping & Recovery Project
P.O. Box .O. Box 248185
Coral Gables, FL 33124

7. This authorization does not have an ending date. This is because the information used and created for the study may be analyzed for many years, and it is not possible to know when this will be complete.

_____ _____
Signature of Patient or Representative Date

_____
Patient Name

HIPAA Research Authorization Template – Form B

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

I agree to permit the ☐ *University of Miami* ☐ *Jackson Health System* ☐ *both*, and any of my doctors or other health care providers (together "Providers"), Principal Investigator and [*his /her/their/its*] collaborators and staff (together "Researchers"), to obtain, use and disclose health information about me as described below.

1. **The health information that may be used and disclosed may include:**
   - ☐ All information collected during the research and procedures described in the Informed consent Form for the Research as described in the accompanying Informed Consent Form ("the Research"): and
   - ☐ Health information in my medical records that is relevant to the Research, includes my past medical history including medical information from my primary care physician and other medical information relating to my participation in the study; and

[The following checked boxes must be separately initialed by you in order to permit access to these records]

_____ ☐ HIV / AIDS status.
HIV-related information, which includes any information indicating that I have had an HIV-related test, or have HIV infection, HIV-related illness or AIDS, or any information which could indicate that I have been potentially exposed to HIV.

_____ ☐ Sexually transmitted diseases (STD's).

_____ ☐ Mental health treatment records governed under state law (including mental health records relating to involuntary or voluntary mental health treatment).
Mental health records may include substance abuse information.

_____ ☐ Substance abuse (drug and alcohol) treatment records.
Substance abuse information may be part of the mental health records.

_____ ☐ Sexual assault information.

2. **The Providers may disclose health information in my medical records to:**
   - the Researchers;
   - representatives of government agencies, any applicable Cooperative Groups, review boards, and other persons who watch over the safety, effectiveness, and conduct of research; and
   - the sponsor of the Research, National Cancer Institute,
     (Print Sponsor Name)
     and its agents and contractors (together "Sponsor").
3. **The Researchers may use and share my health information:**
   - among themselves, with the Sponsor, with any applicable Cooperative Groups, and with other participating Researchers to conduct the Research; and
   - as permitted by the Informed Consent Form.
4. **The Sponsor and any applicable Cooperative Groups may use and share my health information** for purposes of the Research and as permitted by the consent form.
5. **Once my health information has been disclosed to a third party,** federal privacy laws may no longer protect it from further disclosure.

6. **I hereby authorize the Sponsor to observe any medical procedures I undergo as part of the Research.**

7. **Please note that:**
   You do not have to sign this Authorization, but if you do not, you may not participate in the Research. If you do not sign this authorization, your right to other medical treatment will not be affected.

You may change your mind and revoke (take back) this Authorization at any time and for any reason.
To revoke this Authorization, you must write to either of the following:

***Research Study Personnel Name:** Michael Antoni, Ph.D.

Address: 413 Elipse Building

Tel. No.: 305-284-2220

Human Subjects Research Office

Address: 1500 NW 12th AVE, Suite 1002 Miami, FL 33136

Tel. No.: (305) 243-3195

However, if you revoke this Authorization, you will not be allowed to continue taking part in the Research. Also, even if you revoke this Authorization, the Providers, Researchers, any applicable Cooperative Groups and the Sponsor may continue to use and disclose the information they have already collected to protect the integrity of the research or as permitted by the Informed Consent Form.

While the Research is in progress, you may not be allowed to see your health information that is created or collected by the ☐ *University of Miami* ☐ *Jackson Health System* ☐ *both*, in the course of the Research. After the Research is finished, however, you may see this information as described in the ☐ *University of Miami* ☐ *Jackson Health System* ☐ *both*, Notice of Privacy Practices.

***Study personnel must send copies of participant revocations to:**
Office of HIPAA Privacy and Security AND the Human Subjects Research Office.

8. **This Authorization does not have an expiration (ending) date.**

9. **You will be given a copy of this Authorization after you have signed it.**

_____ _____
Signature of participant or participant's legal representative Date

_____ _____
Printed name of participant Printed name of legal representative (if applicable)

_____
Representative's relationship to participant

Study personnel must send copy with signature to the Office of HIPAA Privacy and Security
For questions, contact the Human Subjects Research Office at 305-243-3195.
****

APPENDIX B

PSYCHOSOCIAL MEASURES AND SCORING

Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Mark how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3. I felt that I could not shake off the blues, even with help from my family or friends.	☐	☐	☐	☐
4. I felt I was just as good as other people.	☐	☐	☐	☐
5. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
6. I felt depressed.	☐	☐	☐	☐
7. I felt that everything I did was an effort.	☐	☐	☐	☐
8. I felt hopeful about the future.	☐	☐	☐	☐
9. I thought my life had been a failure.	☐	☐	☐	☐
10. I felt fearful.	☐	☐	☐	☐
11. My sleep was restless.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I talked less than usual.	☐	☐	☐	☐
14. I felt lonely.	☐	☐	☐	☐
15. People were unfriendly.	☐	☐	☐	☐
16. I enjoyed life.	☐	☐	☐	☐
17. I had crying spells.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt that people disliked me.	☐	☐	☐	☐
20. I could not get "going".	☐	☐	☐	☐

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items (4, 8, 12, and 16) is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

Table 2. Standardized factor loadings and residuals for the CES-D items

Factor item	Standardized factor loadings	Standardized residuals
Depressive Affect		
Blues	0.77	0.64
Depressed	0.80	0.60
Failure	0.63	0.78
Fearful	0.62	0.78
Lonely	0.61	0.79
Crying	0.70	0.71
Sad	0.79	0.61
Well-Being		
Good	0.44	0.89
Hopeful	0.57	0.82
Happy	0.79	0.61
Enjoyed Life	0.82	0.57
Somatic		
Bothered	0.59	0.65
Appetite	0.49	0.87
Mind	0.61	0.79
Effort	0.71	0.70
Sleep	0.51	0.86
Talk Less	0.52	0.85
Get Going	0.69	0.72
Interpersonal		
Unfriendly	0.44	0.89
Disliked	0.66	0.75

