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Cognitive Behavioral Stress Management Effects on Social Well-Being, Negative Affect, and Inflammation After Surgery for Breast Cancer

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COGNITIVE BEHAVIORAL STRESS MANAGEMENT EFFECTS ON SOCIAL WELL-BEING, NEGATIVE AFFECT, AND INFLAMMATION AFTER SURGERY FOR BREAST CANCER

By

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Many women experience distress during diagnosis and treatment of breast cancer, and research suggests that satisfaction with access to social resources both decreases psychological distress and improves duration of survival after breast cancer diagnosis. However, biobehavioral mechanisms linking interpersonal processes to mental and physical health are poorly understood. Studies are also needed to elucidate whether psychosocial interventions that improve social well-being and psychological health affect biological outcomes known to promote cancer disease progression (e.g., inflammation).

This study examined a subsample of 78 women enrolled in a 10-week randomized controlled trial of cognitive behavioral stress management (CBSM) at the University of Miami for women diagnosed with early-stage (0 – III) breast cancer. Data for this dissertation were collected at baseline, 2 – 19 weeks after breast cancer surgery (T1), and 6 months later, post-intervention (T2). Aim 1 was to determine whether baseline social well-being related to negative affect, pro-inflammatory and pro-metastatic leukocyte gene expression, and pro-inflammatory serum cytokines. Aim 2 tested whether negative affect mediated the association between social well-being and disease promoting factors. Aim 3 was longitudinal and examined whether CBSM (versus an active control condition)

improved social well-being and decreased negative affect and pro-inflammatory and pro-metastatic leukocyte gene expression. Conditional mediation analyses were planned to determine whether CBSM effects on negative affect were mediated by increased social well-being (Aim 4), and whether CBSM effects on leukocyte gene expression were mediated by negative affect (Aim 5).

The Social/Family Well-Being subscale of the FACT-B assessed social well-being and the Negative Affect subscale of the Affects Balance Scale measured negative affect. Microarray analysis was used to quantify leukocyte gene expression for specific pro-inflammatory (cytokines, chemokines, and COX-2) and pro-metastatic genes, and ELISA was used to quantify serum concentrations of pro-inflammatory cytokines. Multiple regression analyses using SPSS Statistical Software and controlling for age, stage of disease, days since surgery, and education, with and without body mass index (BMI), were conducted.

Results showed that higher levels of social well-being cross-sectionally related to lower levels of negative affect and markers of inflammation and disease-promoting processes at baseline. However, findings did not support the hypotheses that the CBSM intervention would improve social well-being and reduce negative affect and leukocyte gene expression over the 6-month observation period in this sample of women. Meditational hypotheses were not supported. It is possible that the small sample size and short follow-up period limited ability to detect effects. Results have implications for our understanding of the mechanisms linking social resources to biological processes that may relate to health outcomes, and for the development of psychosocial interventions to improve social adaptation to breast cancer.

ACKNOWLEDGMENTS

The results described in this dissertation have been published in Jutagir et al. (2017), and some passages have been quoted verbatim.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: INTRODUCTION

Breast cancer is the second leading cause of cancer deaths among women (American Cancer Society, 2013; Jutagir et al., 2017). Almost half of these women experience significant symptoms of depression, anxiety, or both during diagnosis and treatment of their cancer (Burgess et al., 2005). Studies suggest that perceptions of inadequate social resources deleteriously affect psychological adaptation (Garner et al., 2015) in women at risk of breast cancer and survival (Kroenke et al., 2013) in women diagnosed with breast cancer. However, additional research is needed to uncover the biopsychosocial processes that explain the survival disadvantage in breast cancer patients reporting deficits in such resources.

This study examines whether social well-being, operationalized as satisfaction with perceived resources, relates to biological processes associated with cancer progression in women with breast cancer. The study focuses on molecular indicators of inflammatory signaling. Specifically, this work seeks to understand the association between greater social well-being and markers of lower inflammatory signaling and disease promoting factors, and whether this association is mediated through decreased negative affect among women examined after surgery for breast cancer. Furthermore, this study explores whether a post-surgery group-based cognitive behavioral stress management (CBSM) intervention decreases inflammatory and disease promoting factors 6 months later and whether these changes are explained through social well-being and negative affect as mediators. Understanding the biobehavioral pathways through which social well-being relates to inflammatory and disease-promoting factors during breast cancer treatment as well as the pathway through which CBSM improves these outcomes

has the potential to inform development of interventions to improve psychological and physiological adaptation to breast cancer.

Social Well-Being and Adaptation to Breast Cancer

Defining Social Well-Being

Interpersonal factors play a key role in how women adapt to breast cancer diagnosis and treatment (Andrykowski, Lykins, & Floyd, 2008). Delineating salutary aspects of social interactions is crucial to understanding how they affect health. Much of the prior work on interpersonal factors in cancer has focused on social support. Hupcey (1998) reviewed literature on theories of social support and summarized that researchers concur that social support is multidimensional and consists of social networks, supportive behaviors, and subjective appraisals of support. Given these multiple facets of social support, this construct has been operationalized in a variety of ways. With regard to support network, variables such as size of the network or whether the patient has a spouse or partner are often analyzed as a proxy for social support (Chamie et al., 2012). However, such structural variables are limited; for example, they do not capture whether network members are actively engaging with the patient.

Measuring specific supportive behaviors, specifically the amount and type of support provided to the recipient, provides a more nuanced assessment of social resources. Emotional support, such as being comforted by another person, informational support, such as being given information about breast cancer or treatment options, and instrumental support, such as being given a ride to a medical appointment, have all been proposed to confer health advantages (Helgeson & Cohen, 1996). Emotional support is consistently associated with adjustment to cancer (Helgeson & Cohen, 1996).

It is increasingly understood that a patient must perceive and be *satisfied* with these social support gestures from others before they translate into the feeling of social well-being associated with improved mental and physical health outcomes. For that reason, Helgeson (2003) posits that perceived social support specifically is an essential indicator of adjustment. Simply being part of a large social network or having close relationships does not appear to be sufficient to be protective; rather, it is feeling less lonely that is associated with better health (Rico-Uribe, 2016). Even if breast cancer patients perceive emotional support, they may not feel satisfied by the support offered. Patients may become dissatisfied when family and friends provide a form of support incongruent with the support they want, such as offering a comment that is not perceived as comforting, or by offering emotional support when the patient is more in need of instrumental support (Reynolds & Perrin, 2004). Therefore, studies of adaptation to breast cancer are increasingly collecting self-reports of each patient's *social well-being*. Assessing social well-being in a woman diagnosed with breast cancer is particularly informative given that this construct not only captures a respondent's level of interaction with her social network, but also encompasses her quality of life that stems from relationships and sexuality, social factors that may change after a cancer diagnosis (Ferrell et al., 2003). Given that social well-being assesses satisfaction with perceived social support from a variety of sources, it is possible that it is linked to psychological and physiological adaptation to breast cancer.

Compromised Social Well-Being

Many women note challenges to their social well-being after a breast cancer diagnosis. Some women may have few social connections (i.e., a small social network),

leaving them without anyone to ask for assistance or comfort. However, as noted earlier, even women integrated into sizable social networks may not perceive those in their network as helpful. Nearly half of women surveyed reported that family members and friends minimized their breast cancer diagnosis, avoided facing it, or became uncomfortable when talking about cancer (Mosher et al., 2013).

In fact, a social support network has the capacity to create distress due to the social interactions that are required of the breast cancer patient. Even supposedly supportive social overtures can actually entwine patients in arguments, or create openings for others to criticize them (Lincoln, Taylor, & Chatters, 2003). Some of these conflicts stem from mismatches between the type of support that a patient desires and the type of support that support sources are able to contribute (Antoni, 2003). Each of these types of situations could leave a patient without access to the various domains of support, or feeling lonely (Cole et al., 2007). Notably, social well-being deficits are particularly acute during the stressful phases of breast cancer diagnosis and adjuvant treatment (Hanson Frost et al., 2000). Further research is warranted to understand the implications of level of social well-being in the period after breast cancer diagnosis for psychological and physiological health.

Social Well-Being Relates to Health and Mortality

The existing research suggests that social well-being deficits are detrimental to physical health. Across a range of illnesses, those who report disturbances in social and emotional support are at higher risk of poorer physical health outcomes (Reblin & Uchino, 2008). Lyyra and Heikkinen (2006) found that in older adult women, low perceived emotional support more than doubled mortality risk, even when controlling for

physical health at a baseline assessment 10 years prior. Even among healthy research participants, those who perceived more instances of negative social interactions with their family and friends are at increased risk of developing chronic health conditions including arthritis and diabetes (Hill, Weston, & Jackson, 2014).

In women with breast cancer specifically, it has repeatedly been shown in large samples that social isolation relates to decreased survival. In a study of 2,835 women diagnosed with breast cancer, those who reported limited social networks prior to diagnosis showed a two-fold increase in breast cancer mortality and were also at increased risk of all-cause mortality (Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi, 2006). Another study of women diagnosed with breast cancer showed that social support is protective against mortality from various causes and reduced risk of death by 15 – 28% (Beasley et al., 2010). Epplein et al. (2011) assessed social well-being 6 months and 36 months after breast cancer diagnosis and conducted a follow-up with them at a median of 4.8 years post-diagnosis. Those women who had endorsed high social well-being at 6 months post-diagnosis had a 38% lower mortality rate and a 48% reduction in risk of breast cancer recurrence as compared with women with low social well-being. Notably, this association did not exist when quality of life was reported at 36 months post-diagnosis, indicating the importance of evaluation of social well-being during the months directly following diagnosis and treatment of breast cancer. Thus, poor social well-being is associated with increased morbidity and mortality, and this finding holds among women diagnosed with breast cancer. Further research is needed to understand mechanisms through which social well-being could decrease odds of recurrence and promote survival after diagnosis of breast cancer.

Social Well-Being, Inflammation, and Cancer Progression

The association between social processes and compromised health is well documented, but the specific biopsychosocial pathways through which lack of social well-being advances disease progression or shortens lifespan are less clear. Miller, Chen, and Parker (2011) postulate that deprivation, including lack of social resources, fosters vulnerability to chronic illness through inflammatory processes. Cole (2013) detailed a rationale for why such a causal link between social isolation and increased inflammation may have evolved. According to this theory, lack of social resources contributes to up-regulation of the inflammatory response to protect against bacterial infections, which are more likely to occur in cases of isolation and subsequent vulnerability to physical aggression (Cole, 2013). When lack of social resources becomes chronic, the concomitant elevation in inflammatory reactivity increases susceptibility to illness and promotes cancer progression (Cole, 2013).

In a review of this literature, Antoni, Lutgendorf et al. (2006) describe how psychosocial factors influence immune functioning. Social isolation can result in negative cognitions and emotions, which create a state of mental stress and activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. In response to psychosocial stress, the autonomic nervous system, specifically the sympathetic nervous system (SNS), activates the fight or flight response. Norepinephrine and epinephrine are released and target cardiac, respiratory, and vascular systems, among others. Simultaneously, the hypothalamus produces corticotropin-releasing factor and arginine vasopressin, which trigger the pituitary gland to release adrenocortico-tropic hormone, the effect of which is to stimulate secretion of glucocorticoids. In particular,

cortisol is released and assists in liberating glucose from glycogen in tissue and increasing energy (Kudielka & Kirschbaum, 2005), regulating the activity of biological systems and diverting energy to enhance threat survival.

Although SNS and HPA axis activation have long been studied, the manner in which stress hormones exert influence upon tumor growth is only recently being elucidated. It is possible that this relationship is mediated by inflammatory mechanisms. In response to stress, one manner in which glucocorticoids preserve energy is through inhibiting factors that facilitate transcription of deoxyribonucleic acid (DNA) to ribonucleic acid (RNA) for genes involved in inflammatory pathways in leukocytes (Cole et al., 2007). However, during social isolation, glucocorticoid elevation can become chronic and may actually exist in tandem with upregulated inflammation. It is posited that this counterintuitive phenomenon occurs when cells (e.g., leukocytes) become desensitized to chronically elevated cortisol release; therefore, transcription of genes coding inflammatory cytokines and production of these proteins ceases to be inhibited (Cole et al., 2007). Taken together, these studies suggest that chronic stress can disable a regulatory mechanism for inflammation, leading to increased levels of inflammation accompanying social isolation.

Inflammation, part of the immune system's natural wound healing response, can in turn directly contribute to tumor development. A primary defense against pathogens is production of free radicals by inflammatory cytokines (Rakoff-Nahoum, 2006). Free radicals are positively or negatively charged molecules that contain an unpaired electron. They are highly reactive, stripping electrons from other molecules that are consequently rendered useless. The presence of some free radicals can be beneficial in incapacitating

microbes and pathogens. However, these molecules become detrimental when inflammation is chronic in the absence of a pathogen, and free radicals instead target cells essential to human functioning. One particularly vulnerable target is DNA. Broken DNA strands may be incorrectly repaired, resulting in harmful mutations. If the interruption occurs in a segment coding a gene relevant to tumor suppression, the gene becomes inactive and tumor proliferation may ensue (Khansari, Shakiba, & Mahmoudi, 2009). Via inflammation, stress hormones may damage DNA and thereby contribute to tumor growth.

There is also evidence that the release of stress hormones fuels cancer progression through the mechanism of increased metastasis. Stress hormones can initiate the release of matrix metalloproteases (MMPs) by tumor cells (Lutgendorf & Sood, 2011). These enzymes facilitate remodeling of the extracellular matrix, which is integral to the metastasis of the tumor. They also enhance angiogenesis, the process of creating a network of blood vessels to support the tumor (Rakoff-Nahoum, 2006). Thus, stress hormones may facilitate tumor metastasis and tumor growth via inflammatory processes.

Evidence from studies of women diagnosed with ovarian cancer lends support to the notion of links between social well-being and inflammation and metastasis. Measurements of immune markers among those women who report low levels of emotional support and social well-being indicate increased levels of tumor promoters [vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), matrix metalloproteases (MMPs; Lutgendorf et al., 2002; Lutgendorf et al., 2008)], and leukocyte inflammatory gene expression for these tumor promoters (Lutgendorf et al., 2008). Longitudinal studies of these women reveal that low emotional support is associated with decreased survival

(Lutgendorf et al., 2012). Compromised social well-being in women with cancer thus has the potential to enhance inflammation, increase tumor proliferation, and shorten lifespan.

Initial studies suggest that low social well-being is also associated with immune dysregulation in the context of breast cancer. Fagundes et al. (2012) studied a sample of women who had received abnormal mammograms or were diagnosed with breast cancer. Among highly educated women in this group, those who reported higher levels of perceived social support from their friends also displayed lower levels of Epstein-Barr virus (EBV)-viral capsid antigen (VCA) antibody titers, indicating a more robust cellular immune control over latent EBV-VCA.

In a study investigating social support and inflammation specifically, Hughes et al. (2014) discovered further evidence that low perceived social support weakens immune functioning in breast cancer. The investigators collected blood samples and self-reports of social support and depressive symptoms from women diagnosed with non-metastatic disease before treatment and 6 months after the end of treatment. Findings revealed that lower perceived support predicted higher serum levels of interleukin-6 (IL-6), a pro-inflammatory cytokine, at 6 months, even after controlling for baseline IL-6. Importantly, this study also found that lower baseline social support predicted higher depressive symptoms at 6 months. However, one limitation of this study is that it did not use mediation analysis to examine whether low social support related to inflammation via depression. Furthermore, this study did not examine inflammatory association with social well-being specifically. This growing literature suggests that lack of social support is predictive of immune dysfunction in breast cancer, but the specific pathway through which social well-being could affect inflammation remains under researched.

Negative Affect as a Mediator of the Relationship Between Social Well-Being and Inflammation

Social Well-Being and Negative Affect

Extant research suggests that lower levels of social well-being may dysregulate inflammatory processes by increasing negative affect. Given that women diagnosed with cancer often also report significant distress and fear about their prognosis, substantial literature has explored whether feeling supported by others is protective against such negative emotions. Schleife, Sachtleben, Barboza, Singer, and Hinz (2014) found that high perceived social support was cross-sectionally related to lower anxiety in 107 outpatients diagnosed with breast cancer. Another sample of 114 women diagnosed with non-metastatic breast cancer were assessed by Boinon et al. (2014) through self-report questionnaires on social support, depressive symptoms and cancer-related distress after surgery and again after completion of adjuvant treatment.

Results revealed that higher negative support and avoiding sharing emotional reactions to cancer after surgery were associated with more intrusive thoughts related to cancer at the end of adjuvant treatment. Lower access to social support may also create vulnerability to depressive symptoms in women diagnosed with breast cancer. Lee et al. (2011) found that decreases in emotional support in the year following early-stage breast cancer diagnosis predicted deteriorations in depressive mood in a sample of 286 women. In another sample of women diagnosed with primarily early-stage breast cancer, Talley, Molix, Schlegel, and Bettencourt (2010) found that greater perceived emotional support from partners specifically was associated with decreased depression symptomology during radiation treatment for breast cancer. Taken together, these studies indicate that

poor quality of social support is associated with higher anxiety and depression during cancer treatment, though studies examining social well-being specifically are needed.

Initial studies on the contribution of social well-being to negative affect have been conducted in the context of gynecologic cancer and breast cancer. Kimmel et al. (2014) assessed 187 women diagnosed with a gynecologic malignancy for anxiety and social well-being. Social well-being was significantly negatively related to anxiety, and in fact was more strongly related to anxiety than were history of psychiatric diagnosis, use of a psychotropic medication, age, cancer type, cancer stage, recurrence, and treatment complications. More recently, Gold et al. (2016) found in a study of 335 women post-surgery for breast cancer that those categorized as high in anxiety with subsyndromal depression reported lower social well-being than those with lower anxiety, depressive symptoms, or both. In sum, women can experience a variety of negative psychological reactions over the course of diagnosis and treatment for breast cancer, including depression and anxiety, and those who can discuss these responses with and get assistance from others in their social network may be protected against worsening of these negative emotions. However, further work is needed to demonstrate whether social well-being specifically is associated with negative affect after breast cancer diagnosis.

Negative Affect and Inflammation

There is evidence that in addition to the mental health concerns caused by worry and sadness after diagnosis of breast cancer, these negative emotions may also detrimentally affect physiological adaptation to disease. A significant body of literature links levels of depression and inflammation in community and clinical populations (Howren, Lamkin, & Suls, 2009) as well as in cancer patients (Aldea, Craciun,

Tomuleasa, & Crivii, 2014; Sotelo, Musselman, & Nemeroff, 2014). A study of women diagnosed with ovarian cancer found that transcription of genes related to disease progression was elevated in women characterized as high in depressive symptoms and low in emotional support (Lutgendorf et al., 2009). A recent study examined associations between depressive symptoms and the serum pro-inflammatory cytokines most commonly studied in biobehavioral oncology research, IL-6, IL-1β, and TNF-α, in patients who just underwent surgery for early-stage breast cancer (Bouchard et al., 2016). Higher depressive symptomology was associated with higher levels of IL-1β and TNF-α. Importantly, the significant relationship between depressive symptoms and IL-1β held after controlling for body mass index (BMI). Adipose tissue generates inflammatory markers, and obesity is positively associated with inflammation (O'Connor et al., 2009). Yet, the results published by Bouchard et al. (2016) suggested that depressive symptoms are associated with inflammation above and beyond the influence of BMI. Based on the extant literature, there is reason to believe that depression is associated with inflammation during early-stage breast cancer.

Given the support for an association between depression and inflammation, researchers have explored whether other negative emotions, such as anxiety, are also linked to inflammation during treatment for breast cancer. Jehn et al. (2012) assessed clinical anxiety and depression as well as IL-6 levels in 70 women being treated with chemotherapy for metastatic breast cancer and found that both psychological states were positively associated with inflammation. Another recent study of 398 women diagnosed with non-metastatic breast cancer found that women who were characterized as high in anxiety were more likely to have a specific polymorphism of tumor necrosis factor-α

(TNFα), which encodes a pro-inflammatory cytokine, associated with inflammation and elevated fatigue (Miaskowski et al., 2015). Studies that have not found associations between depression or anxiety and inflammation in breast cancer have been limited by small sample size or by assessment of women during screening rather than post-diagnosis (Kamath et al., 2012), or have indicated that inflammation may be associated with a specific symptom of depression, such as fatigue (Bower et al., 2011). Given findings that depression and worry are associated with inflammation, further research into whether this relationship holds during the sensitive period between surgery and completion of adjuvant treatment for breast cancer is warranted.

In light of these findings that several negative emotions are linked to both social well-being and inflammation, investigating whether a composite construct, namely negative affect, links the two is appropriate. Self-reports of low emotional support from friends and low instrumental support from spouses prior to surgery for stage 0-II breast cancer predicted higher psychological distress after surgery as operationalized by a scale that included anxiety and depression (Alferi, Carver, Antoni, Weiss, & Durán, 2001). Furthermore, in early-stage breast cancer specifically, a measure of negative affect that included assessment of depression and anxiety correlated with greater leukocyte pro-inflammatory gene expression (Antoni et al., 2012).

Additional research is needed to understand the association between negative affect and social well-being during breast cancer, and whether negative affect mediates the relationship between social well-being and inflammation and disease progression. Based on prior literature, candidate markers to study include those coding for pro-inflammatory cytokines, proteins that signal to other cells (*IL1A*, *IL1B*, *IL6*, *TNFSF10*,

TNFRSF21, and *PTGS2*), chemokines, a subset of cytokines that signal for immune activity at wound sites (*CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*), and other pro-inflammatory and tumor-promoting factors that break down extracellular structures and facilitate metastasis (*MMP9* and *LMNA*) (Antoni et al., 2012; see Table 1).

Taken together, literature suggests that low social well-being relates to high negative affect and that high negative affect is also associated with greater inflammation in cancer patients. It is therefore plausible that negative affect mediates the relationship between low social well-being and pro-inflammatory gene expression in this population.

Cognitive Behavioral Stress Management and Adaptation to Breast Cancer

Given that social well-being and negative affect relate to levels of inflammation after diagnosis of breast cancer, it could be hypothesized that participation in a psychosocial intervention designed to enhance social well-being and decrease negative affect could decrease inflammation over the course of treatment for breast cancer. Spiegel, Bloom, Kraemer, and Gottheil (1989) found that women diagnosed with metastatic breast cancer who participated in a group-based supportive therapy intervention lived on average 17 months longer than their counterparts in a usual care control condition. Other psychosocial interventions have been implemented to improve quality of life and multiple domains of health outcomes in women diagnosed with early-stage breast cancer.

Cognitive behavioral stress management (CBSM) was designed specifically to empower groups of medically ill patients with tools to access the forms of social support they need and regulate their mood (Antoni, 2003). Over the course of 10 weekly sessions, patients are taught a variety of relaxation techniques, including progressive muscle

relaxation, and are taught to identify and restructure unhelpful thoughts that lead to negative emotions and maladaptive behaviors. Patients engage in discussion of three interpersonal communication topics: 1) social support, 2) assertiveness, and 3) anger management. Throughout these modules, patients learn to identify types of support they lack, overcome barriers to requesting support from members of their social networks, and navigate disagreements with support sources.