Center for Epidemiologic Studies- Depression measure subscale composites (Knight, Williams, McGee, Olaman, 1997)

Functional Assessment of Cancer Therapy- Breast Cancer

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
Q6	On which side was your breast operation? Left Right (please circle one)					
B10	Movement of my arm on this side is painful	0	1	2	3	4
B11	I have a poor range of arm movements on this side	0	1	2	3	4
B12	My arm on this side feels numb	0	1	2	3	4
B13	I have stiffness of my arm on this side	0	1	2	3	4

Functional Assessment of Cancer Therapy- Breast Cancer Scoring Guidelines

All FACIT scales are scored so that a high score is good. To achieve this, we reverse response scores on negatively-phrased questions, then sum item responses. In cases where individual questions are skipped, scores are prorated using the average of the other answers in the scale. The total FACT-G score is obtained by summing individual subscale scores (PWB + EWB + SWB + FWB). Total scores for the disease-, treatment-, and condition-specific subscales are obtained by summing all subscale scores (PWB + EWB + SWB + FWB + additional concerns subscale). For these scales there is also the option to calculate a Trial Outcome Index (TOI). The TOI can be computed for any FACIT disease-, treatment-, or condition-specific scale. It is the sum of the Physical Well-Being (PWB), Functional Well-Being (FWB), and "additional concerns" subscales. Our experience with this TOI endpoint is that it is an efficient summary index of physical/functional outcomes. It is therefore a common endpoint used in clinical trials, because it is responsive to change in physical/functional outcomes, sometimes more than a total (overall) multidimensional aggregated score, which includes social and emotional well-being. While social and emotional well-being are very important to quality of life, they are not as likely to change as quickly or dramatically over time or in response to physical health interventions such as pharmaceutical treatments in clinical trials.

When there are missing data, prorating subscale scores is acceptable as long as *more than* 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc). The total (FACT-G) score is considered appropriate to score as long as *overall item response rate* is greater than 80% (e.g., at least 22 of 27 FACT-G items completed).

(Webster, Cella Yost, 2003)

Affect Balance Scale (ABS)

ABS

Next is a list of words that describe the way people sometimes feel. Please indicate whether you have been having any of these feelings **during the past week, including today.** Indicate the degree to which you have felt *each emotion* by choosing from one of the following responses:

1 = Never
2 = Rarely
3 = Sometimes
4 = Frequently
5 = Always

_____ 1. nervous	_____ 14. calm	_____ 27. guilty
_____ 2. sad	_____ 15. energetic	_____ 28. enraged
_____ 3. regretful	_____ 16. loving	_____ 29. delighted
_____ 4. irritable	_____ 17. tense	_____ 30. relaxed
_____ 5. happy	_____ 18. worthless	_____ 31. vigorous
_____ 6. pleased	_____ 19. ashamed	_____ 32. affectionate
_____ 7. excited	_____ 20. angry	_____ 33. afraid
_____ 8. passionate	_____ 21. cheerful	_____ 34. unhappy
_____ 9. timid	_____ 22. satisfied	_____ 35. remorseful
_____ 10. hopeless	_____ 23. active	_____ 36. bitter
_____ 11. blameworthy	_____ 24. friendly	_____ 37. joyous
_____ 12. resentful	_____ 25. anxious	_____ 38. contented
_____ 13. glad	_____ 26. miserable	_____ 39. lively
		_____ 40. warm

(Derogatis, 1975)

Primary Measurement Constructs: Principal dimensions of positive and negative emotional experience, with a particular emphasis on affects balance.

Description

The DABS is a multidimensional self-report mood and affects inventory comprised of 40 adjective-items. The DABS measures affectivity and affects balance via 8 primary affects dimensions and five global scores. The positive affects dimensions are labeled joy, contentment, vigor and affection. The negative dimensions are anxiety, depression, guilt and hostility. The DABS global scores consist of the Positive Total score (PTOT), Negative Total score (NTOT), and the Affects Balance Index (ABI). Recently, two additional globals, the Affects Expressiveness Index (AEI) and the Positive Affects Ratio (PAR), were developed, and a brief form of the scale, the DABS-SF, has been normed and introduced.

The primary dimensions of the DABS are designed to reflect the principal components of positive and negative emotional experience, while the five global scores are intended to communicate an overall or summary picture of the respondent's emotional status and well- being. The Positive Affects Total (PTOT) is defined as the sum of all scores on the four positive affects dimensions of joy, contentment, vigor and affection. Similarly, the Negative Affects Total (NTOT) is represented as the sum of scores on the four negative dimensions of anxiety, depression, guilt and hostility. The Affects Balance Index (ABI) is algebraically defined as (PTOT-NTOT)/ 20, and conveys the degree of balance or symmetry between positive and negative emotional experiences. The Affects Expressiveness Index (AEI) is defined as the sum total of affective expression, regardless of valence (i.e., regardless of positive or negative direction). It illustrates the individual's affective "charge" or total level of affectivity. The Positive Affects Ratio (PAR) illustrates a distinct approach to measuring global affective status. It is defined as the ratio of positive affectivity to total affectivity (i.e., positive plus negative affectivity) on the DABS. The PAR reflects the proportion of affective experience represented as positive emotion.

Derogatis, LR (1996) Derogatis Affects Balance Scale (DABS): Preliminary Scoring, Procedures & Administration Manual. Baltimore, MD, Clinical Psychometric Research.