Randomized controlled trials have found that CBSM succeeds at improving psychological adaptation to breast cancer as compared with control groups. One study of CBSM randomized 199 women diagnosed with non-metastatic breast cancer to a 10-week CBSM intervention or to a 5-hour seminar that consolidated CBSM material into an educational format. At 6 months after enrollment, women in the experimental condition reported that they experienced less intrusive thoughts about breast cancer (Antoni, Wimberly et al., 2006). This reduction in intrusive thoughts persisted until 1 year after enrollment, at which time interviewer-rated anxiety and negative affect were also lower in women who had received CBSM (Antoni, Wimberly et al., 2006). Although the study did not report on social well-being per se, Antoni, Lechner et al. (2006) did find lower reports of illness-related disruption in social interactions at both the 6-month and 1-year timepoints. It is possible that women who participated in CBSM internalized skills on communicating about breast cancer with others in their social networks and therefore felt less compelled to avoid social activity.

It should be noted that the studies discussed above were limited in comparing CBSM to a one-day seminar, so the effect of developing relationships through weekly meetings with a group of women encountering similar challenges was not controlled.

Nevertheless, results are consistent with outcomes from another randomized controlled intervention trial in which some participants were assigned to an 18-week group to learn stress management skills, including how to build support networks (Andersen et al., 2004). Women in the intervention group reported reduced anxiety and improved perceived social support from family 4 months later, as compared with participants only receiving treatment as usual. However, more research is needed to understand whether CBSM is effective in providing women with resources for enhancing their social networks during treatment for breast cancer.

The effects of CBSM intervention for breast cancer are long lasting. Five years after enrolling in CBSM, women with breast cancer still reported fewer depressive symptoms than their counterparts in the control condition (Stagl et al., 2014). Eleven years after the intervention commenced, self-reported depressive symptoms remained lower in CBSM participants, and women reported that they were more satisfied with their physical and emotional quality of life (Stagl, Bouchard et al., 2015).

Overall, recent randomized controlled trials indicate that CBSM components, not simply weekly group meetings, enhance wellbeing. One recent study of black breast cancer survivors who participated in CBSM or a time- and attention-matched control group after completing treatment for breast cancer did find that depression was reduced in both groups (Lechner et al., 2014). These findings initially suggest that simply gathering regularly with a group of women from the same cultural background may account for health effects. However, Lechner et al. (2014) note that the active control condition also introduced participants to information on treatment of breast cancer and communication with the health-care team that may have been sufficient to decrease

anxiety in this largely low-income group. It should also be noted that psychosocial issues change after the end of treatment for breast cancer; therefore, the results of this study may not generalize to women who have just been diagnosed and begun treatment for breast cancer.

In a more recent study, Gudenkauf et al. (2015) randomized women post-surgery who were receiving treatment for breast cancer to 2 groups training different active components of CBSM, cognitive behavioral therapy (CBT) and relaxation training (RT), and compared their outcomes to those of women randomized to a health education (HE) time- and attention-matched control group. Compared to women receiving RT and HE, women trained in CBT, who learned to break down psychological barriers to mobilizing their support networks, reported greater increases in their perception of instrumental support and in their emotional well-being and also reported less intrusive thoughts about cancer post-intervention. Taking into account limitations of CBSM intervention trials and considering the most recent trial, research suggests that the components of CBSM enhance social support and improve psychological adaptation to breast cancer beyond the effects of gathering in a group.

Although CBSM was designed to enhance social support and decrease psychological stress, it has recently been found to decrease all-cause mortality and breast cancer-related mortality (Stagl, Lechner et al., 2015), and it is possible that these effects are due to improved physiological adaptation to breast cancer in women who receive CBSM. In the trial described above by Antoni, Wimberly et al. (2006), serum cortisol levels decreased from baseline to 12 months only among women who had been randomized to CBSM (Phillips et al., 2008). Women in the CBSM condition also showed

greater production of interleukin-2 and interferon-γ by anti-CD3 stimulated peripheral blood mononuclear cells (PBMCs) 6 months after the intervention (Antoni et al., 2009).

These results were consistent with those from a prior trial in which participants of the CBSM condition had lower cortisol levels after the intervention than the control condition counterparts (Cruess et al., 2000), as well as higher lymphocyte proliferative responses to anti-CD3 stimulation 3 months after the intervention (McGregor et al, 2004). These findings suggest that CBSM may improve recovery of anti-viral immune functioning over the period of breast cancer treatment and does so in tandem with reductions in cortisol secretion.

Additionally, CBSM participants showed increased levels of anti-viral immune-associated genes (interferon Type I and II), and lower levels of pro-inflammatory and pro-metastatic leukocyte gene expression in tandem with decreases in negative affect, as compared with women in the control condition at 6-12 month follow-up (Antoni et al., 2012). Thus CBSM appears to improve immune system regulation—up-regulation of protective anti-viral signaling, and down-regulation of potentially disease-promoting inflammatory signaling—in parallel with improvements in psychological adaptation (reductions in negative affect). These findings are consistent with results from the 18-week psychosocial intervention described above, which found that at 12-month follow-up, the intervention decreased inflammation by lowering depressive symptoms (Thornton, Andersen, Schuler, & Carson, 2009). Taken together, data from psychosocial intervention trials to date demonstrate that such interventions can increase social support, decrease negative affect, and improve immune response, and that psychosocial variables mediate effects on physiological functioning.

Despite these findings that link psychosocial intervention, and CBSM specifically, to improved physiological processes, to date, no studies have investigated whether a psychosocial intervention targeting interpersonal skills training and stress management after surgery for breast cancer increases levels of perceived social well-being in tandem with decreases in negative affect and markers of inflammation and disease progression. The proposed study explores whether CBSM—a group-based intervention—can reduce inflammation by increasing social well-being and decreasing negative affect in women undergoing treatment for breast cancer.

The Current Study

This study aims first to examine whether social well-being relates to negative affect and inflammatory and disease promoting factors in women who have recently undergone surgery for early-stage breast cancer. Importantly, this project encompasses a period of time when women have not yet begun adjuvant therapy, thus enhancing the ability to observe associations among these variables without the potentially confounding effects of radiation, chemotherapy and immunotherapy, which occur later in the breast cancer treatment regimen. It then seeks to determine whether a CBSM intervention can increase social well-being and decrease negative affect and markers of inflammation concurrently during the first 6 months of treatment, while controlling for potential disease- and treatment confounding variables.

Furthermore, the study seeks to understand whether negative affect mediates the relationship between social well-being and inflammation, and whether changes in social well-being and negative affect mediate the association between CBSM participation and inflammation 6 months later. Figure 1 depicts the theoretical model guiding the aims of

the study. Data analyzed in this study are from women who participated in a 10-week CBSM trial and were assessed for perceived social well-being and serum inflammatory markers. The subsample of 78 women analyzed in this study also provided leukocyte gene expression data at 2-19 weeks after surgery for breast cancer (T1) and 6 months later (T2).

Specific Aims

Specific Aim 1.1: Examine whether social well-being is cross-sectionally associated with psychological adaptation and inflammatory and disease promoting factors in women who have recently undergone surgery for early-stage breast cancer.

Hypothesis 1.1a: Greater T1 social well-being will relate to lower T1 negative affect scores.

Hypothesis 1.1b: At T1, women who report more social well-being will exhibit less expression of genes for pro-inflammatory cytokines (*IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21*, and *PTGS2*), chemokines and their receptors (*CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*), other pro-inflammatory and tumor-promoting factors (*MMP9* and *LMNA*), and composites of these three categories of genes.

Hypothesis 1.1c: Greater T1 social well-being will relate to lower T1 serum levels of IL-6, IL-1β, and TNF-α.

Specific Aim 1.2 (Exploratory): Examine whether social well-being is cross-sectionally associated with psychological adaptation and inflammatory and disease promoting factors in women who have recently undergone surgery for early-stage breast cancer after controlling for BMI.

Hypothesis 1.2a: Greater T1 social well-being will relate to lower T1 negative affect scores, controlling for BMI.

Hypothesis 1.2b: At T1, women who report higher social well-being will exhibit less expression of genes for pro-inflammatory cytokines (*IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21*, and *PTGS2*), chemokines and their receptors (*CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*), other pro-inflammatory and tumor-promoting factors (*MMP9* and *LMNA*), and composites of these three categories of genes after BMI is controlled.

Hypothesis 1.2c: Greater T1 social well-being will relate to lower T1 serum levels of IL-6, IL-1β, and TNF-α after controlling for BMI.

Specific Aim 2.1 (Conditional): Examine whether the relationship between social well-being and inflammatory and disease promoting factors in women after surgery for breast cancer is mediated by negative affect at T1.

Hypothesis 2.1a: After surgery, negative affect will mediate the relationship between social well-being and gene expression for pro-inflammatory cytokines (*IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21*, and *PTGS2*), chemokines and their receptors (*CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*), other pro-inflammatory and tumor-promoting factors (*MMP9* and *LMNA*), and composites of these three categories of genes.

Hypothesis 2.1b: Negative affect will mediate the association between social well-being and serum levels of IL-6, IL-1β, and TNF-α after surgery for breast cancer.

Specific Aim 2.2 (Conditional; Exploratory): Test whether the relationship between social well-being and inflammatory and disease promoting factors in women

after surgery for breast cancer is mediated by negative affect at T1 after controlling for BMI.

Hypothesis 2.2a: When controlling for BMI, negative affect will mediate the relationship between social well-being and gene expression for pro-inflammatory cytokines (*IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21*, and *PTGS2*), chemokines and their receptors (*CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*), other pro-inflammatory and tumor-promoting factors (*MMP9* and *LMNA*) and composites of these three categories of genes.

Hypothesis 2.2b: When controlling for BMI, negative affect will mediate the association between social well-being and serum levels of IL-6, IL-1β, and TNF-α.

Specific Aim 3: Examine whether participation in a CBSM intervention increases levels of social well-being, decreases negative affect, and decreases inflammatory and disease promoting factors over 6 months.

Hypothesis 3a: At T2, women who participated in a CBSM intervention will report greater social well-being than women who participated in a control condition.

Hypothesis 3b: At T2, women who participated in a CBSM intervention will report lower negative affect scores than women who participated in a control condition.

Hypothesis 3c: At T2, women who participated in a CBSM intervention will reveal less expression of genes for pro-inflammatory cytokines (*IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21*, and *PTGS2*), chemokines and their receptors (*CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*), and other pro-inflammatory and tumor-promoting factors (*MMP9* and *LMNA*), and of composites of these three categories of genes than their counterparts in a control condition.

Specific Aim 4 (Conditional): Examine whether the relationship between CBSM participation and reductions in negative affect is mediated by increases in social well-being.

Hypothesis 4: Increases in social well-being from T1 to T2 will mediate the effect of CBSM participation on decreases in negative affect.

Specific Aim 5 (Conditional): Examine whether the relationship between CBSM participation and reductions in inflammatory and disease promoting factors is mediated by decreases in negative affect.

Hypothesis 5: Decreases in negative affect from T1 to T2 will mediate effects of CBSM versus control participation on decreases in expression of genes for pro-inflammatory cytokines (*IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21*, and *PTGS2*), chemokines and their receptors (*CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*), and other pro-inflammatory and tumor-promoting factors (*MMP9* and *LMNA*), and of composites of these three categories of genes.

CHAPTER 2: METHOD

Participants

The sample consists of women recruited from cancer treatment centers and physician's offices in South Florida to participate in a previously described randomized controlled trial of a CBSM intervention between 1998 and 2005 (Antoni, Lechner et al., 2006). Women were eligible for the study if they were 2 – 12 weeks post-surgery for early-stage (0 – III) breast cancer and were excluded via a phone screen if they had a prior history of cancer (except minor skin cancers), already started radiation treatment or chemotherapy, had stage IV cancer (metastatic disease), did not speak English fluently, or were diagnosed with a severe psychiatric disorder. Out of 240 participants enrolled in the study, data from a subgroup of 78 (43 CBSM, 35 controls) women with cryopreserved biological samples for gene expression analysis were included in this study. Figure 2 depicts the flow of participants through the study.

Procedures

Women, in fact, completed baseline assessments 2 – 19 weeks after surgery for breast cancer, due to a few cases outside of the 2 – 12 week target window who had still not yet received adjuvant therapy. Baseline (T1) assessments consisted of a paper-and-pencil questionnaire as well as a blood draw. After completing baseline assessments, women were randomized to either a 10-week CBSM intervention condition, or to a 1-day active control seminar (Antoni, Lechner et al., 2006). Both types of interventions were co-led by female postdoctoral fellows and advanced predoctoral psychology students. Assessors were only assigned to a case if they had not led that participant's intervention group. Regardless of condition, intervention sessions took place in a room that contained

couches and a table and chairs. Assessment data were collected again 6 months after baseline, which was 3 months post-intervention (T2). The CBSM intervention trial (described below) was approved by the Institutional Review Board at the University of Miami, and women were compensated $50 for completion of each assessment.

Cognitive Behavioral Stress Management Intervention

The CBSM groups were composed of between three and eight patients who met weekly with the interventionists for 2-hour sessions (Antoni, Lechner et al., 2006). Table 2 outlines the intervention content. Each session introduced participants to a different cognitive behavioral technique and relaxation exercise (Antoni, 2003). Cognitive behavioral skills included building stress awareness, recognizing maladaptive automatic thoughts and cognitive distortions, cognitive restructuring, coping strategies, social support, anger management, and assertiveness training. Relaxation training included diaphragmatic breathing, progressive muscle relaxation, imagery, autogenics, and meditation. Skills were taught in session through didactics, during which women were encouraged to practice the techniques. Women were also given weekly homework assignments to continue using the techniques outside of the weekly sessions. Monitoring of videotapes by clinical psychologists was instituted in order to maintain fidelity to the intervention design. Average group attendance was 7.15 sessions (SD = 2.55).

Active Control Condition

The control condition was comprised of a 1-day, 5 – 6 hour psychoeducation seminar occurring midway through the 10-week CBSM period and consisted of eight or fewer participants (Antoni, Lechner et al., 2006). In this condition, interventionists presented a condensed version of the CBSM material to participants in an

educational/lecture format. It should be noted that although all women in the study had access to an abbreviated form of the same material, the women in the control condition were not exposed to the supportive elements of being members of a weekly therapy group. They also did not partake in weekly discussions about the material, role-plays of techniques, and application of skills outside of the session. The structure of this condition did not control for attention. However, it was designed to avoid differential attrition by providing women with access to some of the same content.

Measures

Demographics. Participants self-reported age, stage of disease, number of days since surgery, and education on a paper and pencil questionnaire at T1. BMI was calculated based on height and weight, which were self-reported or collected from medical charts. At T2, participants self-reported whether they had received treatment with radiation, chemotherapy, or hormones during the prior 6 months.

Social Well-Being. The Social/Family Well-Being subscale of the Functional Assessment of Cancer Therapy – Breast (FACT-B) was administered to assess social well-being over the past 7 days (Brady et al., 1997) at T1 and T2. The FACT-B is a 36-item scale with 5 response choices ranging from 1 (not at all) to 5 (very much). The Social/Family Well-Being subscale consists of 7 items (e.g., "I get support from my friends"). This subscale has been found to be reliable and valid in women diagnosed with breast cancer (Brady et al., 1997) and has been found to be associated with inflammatory cell-signaling in women with ovarian cancer (Lutgendorf et al., 2002). The FACT-B Social/Family Well-Being subscale had adequate internal consistency ($\alpha = 0.79$) in this sample.

Social Support. The Sources of Social Support Scale (SSSS; Kinsinger, Laurenceau, Carver, & Antoni, 2011) was administered to further characterize the sources of self-reported social support at study entry in order to help provide a context for differences in Social/Family Well-Being scores. The SSSS measured multiple types of social support subdivided by support source within each type. Items assessed emotional, informational, instrumental, and negative support. Participants self-reported levels of support on each item four times, once with regard to support from each source: husband/partner, adult women family members, children and male adult family members, and friends. Each item is evaluated on a 5-point Likert-type scale ranging from 1 (not at all) to 5 (a lot). Internal consistency of the subscales was adequate in a sample of partnered women diagnosed with early-stage breast cancer that overlapped with this one (Kinsinger et al. 2011): emotional support α=0.90; negative support α=0.81.

Negative Affect. The Negative Affect Scale of the Affects Balance Scale (ABS) was analyzed as a measure of negative affect (Derogatis, 1975). The ABS is a self-report questionnaire that lists 40 adjectives describing positive and negative feelings. Participants were asked to rate how often in the past week they experienced each emotion (e.g., "sad"). Five possible response options ranged from 1 (never) to 5 (always). The internal consistency of the ABS has been found to be high in a sample of women diagnosed with breast cancer (α = 0.86) (Antoni, Wimberly et al., 2006). Internal consistency for the Negative Affect Scale, composed of 20 items, was also found to be high in this sample (α = 0.93).

Depressive symptoms. Interviewers administered the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) to participants at T1 and T2 to assess

depressive symptoms. This measure was included in this study for the purpose of characterizing depression levels in the sample as they relate to negative affect. This measure has previously been used in studies of women with breast cancer (Musselman et al., 2006) and reliability was adequate in this sample (T1 $\alpha = 0.80$).

Leukocyte Gene Expression. This study examined leukocyte RNA expression of pro-inflammatory cytokines (*IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21*, and *PTGS2*), pro-inflammatory chemokines and their receptors (*CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*), and other tumor-promoting factors (*MMP9* and *LMNA*) in circulating peripheral blood mononuclear cells (PBMCs). Table 1 defines each of these genes according to description and function. Genes were selected due to their central function in inflammation (Cole, 2013), their involvement in cancer progression (Lutgendorf et al., 2008), and their demonstrated association with psychological states in breast cancer patients (Antoni et al., 2012).

Transcripts were examined from PBMCs collected at T1 and T2. Samples were analyzed with Illumina Human HT-12 v3 Expression BeadChips. Human gene expression was derived from low-level fluorescence intensity values and quantile normalized with Illumina Genome Studio software as described elsewhere (Antoni et al., 2012). Composite scores of gene expression for pro-inflammatory cytokines, for pro-inflammatory chemokines and their receptors, and for tumor-promoting factors were created by averaging the scores of expression of genes in each category as divided above based on their known function (Antoni et al., 2012; Basavaraju et al., 2015).

Serum Cytokines. Serum pro-inflammatory cytokines were measured from a blood sample collected by a phlebotomist at T1, but not at T2. All blood samples were

collected between 4:00pm and 6:30pm in order to allow for direct comparison of measurements between participants. Tubes without anticoagulants were used for blood collection. Circulating pro-inflammatory cytokines IL-6, IL-1β, and TNF-α were measured from serum samples by ELISA as described elsewhere (Bouchard et al., 2016). Five participants had cytokine values below the detectable level. Values below the detectable level were replaced with the lowest value detectable in the sample. The lowest detectable value for IL-6 was 0.09 pg/ml. The lowest detectable value for IL-1β was 0.06 pg/ml. The lowest detectable value for TNF-α was 0.10 pg/ml. Numerical levels were log transformed.

Data Analysis Approach

Data were analyzed using IBM SPSS Version 22.00. Descriptive statistics were examined to characterize participants with regard to demographic, medical, and study variables.

Preliminary Analyses

All variables were checked for normal distribution (skewness < 3.0, kurtosis < 8.0; Kline 2011). Outliers 3.0 or more standard deviations outside the mean of the self-report measure levels were winsorized (Wilcox 1993). Participants missing data were excluded from analyses that included the missing data points.

Independent sample t-tests and chi-square tests were conducted on demographic, medical, and study variables to determine whether the subsample analyzed for this study differed from the overall trial sample, and whether the subsample participants in the CBSM condition differed from those in the control condition. Two-way repeated

measures ANOVAs were conducted on the SSSS to compare levels of different sources of support and types of support in order to characterize the sample at T1 and at T2.

Primary Analyses

This study used multiple regression analysis to test hypotheses associated with the following aims:

Aim 1.1: Multiple regression analysis controlling for age, stage of disease, days since surgery, and education (O'Connor et al., 2009) were conducted to examine T1 associations between perceived Social/Family Well-Being and ABS Negative Affect, leukocyte gene expression, leukocyte gene expression composite scores, and serum cytokines.

Aim 1.2 (Exploratory): Aim 1.1 analyses were repeated using multiple regression analyses controlling for BMI (O'Connor et al., 2009) in the participants with available BMI data.

Aim 2.1 (Conditional): Multiple regression controlling for age, stage of disease, days since surgery, and education (O'Connor et al., 2009) examined whether T1 ABS Negative Affect could mediate the relationship between Social/Family Well-Being and leukocyte gene expression, leukocyte gene expression composite scores, and serum cytokines. Regressions examined whether the proposed mediator, negative affect, was associated with the dependent variables, leukocyte gene expression, leukocyte gene expression composite scores, and serum cytokines. Use of RMediation (Tofighi & MacKinnon, 2011) was planned to evaluate mediation contingent upon significant associations between negative affect and indicators of inflammation. These tests were

ultimately not conducted because negative affect was not related to the markers of inflammation.

Aim 2.2 (Conditional; Exploratory): Aim 2.1 multiple regression analyses were repeated controlling for BMI (O'Connor et al., 2009) in addition to the covariates used in Aim 2.1, in the subsample containing BMI data. RMediation (Tofighi & MacKinnon, 2011) was planned to assess mediation but was not used due to lack of association between the mediator and the outcome variable when controlling for BMI.

Aim 3: Multiple regression analysis, controlling for covariates that were significantly related to gene expression at T1 (O'Connor et al., 2009), treatment type (radiation, chemotherapy, and hormone treatment; Antoni et al., 2012) if significantly associated with gene expression at T2, and baseline levels of the dependent variable were conducted to assess whether CBSM versus control condition participation predicted T2 Social/Family Well-Being, ABS Negative Affect, leukocyte gene expression, and leukocyte gene expression composite scores.

Aim 4 (Conditional): Multiple regression controlling for covariates that were significantly related to gene expression at T1 (O'Connor et al., 2009) as well as radiation treatment, chemotherapy, and hormone treatment (Antoni et al., 2012) if significantly associated with gene expression at T2, and baseline levels of the dependent variable were used to determine whether the effect of group assignment (CBSM versus control) on changes in ABS Negative Affect was mediated by changes in perceived Social/Family Well-Being from T1 to T2. RMediation (Tofighi & MacKinnon, 2011) was intended for use to evaluate mediation, but was not ultimately used given that the proposed

independent variable, intervention condition, did not predict the dependent variable, negative affect.

Aim 5 (Conditional): Multiple regression analysis controlling for covariates that were significantly related to gene expression at T1 (O'Connor et al., 2009) as well as radiation treatment, chemotherapy, and hormone treatment (Antoni et al., 2012) if significantly associated with gene expression at T2 and baseline levels of the dependent variable were conducted to determine whether the effect of group assignment (CBSM versus control) on pro-inflammatory and pro-metastatic leukocyte gene expression was mediated by changes in ABS Negative Affect from T1 to T2. Although analysis with RMediation (Tofighi & MacKinnon, 2011) was planned to assess mediation, it was not used given that the proposed independent variable, intervention condition, did not predict the dependent variable, inflammatory leukocyte gene expression.

The Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) was selected to correct for multiple comparisons by controlling the false discovery rate to 0.10 (Jansen et al., 2016) since it is more powerful than other methods. Other techniques, such as the Bonferroni adjustment, control the familywise error rate by dividing the significance level by the number of tests conducted. *P*-values below that threshold are considered significant. While Type I error is likely avoided, the power to detect significant effects also drops. In contrast, the Benjamini-Hochberg procedure controls for the proportion of statistically significant tests for which the null hypothesis is actually true (Glickman, Rao, & Schultz, 2014). This approach is therefore recommended in the context of hypothesis driven research when the null hypotheses are likely to be false.

CHAPTER 3: RESULTS

Sample Characterization

Table 3 displays demographic information about the participants in the sample. Participants were middle aged on average (M = 49.55, SD = 7.51) and had an average of 15.86 years of education (SD = 2.58). The majority of women (82.1%) reported being employed full time, contributing to an average household income of $76,190 (SD = $49,203). The majority of women self-identified as non-Hispanic White (69.2%), but the sample also represented Hispanic (20.5%) and African American/Black women (9.0%). Most women were married or partnered (67.9%). Approximately one third of participants had children (30.8%), and the average number of children was 2.11 (SD = 0.85).

On average, participants were approximately 5 weeks post-surgery (M = 38.58 days, SD = 24.22) for breast cancer at study entry, with the greatest percentage of women diagnosed with stage I breast cancer (stage 0 = 12.8%, stage I = 47.4%, stage II = 30.8%, stage III = 9.0%). Slightly more than half of participants underwent a mastectomy (56.4%) and the rest had a lumpectomy (43.6%). According to their BMI scores, women were classified as overweight on average (M = 27.00kg/m^2, SD = 6.49). Of those with BMI data, 52% had normal weight ($\leq$25.0 kg/m^2), 28% were categorized as overweight (25.1 – 29.9kg/m^2), and 20% were obese ($\geq$30 kg/m^2). Over half of the women were estrogen receptor positive (55.1%), approximately one third were progesterone receptor positive (35.9%), and 14.1% were HER2/neu positive. At study entry, women in the sample reported use of medication for depression (6.4%), anxiety (16.7%), sleep (15.4%), and pain (28.2%). Average T1 Hamilton Depression Rating Scale Score was 6.68 (SD = 5.52), which is in the normal range. During the period between T1 and T2, 32.1% of

women reported receiving radiation therapy, 42.3% reported undergoing chemotherapy, and 48.7% received hormone therapy. At randomization, 43 women (55.1%) were in the CBSM condition and 35 (44.9%) were in the control condition.

ANOVAs were conducted at T1 and then at T2 on the results of the SSSS to compare levels of different types of support. At T1, the social support "type" main effect was significant, $\Lambda = 0.07$, $F(3, 37) = 163.31$, $p < .01$. Specifically, emotional support ($M = 4.13$, $SE = 0.11$) was the type of support with the highest level reported and was significantly higher than negative support, informational support, and instrumental support (all ps $< .001$). Negative support ($M = 1.28$, $SE = 0.04$) was the lowest type of support received and was lower than emotional support, informational support, and instrumental support (all ps $< .001$). Instrumental support ($M = 2.87$, $SE = 0.15$) and informational support ($M = 2.73$, $SE = 0.16$), while both significantly lower than emotional support ($p < .001$) and higher than negative support ($p < .001$), did not differ from one another ($p = .40$).

Table 4 shows the results of paired samples t-tests conducted to compare amounts of each "type" of social support provided by each "source." Emotional support from husbands/partners was not significantly different from emotional support from adult women family ($p = .97$) or from emotional support from friends ($p = .14$), although emotional support from friends was significantly higher than emotional support from adult women family members ($p = .02$). It should be noted that emotional support from children and male adult family was significantly lower than emotional support from all other sources (all ps $< .01$). With regard to negative support, support from husbands/partners was significantly higher than from any other source (all ps $< .05$).

Negative support from adult women family was the next numerically highest score and was significantly higher than negative support from friends (p = .02), but not higher than negative support from children and male adult family (p = .24). Informational support from friends was higher than support from all other sources (all ps < .05), and informational support from children and male adult family was lower than from all other sources (all ps < .05). Informational support from husbands/partners and from adult women family both ranked in the middle and did not differ significantly from one another (all ps > .05). Husbands/partners provided more instrumental support than all other sources (all ps < .01), and children and male adult family provided the least amount of this type of support (all ps < .05). Support from adult women family and friends ranked in the middle, and did not differ from one another (p = .43).

Overall at T1, husbands and partners were high providers of support, but particularly of instrumental support, which may have provided opportunities for conflict as represented by the high negative support ratings for husband/partners when compared with that from other sources. Support from children and male adult family ranked as significantly lower than from other sources across types of support.

At T2, ANOVAs revealed that the social support "type" main effect was significant, $\Lambda = 0.83$, $F(3, 31) = 114.53$, $p < .01$, meaning that patients reported receiving more of some types of support than of others. As was the case at T1, emotional support (M = 3.91, SE = 0.14) was the highest form received, higher than negative support (difference = 2.82, $p < .001$), than informational support (difference = 1.91, $p < .001$), and than instrumental support (difference = 1.70, $p < .001$). Negative support (M = 1.09, SE = 0.03) was the lowest type of support received and was significantly lower than all

other types of support (all *p*s < .001). Informational support (M = 2.00, SE = 0.13) and instrumental support (M = 2.21, SE = 0.14) were both lower than emotional support and higher than negative support (all *p*s < .01), but did not differ significantly from one another (*p* = .12).

Within the emotional support subscale at T2, emotional support from husbands/partners, adult women family, and friends did not differ (all *p*s > .05). Emotional support from children and male adult family was numerically lower than the same kind of support from other sources, and was statistically significantly lower than support from adult women family and from friends (all *p*s < .05). Again, negative support was higher from husbands/partners than from children and male adult family and from friends (all *p*s < .01). Negative support from husbands/partners was not significantly different from negative support from adult women family (*p* = .07), which was also higher than negative support from friends (*p* = .01). Within informational support, support from friends was significantly higher than all other types of support (all *p*s < .05), and support from children and male adult family was significantly lower than from the other sources (all *p*s < .05). Support from husbands/partners and from adult women family did not differ and ranked in the middle (all *ps* > .05). Within instrumental support, support from husbands/partners was numerically highest and was statistically higher than support from adult women family and from friends (all *p*s < .05). Instrumental support from adult women family, children and male adult family, and friends did not differ significantly (all *ps* > .05).

Overall at T2 husbands/partners remained strong providers of support relative to other sources, while children and male adult family did not provide as much support as

other sources. However, husbands/partners continued to be a relatively high source of negative support at T2.

Preliminary Analyses

Subsample versus Parent Sample

Independent samples 2-tailed t-tests were conducted to assess whether the subsample of women who provided blood samples for leukocyte gene expression data differed from the parent sample on demographic variables and study variables. The two samples did not differ significantly in age [$t(316) = 0.699$, $p = .49$], educational level [$t(316) = -0.883$, $p = .38$], days elapsed between breast cancer surgery and randomization [$t(316) = 0.678$, $p = .50$], BMI [$t(197) = -0.627$, $p = .53$], T1 Hamilton Depression Rating Scale [$t(307) = 1.172$, $p = .24$], annual household income [$t(280) = 0.392$, $p = .70$], number of children [$t(225) = -0.424$, $p = .67$], baseline FACT-B Social/Family Well-Being [$t(316) = -0.306$, $p = .76$], T2 FACT-B Social/Family Well-Being [$t(252) = 0.458$, $p = .65$], baseline ABS Negative Affect [$t(314) = 0.707$, $p = .48$], T2 ABS Negative Affect [$t(252) = -0.142$, $p = .89$], baseline serum IL-6 [$t(138) = 0.682$, $p = .50$], baseline serum IL-1β [$t(131) = 1.872$, $p = .06$], or baseline serum TNF-α [$t(133) = 1.361$, $p = .18$].

Chi square tests indicated that being in the parent sample versus the subsample was not related to categorical variables such as race/ethnicity [Pearson $\chi^2(3, N = 316) = 2.54$, $p = .47$, Cramér's V = 0.09], employment status [Pearson $\chi^2(1, N = 318) = 2.01$, $p = .16$, Cramér's V = 0.08], marital status [Pearson $\chi^2(4, N = 318) = 5.55$, $p = .24$, Cramér's V = 0.13], having children [Pearson $\chi^2(1, N = 318) = 0.40$, $p = .53$, Cramér's V = 0.03], surgery type [Pearson $\chi^2(1, N = 318) = 1.24$, $p = .27$, Cramér's V = 0.06], disease stage [Pearson $\chi^2(3, N = 316) = 2.71$, $p = .44$, Cramér's V = 0.09], estrogen receptor status

[Pearson $\chi^2(1, N = 212) = 0.88, p = .35$, Cramér's V = 0.06], progesterone receptor status [Pearson $\chi^2(1, N = 169) = 2.01, p = .16$, Cramér's V = 0.11], HER2/neu status [Pearson $\chi^2(1, N = 161) = 0.33, p = .57$, Cramér's V = 0.05], use of depression medication [Pearson $\chi^2(1, N = 318) = 1.31, p = .25$, Cramér's V = 0.06], use of anxiety medication [Pearson $\chi^2(1, N = 318) = 0.03, p = .87$, Cramér's V = 0.01], use of sleep medication [Pearson $\chi^2(1, N = 318) = 0.26, p = .61$, Cramér's V=0.03], use of pain medication [Pearson $\chi^2(1, N = 318) = 0.32, p = .57$, Cramér's V = 0.03], BMI category [Pearson $\chi^2(2, N = 199) = 0.30, p = .86$, Cramér's V = 0.04], study condition [Pearson $\chi^2(1, N = 318) = 0.62, p = .43$, Cramér's V=0.04], receiving radiation [Pearson $\chi^2(1, N = 254) = 1.97, p = .16$, Cramér's V = 0.09], receiving chemotherapy [Pearson $\chi^2(1, N = 254) = 0.10, p = .92$, Cramér's V = 0.01], or receiving hormone therapy [Pearson $\chi^2(1, N = 254) = 1.23, p = .31$, Cramér's V = 0.64]. Therefore, it can be assumed that the study sample was reasonably representative of the parent trial sample.

CBSM Group versus Control Group

Two-tailed t-tests and chi square tests were also used to determine whether the participants randomized to receive the CBSM intervention differed from those who participated in the control group on demographic, medical, and study variables. Table 3 displays the demographic and medical characteristics of the group randomized to CBSM and of the control group before winsorization. At T1, the CBSM group reported lower emotional support from friends [$t(68.439) = 2.929, p = .01$], and lower informational support from husbands/partners [$t(60) = 2.328, p = .02$] and from friends [$t(75) = 2.341, p = .02$]. At T2, CBSM participants reported lower emotional support from adult women family members [$t(50) = 2.025, p = .05$], children and male adult family members [$t(43)$

= 3.442, $p < .01$], and friends [$t(58) = 3.088$, $p < .01$], lower informational support from husbands/partners [$t(49) = 2.077$, $p = .04$] and from friends [$t(58) = 1.999$, $p = .05$], and lower instrumental support from friends *[*$t(58) = 2.299$, $p = .03$]. They also reported greater negative support from adult women family members [$t(42.617) = -2.135$, $p = .04$].

The groups did not differ with regard to age [$t(76) = -0.795$, $p = .43$], race/ethnicity [Pearson $\chi^2(3, N = 78) = 2.45$, $p = .48$, Cramér's V = 0.18], years of education [$t(76) = 1.098$, $p = .28$], income [$t(67) = 0.615$, $p = .54$], employment status [Pearson $\chi^2(1, N = 78) = 0.18$, $p = .67$, Cramér's V = 0.05], marital status [Pearson $\chi^2(1, N = 78) = 4.99$, $p = .17$, Cramér's V = 0.25], having children [Pearson $\chi^2(1, N = 78) = 0.37$, $p = .54$, Cramér's V = 0.07], number of children [$t(51) = 0.166$, $p = .87$], surgery type [Pearson $\chi^2(1, N = 78) = 0.64$, $p = .42$, Cramér's V = 0.09], days since surgery [$t(76) = 1.905$, $p = .06$], stage [Pearson $\chi^2(1, N = 78) = 3.01$, $p = .20$, Cramér's V = 0.05], estrogen receptor status [Pearson $\chi^2(1, N = 78) = 1.85$, $p = .17$, Cramér's V = 0.19], progesterone receptor status [Pearson $\chi^2(1, N = 78) = 0.59$, $p = .44$, Cramér's V = 0.12], HER2/neu status [Pearson $\chi^2(1, N = 42) = 1.22$, $p = .27$, Cramér's V = 0.17], use of depression medication [Pearson $\chi^2(1, N = 78) = 0.49$, $p = .48$, Cramér's V = 0.08], use of anxiety medication [Pearson $\chi^2(1, N = 78) = 0.26$, $p = .61$, Cramér's V = 0.06], use of sleep medication [Pearson $\chi^2(1, N = 78) = 0.76$, $p = .38$, Cramér's V=0.10], use of pain medication [Pearson $\chi^2(1, N = 78) = 0.20$, $p = .66$, Cramér's V = 0.05], BMI [$t(48) = 0.169$, $p = .87$], BMI category [Pearson $\chi^2(2, N = 50) = 0.52$, $p = .77$, Cramér's V = 0.10], T1 depression [$t(76) = -0.443$, $p = .66$], T2 depression [$t(60) = 0.319$, $p = .75$], radiation therapy [Pearson $\chi^2(1, N = 61) = 0.20$, $p = .66$, Cramér's V = 0.06], chemotherapy

[Pearson $\chi^2(1, N = 61) = 0.00$, $p = .99$, Cramér's V = 0.00], or hormone therapy [Pearson $\chi^2(1, N = 61) = 0.32$, $p = .57$, Cramér's V = .07].

Table 5 shows the study variables according to randomization group before winsorization. At baseline, participants in the control group reported higher levels of social well-being [$t(71.737) = 2.750$, $p = .01$]. Groups did not differ with regard to negative affect [$t(76) = -1.075$, $p = .29$]. The CBSM group showed higher levels of pro-inflammatory leukocyte gene expression, including of *IL1A* [$t(76) = -2.102$, $p = .04$], *IL1B* [$t(58.731) = -3.086$, $p < .01$], *CCL3* [$t(60.256) = -2.673$, $p = .01$], *CCL20* [$t(68.266) = -2.549$, $p = .01$], *CCL3L1* [$t(76) = -2.224$, $p = .03$], *CCL4L2* [$t(76) = -2.018$, $p = .05$], *CXCR7* [$t(72.198) = -2.897$, $p = .01$], *PTGS2* [$t(76) = -2.553$, $p = .01$], *LMNA* [$t(76) = -3.628$, $p < .01$], the cytokine composite [$t(76) = -2.023$, $p = .05$], the chemokine composite [$t(76) = -2.687$, $p = .01$], and the pro-metastatic composite [$t(75.991) = -2.955$, $p < .01$]. Groups did not differ with regard to serum IL-6 [$t(49) = 0.573$, $p = .57$], serum IL-1β [$t(49) = -0.218$, $p = .30$], or serum TNF-α [$t(49) = 0.341$, $p = .74$].

Table 6 shows the results of bivariate correlations that were conducted to determine relationships between expression of genes for pro-inflammatory cytokines, between genes encoding pro-inflammatory chemokines, and between pro-metastatic genes at T1 and at T2. At T1, the statistically significant correlations between pro-inflammatory cytokines *IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21* and *PTGS2* were positive and ranged in effect size from small to large (Cohen, 1988). The association between *IL1B* and *TNFSF10* was also positive, but was small and not statistically significant. At T2, the statistically significant correlations between pro-inflammatory cytokines remained positive and ranged from moderate to large, although the association

between *IL1B* and *TNFSF10* remained nonsignificant and the associations between *TNFSF10* and *IL1A*, between *TNFRSF21* and *TNFSF10*, and between *TNFSF10* and *PTGS2* lost significance. With regard to the pro-inflammatory chemokine composites, at T1 the correlations between *CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7* were all positive and statistically significant, with effect sizes ranging from moderate to large. At T2, significant associations ranged from moderate to large, but the relationships between *CXCR7* and *CCL3* and between *CXCR7* and *CCL3L1* lost significance. Within the pro-metastatic leukocyte gene expression composite, expression of *MMP9* was strongly positively correlated with that of *LMNA* at both T1 and T2.

Missing Data

Within the subsample of 78 participants who provided blood samples for gene expression data, missing data for the variables included in analyses ranged from 0.0% to 48.7%. Regarding aims 1.1, 1.2, 2.1, and 2.2, T1 social well-being, negative affect, and leukocyte gene expression were complete. Data were missing for serum IL-6 (34.6%), serum IL-1β (38.5%), and serum TNF-α (37.2%). For variables used in Aim 3, there were complete data for intervention condition but missing data for T2 social well-being and negative affect (21.8%), and for gene expression (48.7%). With regard to covariates, data were complete for stage, days since surgery, age, and education. BMI was incomplete (35.9%), as were radiation, chemotherapy, and hormone therapy (21.8%).

Primary Analyses

Specific Aim 1.1

It was hypothesized that social-well being would significantly negatively relate to negative affect, expression of pro-inflammatory and pro-metastatic leukocyte gene

expression, and circulating serum cytokines after surgery for breast cancer (T1), when controlling for age, stage of disease, days since surgery, and education. Results of these multiple regression analyses are displayed in rows categorized as Aim 1.1 in the first column of Table 7.

Social well-being and negative affect. Multiple regression analyses controlling for age, stage of disease, days since surgery, and years of education in Step 1 and adding social well-being in Step 2 showed that higher social well-being significantly accounted for less negative affect (β = -0.432, $p < .01$). The change in R^2 in Table 7 indicates that an additional 18.3% of variance in negative affect was contributed by social well-being over and above the covariates. The scatterplot in Figure 3 illustrates this association and does not indicate that outliers influenced the results.

Social well-being and leukocyte gene expression. When gene expression data were analyzed using multiple regression with covariates entered in Step 1 and social well-being in Step 2, greater social well-being also accounted for significantly lower expression of *IL1A* (β = -0.224, $p < .05$), *MMP9* (β = -0.239, $p < .05$), and *LMNA* (β = -0.273, $p < .05$). Social well-being was negatively related to the pro-metastatic leukocyte gene expression composite made up of *MMP9* and *LMNA* (β = -0.277, $p < .05$). Figure 4 depicts scatterplots of the association between social well-being and gene expression composites, which suggest that the associations were not driven by extreme values.

For descriptive purposes, Figure 5 depicts fold differences in pro-inflammatory and pro-metastatic gene expression in participants with low social well-being as compared with high social well-being as determined by median split. According to the graph, the low social well-being group had higher levels of gene expression for every

pro-inflammatory cytokine, chemokine, and pro-metastatic protein. Women who reported low social well-being had gene expression approximately 2 – 2.5 times larger than their counterparts who reported high social well-being. The composite gene expression values were also higher in the group that reported lower social well-being, revealing a similar fold difference of approximately 2 – 2.5 times. Exploratory post hoc ANCOVAs controlling for age, stage, days since surgery, and education found that *MMP9* expression was significantly higher in women with low social well-being as compared to women with high social well-being $F(1, 72) = 5.23$, $MSE = 0.88$, $p < .05$, partial $\eta^2 = 0.07$. Pro-metastatic gene expression, the composite encompassing *MMP9* and *LMNA*, was also significantly higher in women with low versus high social well-being, $F(1, 72) = 5.23$, $MSE = 0.65$, $p < .05$, partial $\eta^2 = 0.55$. It should be noted that *MMP9* and the pro-metastatic composite gene expression did not meet the assumption of homogeneity of variances due to larger variance in the control group, which may have increased Type I error probability. ANCOVAs did not reveal significant differences in any other individual gene or gene expression composite scores between women with high versus low social well-being ($p > .05$).

Social well-being and serum cytokines. When covariates were entered in Step 1 and social well-being was entered in Step 2, greater social well-being accounted for significantly lower levels of serum IL-6 ($\beta = -0.410$, $p < .01$), serum IL-1β ($\beta = -0.318$, $p < .05$), and serum TNF-α ($\beta = -0.330$, $p < .05$). Based on Figure 6, which shows scatterplots of the relationships between social well-being and circulating serum cytokines, it does not appear that the statistical significance of these results can be attributed to outliers.

After application of the Benjamini-Hochberg procedure, the relationships between social well-being and negative affect, *IL1A*, *MMP9*, *LMNA*, the pro-metastatic gene expression composite, as well as serum IL-6, serum IL-1β, and serum TNF-α remained significant. In Table 7, daggers following the dependent variable name indicate results that remained significant after the Benjamini-Hochberg procedure.

Specific Aim 1.2 (Exploratory)

It was hypothesized that when controlling for BMI in addition to age, stage of disease, days since surgery, and education, social-well being would continue to significantly negatively relate to negative affect, expression of pro-inflammatory and pro-metastatic leukocyte gene expression, and circulating serum cytokines after surgery for breast cancer. Results of the multiple regression analyses when also controlling for BMI are shown in Table 7, labeled as Aim 1.2 in the first column.

Social well-being and negative affect. When covariates, including BMI, were entered in Step 1 and social well-being was entered in Step 2, multiple regression analysis indicated that social well-being continued to account for less negative affect (β = 0.589, $p < .01$). The association is depicted in Figure 7, which shows that the directionality of the relationship did not change after BMI was controlled. Outliers did not appear to be influencing the results.

Social well-being and leukocyte gene expression. When BMI was controlled in addition to age, stage of disease, days since surgery, and education in Step 1 and social well-being was added to the model in Step 2, greater social well-being was still associated with lower gene expression for *IL1A* (β = -0.397, $p < .05$), *MMP9* (β = -0.353, $p < .05$), and *LMNA* (β = -0.504, $p < .01$). However, in this model, greater social well-

being also related to lower *CCL20* (β = -0.332, $p < .05$), and less expression of the COX-2 pathway *PTGS2* gene (β = -0.353, $p < .05$). With BMI controlled, greater social well-being also related to lower levels of the pro-inflammatory cytokine gene expression composite, (β = -0.328, $p < .05$) and lower levels of the chemokines and receptors gene expression composite (β = -0.311, $p < .05$). The negative association between social well-being and the pro-metastatic leukocyte gene expression composite remained significant when controlling for BMI (β = -0.458, $p < .01$). Figure 8 depicts the statistically significant associations between social well-being and the 3 gene expression composites, and does not suggest that the results were driven by extreme values.

According to Figure 9, which depicts fold differences in pro-inflammatory and pro-metastatic gene expression in participants with low social well-being as compared with high social well-being as determined by median split after BMI is controlled, the low social well-being group had numerically higher levels of gene expression for every pro-inflammatory cytokine, chemokine, and pro-metastatic protein and every composite score. Gene expression was approximate 2 – 3 times larger in women who reported low social well-being than in women who had high social well-being scores.

Exploratory post hoc ANCOVAs controlling for age, stage, days since surgery, education, and BMI found that *TNFRSF21* expression was significantly higher in women with low social well-being as compared to women with high social well-being $F(1, 43) = 4.03$, MSE = 0.61, $p < .05$, partial $\eta^2 = 0.09$. Pro-metastatic gene expression was also significantly higher in women with low social well-being, as operationalized by *MMP9* expression [$F(1, 43) = 4.93$, MSE = 0.99, $p < .05$, partial $\eta^2 = 0.10$], *LMNA* expression [$F(1, 43) = 4.61$, MSE = 0.63, $p < .05$, partial $\eta^2 = 0.10$] and expression of the pro-

metastatic gene composite [$F(1, 43) = 5.23$, $MSE = 0.9$, $p < .05$, partial $\eta^2 = 0.12$]. However, expression of *TNFRSF21*, *MMP9*, *LMNA* and the pro-metastatic gene composite did not meet the assumption of homogeneity of variances due to larger variance in the control group, which may have increased Type I error probability. ANCOVAs did not reveal significant differences in any other individual gene or gene expression composite scores between women with high versus low social well-being when controlling BMI ($p > .05$).

Social well-being and serum cytokines. After controlling for age, stage of disease, days since surgery, education, and BMI in Step 1 and social well-being in Step 2, the negative relationship between social well-being and circulating serum IL-6 held as significant ($\beta = -0.382$, $p < .05$) although the associations with serum IL-1β ($\beta = -0.325$, $p = .08$) became marginally significant and TNF-α ($\beta = -0.279$, $p = .14$) became non-significant. The loss of statistical significance is likely due to the loss of cases and power in this subsample of participants with BMI. According to Figure 10, these linear relationships all remained in the same direction as in the full sample, and were consistent with the hypotheses. The results do not appear to have been influenced by outliers.

As indicated by daggers next to the dependent variable in Table 7, when the Benjamini-Hochberg procedure was applied to these analyses, social-well-being was statistically significantly associated with negative affect, *IL1A*, *IL6*, *TNFRSF21*, *CCL20*, *CXCR7*, *PTGS2*, *MMP9*, *LMNA*, the pro-inflammatory cytokine gene expression composite, the pro-inflammatory cytokine gene expression composite, and the pro-metastatic gene expression composite. *TNFRSF21* and *CXCR7* did not have *p*-values below .05 yet became significant after application of the Benjamini-Hochberg procedure,

which is common when the false discovery rate is higher than 0.05 (McDonald, 2014).

Specific Aim 2.1 (Conditional)

It was hypothesized that after surgery for breast cancer, negative affect would mediate the relationship between social well-being and inflammation and pro-metastatic gene expression when controlling for age, stage of disease, days since surgery, and education. Given that social well-being was found to relate to negative affect in Aims 1.1 and 1.2, further analyses were conducted to determine whether negative affect was significantly related to indicators of inflammation. Step 1 of the regression analysis included age, stage, days since surgery, and education and Step 2 included social well-being and negative affect. Table 8 displays the results of these analyses in rows indicated as Aim 2.1 in the first column. No findings were statistically significant (all *p*s > .05).

Specific Aim 2.2 (Conditional; Exploratory)

It was hypothesized that when also controlling for BMI, negative affect would mediate the relationship between social well-being and inflammation and pro-metastatic gene expression after surgery for breast cancer, when controlling for age, stage of disease, days since surgery, and education. Step 1 of the analysis included the covariates, and social well-being was entered into the model in Step 2. Table 8 shows the results of these analyses in rows indicated as Aim 2.2 in the first column, which were not statistically significant (all *p*s > .05). Taken together with the Aim 2.1 analyses, these results indicate that negative affect did not mediate the association between social well-being and leukocyte gene expression.

Specific Aim 3

It was hypothesized that at T2, 6 months after baseline, women who received a CBSM intervention would report higher levels of social well-being, lower negative affect, and lower levels of pro-inflammatory and pro-metastatic leukocyte gene expression than women who participated in a control condition. Covariates were carried forward into Aim 3 analyses if they were significantly associated with gene expression at baseline. Bivariate correlations were used in order to determine which covariates used in Aim 1 were significantly associated with gene expression. The covariate was included in all regression analyses if it was significantly related to any gene expression variable at a level of $p < .05$.

Age was significantly associated with *CXCR7* ($r = 0.291$, $p = .01$) such that older participants showed higher levels of this pro-inflammatory gene. Longer duration of time since surgery was significantly associated with lower levels of *IL1A* ($r = -0.274$, $p = .02$), *IL1B* ($r = -0.279$, $p = .01$), *TNFRSF21* ($r = -0.378$, $p < .01$), *CCL3* ($r = -0.263$, $p = .02$), *CCL7* ($r = -0.349$, $p < .01$), *CCL20* ($r = -0.256$, $p = .02$), *CCL3L1* ($r = -0.270$, $p = .02$), *CXCR7* ($r = -0.293$, $p = .01$), *PTGS2* ($r = -0.278$, $p = .01$), *MMP9* ($r = -0.415$, $p < .001$), *LMNA* ($r = -0.223$, $p = .05$), the pro-inflammatory cytokine composite ($r = -0.290$, $p = .01$), the pro-inflammatory chemokine composite ($r = -0.316$, $p = .01$), and the pro-metastatic composite ($r = -0.359$, $p < .01$). Stage, education, and BMI were not significantly associated with gene expression (all ps $> .05$).

Two-tailed t-tests were conducted to determine whether receiving radiation, chemotherapy, or hormone therapy was significantly associated with gene expression at T2. Women who received radiation had lower levels of *TNFRSF21* [$t(34) = 2.297$, $p =$

.03] and higher levels of the pro-metastatic composite [$t(59) = -2.043$, $p = .05$]. Those who received chemotherapy had lower levels of *TNFSF10* [$t(18.622) = 2.272$, $p = .04$]. Women who underwent hormone treatment had higher levels of *CCL3L1* [$t(34) = -2.282$, $p = .03$] and *CCL4L2* [$t(34) = -2.214$, $p = .03$] expression at T2 versus those who did not. Therefore, age, days since surgery, radiation treatment, chemotherapy, hormone therapy, and baseline levels of the dependent variable were included in all analyses.

The results of Aim 3 analyses are shown in Table 9. Age, days since surgery, radiation treatment, chemotherapy, hormone therapy, and the baseline level of the dependent variable were entered in Step 1. Intervention condition was entered in Step 2. CBSM participation did not predict T2 social well-being, negative affect, pro-inflammatory leukocyte gene expression, pro-metastatic gene expression, or gene expression composites (all *p*s > .05). According to these results, the hypothesis that CBSM versus control condition would predict social well-being, negative affect, and leukocyte gene expression was not supported.

Given that participants in the CBSM condition and the control condition differed in some SSSS subscales at baseline, these analyses were repeated, first controlling for emotional support from friends, next controlling for informational support from husbands/partners, and finally controlling for informational support from friends. The results remained nonsignificant (all *p*s > .05).

Specific Aim 4 (Conditional)

Given that Specific Aim 3 did not support the hypothesis that intervention condition would predict social well-being, negative affect, and gene expression, no Specific Aim 4 analyses could be carried out to test meditation models.

Specific Aim 5 (Conditional)

Specific Aim 3 analyses were not statistically significant, therefore no further tests for mediation as proposed in Specific Aim 5 were conducted.

Post-Hoc Exploratory Analyses

It is possible that a mechanism other than mediation through negative affect accounts for the association of social well-being with disease promoting factors. Given the direct association of social well-being with inflammation, an exploratory moderation analysis was conducted to test whether marital status moderated the effect of social well-being on inflammation. Step 1 consisted of covariates age, days since surgery, stage, education, and BMI. Step 2 consisted of social well-being and marital status, and Step 3 contained the interaction of social well-being and marital status. The interaction of social well-being and marital status did not account for baseline *IL1A* (β = -0.107, p > .05), *IL1B* (β = 0.028, p > .05), *IL6* (β = -0. 089, p > .05), *TNFSF10* (β = -0.164, p > .05), *TNFRSF21* (β = -0.018, p > .05), *CCL3* (β = 0.018, p > .05), *CCL7* (β = 0.060, p > .05), *CCL20* (β = -0.068, p > .05), *CCL3L1* (β = -0.008, p > .05), *CCL4L2* (β = -0.026, p > .05), *CXCR7* (β = -0.099, p > .05), *PTGS2* (β = 0.115, p > .05), *MMP9* (β = -0.033, p > .05), *LMNA* (β = -0.048, p > .05), the pro-inflammatory cytokine composite (β = -0.056, p > .05), the pro-inflammatory chemokine composite (β = -0.021, p > .05), the pro-metastatic composite (β = -0.043, p > .05), serum IL-6 (β = -0.474, p > .05), serum IL-1β (β = -0.619, p > .05), or serum TNF-α (β = -0.472, p > .05). These results did not support an exploratory hypothesis that marital status would moderate the effect of social well-being on inflammation.

It is also possible that the women's partnership status influences the effect of CBSM on social well-being. Given that significant interaction effects may exist even when there are no significant main effects of an independent variable on a dependent variable, additional exploratory analyses were conducted to determine whether the effect of intervention condition on social well-being was moderated by marital/partner status. It was predicted that receiving CBSM improved social well-being for those women who were married and therefore had the opportunity to apply their new skills in building social support. Multiple regression analyses was conducted with age, days since surgery, radiation treatment, chemotherapy, hormone therapy, and baseline social well-being in Step 1, marital status entered into Step 2, and the interaction term of condition and marital status in Step 3. The interaction of intervention condition and marital status did not predict T2 social well-being ($\beta = 0.250$, $p = .18$).

CHAPTER 4: DISCUSSION

In light of literature demonstrating that satisfaction with social resources relates to survival in women diagnosed with breast cancer, this study proposed a biobehavioral pathway through which social well-being could relate to markers of inflammation and cancer progression in ways that might explain previously reported relations between social resources and survival time (Kroenke et al., 2013). Specifically, I used multiple regression to evaluate whether social well-being was associated with negative affect, pro-inflammatory and pro-metastatic leukocyte gene expression, and serum cytokine levels in women who recently underwent surgery for early-stage breast cancer. Next, I examined whether negative affect mediated the association between social well-being and markers of inflammation and disease-promotion factors. Finally, I tested whether participation in a CBSM intervention enhanced social well-being, decreased negative affect, and lowered levels of pro-inflammatory and pro-metastatic gene expression. Tests were planned, but not conducted, to determine whether CBSM participation reductions in negative affect were mediated by increases in social well-being, and whether the relationship between CBSM participation and reductions in inflammatory and disease promoting factors were mediated by negative affect decreases.

First, it was hypothesized that greater social well-being would be associated with lower negative affect, lower leukocyte gene expression, and lower serum cytokine levels after surgery for early-stage breast cancer. Findings supported this hypothesis, as greater social well-being accounted for lower negative affect, less pro-inflammatory and pro-metastatic gene expression, and lower serum cytokine levels in women both before and, in most analyses, after controlling for BMI. Furthermore, the findings held as significant

after correction for multiple comparisons using the Benjamini-Hochberg procedure. These findings are consistent with prior literature demonstrating upregulation of pro-inflammatory genes in socially isolated individuals (Cole et al., 2007). They also extend to breast cancer patients prior findings that social well-being and social support are associated with cytokines and other proteins that promote tumor growth and angiogenesis after diagnosis of ovarian cancer (Lutgendorf et al., 2002; Lutgendorf et al., 2008). Notably, greater expression of *MMP9* was consistently associated with lower social well-being when analyses were conducted using multivariate regression and using ANCOVA, both with and without BMI in the model. This evidence suggests that social well-being has a particularly strong association with *MMP9*. Matrix metalloproteinases are derived from monocytes, are known to be involved in wound healing responses, and are relevant at the site of the tumor microenvironment (Lutgendorf et al., 2008). Stress hormones have previously been shown to regulate production of matrix metalloproteinases (Lutgendorf & Sood, 2011), and the present study suggests that social well-being may also contribute to MMP levels.

Next, it was hypothesized that negative affect would mediate the relationship between social well-being and markers of inflammation and disease progression. Multiple regression analyses both with and without BMI included in the model as a covariate did not find a significant association between negative affect and leukocyte gene expression or serum cytokines; therefore, further tests of mediation could not be conducted and the hypothesis was not supported. These findings are in contrast with literature demonstrating a relationship between negative affect and inflammation (Antoni et al., 2012). It is possible that the sample size of 78 women was too small to detect an

effect. Alternatively, negative affect may not mediate the relationship between social well-being and inflammation and disease progression.

Social well-being was not associated with expression of some inflammatory genes (e.g., *IL1B*) that were previously found to relate to negative affect in this same sample (Antoni et al., 2012). It is possible that social well-being directly relates to a unique pattern of inflammatory and disease-promoting factors, and that this pathway is not mediated by negative affect. However, it must also be considered that negative affect may be too broad a measure. Distilling reports of depression could have yielded an association with markers of inflammation and disease progression (Bouchard et al., 2016). However, the average Hamilton Depression Rating Scale Scores for this sample were in the normal range, and this limited range of scores could reduce the ability to detect an association. Therefore, a sample of more distressed women could be necessary to find a relationship between negative affect and inflammation, or between depression and inflammation, in the period after breast cancer surgery.

The study also tested the hypothesis that a 10-week CBSM intervention after breast cancer surgery would increase social well-being, decrease negative affect, and decrease leukocyte gene expression. Multiple regression analyses did not find significant CBSM effects; therefore these hypotheses were not supported. These results were also at odds with prior findings from this sample that showed that CBSM decreased negative affect and downregulated pro-inflammatory and pro-metastatic gene expression in women with early-stage breast cancer (Antoni et al., 2012).

However, it should be noted that the statistical analyses generating those results used a mixed modeling technique in which CBSM predicted negative affect and

leukocyte gene expression outcomes at a combination of either 6-month or 1-year timepoints, depending on which data were available. That modeling technique allowed for use of the full sample of 78 women in the longitudinal analyses. In contrast, this study predicted only 6-month outcomes and only included participants in analyses when full data were available, which reduced the sample size available for longitudinal analyses to 36 women. A post hoc power analysis (G*Power Software Version 3.1.3) set at two-tailed, $\alpha = 0.05$ indicated inadequate power (0.62) to detect a large effect size ($D = 0.80$) for Aim 3 (Faul, Erdfelder, Buchner, & Lang, 2009). A sample size of approximately 52 participants would have been needed to detect a large effect size. It is likely that the lack of use of 1-year outcomes and the resulting small sample size of this study explain discrepancies in the results when compared to the findings published by Antoni et al. (2012).

Another possibility is that the CBSM intervention tested here was too brief to create changes in social well-being. The psychological intervention conducted by Andersen et al. (2004) that showed improved social adjustment in intervention participants used a program that lasted for 18 weekly sessions over the course of 4 months followed by 8 monthly booster sessions. Although participants studied by Gudenkauf et al. (2015) who received the cognitive-behavioral components of the intervention over the course of only 5 weeks did report higher levels of perceived social support post-intervention than counterparts in other treatment conditions, parallel increases in the measure of social well-being were not documented. Perhaps an intervention longer than the 10-week CBSM design tested here is necessary in order to

produce changes in social resources. It is possible that *satisfaction* with social support takes longer to foster than changes in social support.

Another interpretation for the lack of CBSM effects on social well-being is that the 6-month follow-up time may not have been long enough to reveal improvements in social well-being. The CBSM modules on social support, assertiveness, and anger management may require extensive practice before the lessons are internalized and the social network and quality of interactions with members of the social network are modified. Therefore, it is possible that satisfaction with social well-being does not increase until one or more years post-intervention. Andersen et al. (2004) did find intervention effects on a measure of perceived social support from family as soon as 4 months post-intervention, but changes in social well-being were not studied. Increases in social well-being may take time and require a complex cascade of changes following increases in levels social support.

Another possible explanation for the lack of intervention effects has to do with the distribution of participants in the CBSM versus the control condition in this subsample. As can be seen in Table 3, the results of SSSS subscale comparisons between CBSM versus control participants indicate that social support from various sources was not equally distributed across groups. The CBSM group reported lower types of positive support and higher types of negative support from multiple sources. These participants also reported lower social well-being than controls at study entry. CBSM participants appear to have already been at a disadvantage in terms of their social networks, which may have impaired our ability to see CBSM effects on social well-being.

The planned analyses also hypothesized tests of mediators of CBSM effects. However, lack of statistical significance of CBSM effects precluded mediation analyses.

Importantly, the null findings of this study cannot be viewed as conclusive, due to the small sample size available for these analyses and limited follow-up period. A prior study did show CBSM effects upon negative affect and leukocyte gene expression in a larger sample that included data collected after a longer follow-up time of 12-months (Antoni et al., 2012). However, the study discussed here may have lacked sufficient power to detect effects. It is therefore possible that a mediation pathway does connect CBSM, social well-being, negative affect, and inflammation, although only partial evidence to support this theory was revealed here.

To explore whether a mechanism other than mediation by negative affect accounted for the effect of social well-being on disease promoting factors, an exploratory moderation analysis was conducted to test whether marital status moderated the effect of social well-being on inflammation. It was found that the interaction of social well-being and marital status did not account for baseline inflammation. Once again, these results should be interpreted in the context of the small sample size, which may have lacked power to detect an effect. As such, this exploratory moderation analysis does not definitively eliminate the possibility of such an alternative biobehavioral pathway.

Similarly, additional exploratory analyses were conducted to test the hypothesis that receiving CBSM would improve social well-being to a greater degree for partnered versus non-partnered women. It was found that marital status did not moderate the effect of intervention condition on T2 social well-being. Although that result does not support the notion that partnered women benefit more from CBSM in terms of their social well-

being, these analyses were largely preliminary and were limited by a small sample size and therefore cannot be interpreted as conclusive.

Comparing SSSS subscale scores revealed patterns in the amount of different types of social support provided by different sources after surgery for breast cancer and 6 months later. At T1 and T2, husbands/partners provided high levels of positive support relative to other sources, particularly instrumental support, yet were also rated as higher in negative support than other sources. Of note, this finding is consistent with a prior study in a partially overlapping sample that found high negative support from male family members of women with breast cancer, yet that study conducted on this sample found higher levels of negative support from male family members of Hispanic women (Jutagir et al., 2015). Therefore, it is possible that the Hispanic women in the study may have driven this effect. Nevertheless, this finding raises the possibility that a psychosocial intervention like CBSM that included the husband/partner could further enhance a breast cancer patient's social well-being by instilling the partner with interpersonal skills that could reduce arguments and conflict. Another avenue for improving social well-being could be enhancing the amount of support provided by male adult family members. These family members generally appeared to provide less support than other sources both at T1 and T2, but psychosocial interventions could be designed to increase support from this relatively underutilized source.

Strengths

This study had several notable strengths. First, the women participated during an exceptionally stressful time when social resources are particularly important, initiating participation right after surgery for breast cancer and continuing through adjuvant

treatment. Next, the concept of social resources was assessed using a measure of social well-being, which is a strength given that the social well-being construct captures subjective satisfaction with social support. Such satisfaction with perceived support is associated with physiological and psychological outcomes during cancer treatment. Analyzing the impact of social well-being and CBSM on both individual genes as well as on gene composite scores was another strength. Studying gene composite scores was a parsimonious approach, while examining the effects of social well-being on individual genes allowed for an examination of which specific genes might be driving the significant composite score findings.

Several aspects of the data analysis strategy suggest that the findings reported in this study are robust. First, the majority of the significant effects of social well-being on negative affect and pro-inflammatory and pro-metastatic gene expression persisted above and beyond the effects of BMI, which is strongly and consistently associated with inflammation in the literature (O'Connor et al., 2009). Secondly, most of the statistically significant findings survived correction for multiple comparisons using the Benjamini-Hochberg procedure, which is a recommended technique when analyzing medical data in the context of directional hypotheses (Glickman, Rao, & Schultz, 2014). Finally, the association between social well-being and multiple measurements of inflammatory outcomes, specifically leukocyte gene expression in addition to serum cytokine levels, also speaks to the robustness of the association between social well-being and inflammation.

Limitations

Some limitations should be taken into account when interpreting the results of this study. The small sample size and proportion of missing data may have limited ability to detect effects. Multiple imputation was attempted to replace missing data, but would not run due to the numerous variables in the study and the degree of missing data. Therefore, excluding participants with missing data from analyses that required that data was considered to be a conservative alternative strategy, as the low sample size biased the results in the direction of false negatives. Due to this small sample size, the mediation analyses were considered exploratory. So as not to further diminish the small sample size (Babyak, 2004), some variables previously found to be associated with inflammation were not included in the study as control variables due to incomplete information.

Another study limitation was that the subgroup of participants with gene expression data randomized to the control condition differed from those in the CBSM condition on several outcome measures, specifically social well-being and markers of inflammation. However, baseline levels of these variables were entered as control variables in all Aim 3 analyses. The CBSM participants also appeared to have social networks that were less favorable than control participants. Thus the social context may have created barriers for intervention effects to work against in improving women's social well-being. Follow-up analyses were conducted to control for SSSS subscale scores that differed between groups at baseline to address this issue, but did not reveal any CBSM effects after making these adjustments.

With regard to the design of the original randomized controlled trial, it should be noted that the control condition was not attention-matched to the CBSM condition.

However, this design may have actually been a strength of this study, given that social support from other breast cancer patients over the course of 10 weeks was uniquely provided in the experimental CBSM condition. Some patients may have varied in the amount of chemotherapy they received and the time elapsed between chemotherapy and T2, but detailed assessments on chemotherapy dosage and administration schedule were not collected.

The measures used in the study had some flaws. Social well-being and negative affect were measured with retrospective self-report measures. Participants may not have accurately remembered their feelings, or may have underreported negative affect and dissatisfaction with social support in an attempt to appear socially desirable. The SSSS included several single-item scales, which may have limited reliability. However, Zimmerman et al. (2006) showed reliability and validity of single-item psychological measures.

There are some limitations to the generalizability of the results. Given that the women who participated in this trial were predominantly non-Hispanic White, highly educated, and had early-stage breast cancer, the generalizability of the results to diverse, low-income women and women with metastatic disease may be limited. Furthermore, the data analyzed here were collected between 1998 and 2005. Cancer treatment and preference for cancer treatments (e.g., lumpectomy versus mastectomy) have evolved since that time, which may reduce generalizability to current patients.

Future Directions

The cross-sectional relationships between social well-being and indicators of inflammation and metastasis are suggestive, but additional longitudinal studies with

larger sample sizes are needed to examine the directionality of this relationship, as well as whether interventions that enhance satisfaction with social resources also decrease inflammation. These interventions should specifically address interpersonal conflicts that can occur between patients and their caregiving partners, and should seek to increase support provided by other adult family members, particularly males. Randomized controlled trials of interventions that investigate other novel strategies of increasing social well-being during adaptation to cancer should be designed.

Given that social well-being has been found to be a correlate of disease promoting factors in women diagnosed with numerous types of cancer, it will be important to develop more nuanced scales of social well-being to determine whether there exist specific domains of social well-being that are most strongly related to physiological outcomes. Studies of more diverse samples are needed to examine whether these findings hold across different ethnic and racial groups, especially given the culture-specific nature of social interactions (Jutagir et al., 2015).

Conclusions

To elucidate pathways connecting availability of social resources to longer survival time, this study tested associations between social well-being and negative affect and markers of inflammation and disease progression in women recovering from surgery for early-stage breast cancer. Follow-up tests were conducted to determine whether negative affect mediated the relationship between social well-being and inflammation. Next, this study tested the effects of a 10-week CBSM intervention on social well-being, negative affect, and inflammatory leukocyte gene expression.

Results suggested robust cross-sectional negative relationships between social well-being and negative affect, and between social well-being and pro-inflammatory and pro-metastatic leukocyte gene expression and pro-inflammatory serum cytokines 2 – 19 weeks after surgery for breast cancer. However, evidence supporting the hypothesized mediation of this relationship by negative affect was not found. Furthermore, this study did not find that CBSM influenced social well-being, negative affect, or leukocyte gene expression. It is possible that the lack of mediation and intervention effects is due to the small sample size available for these analyses. Nevertheless, future research should be conducted exploring alternative biobehavioral pathways linking social well-being to survival after cancer diagnosis. More research is also needed to develop strategies of enhancing social well-being that can be incorporated into psychosocial interventions for patients diagnosed with breast cancer.

TABLES

Table 1. Gene symbols defined by description and function.

Gene Symbol	**Gene Description**	**Gene Function** (Pruitt et al., 2014)
IL1A	Interleukin 1 Alpha	Encodes cytokine IL-1α , which is produced by white blood cells (leukocytes) in response to wounds and contributes to inflammation and programmed cell death (apoptosis).
IL1B	Interleukin 1 Beta	Encodes cytokine IL-1β, which is produced by leukocytes and contributes to inflammation and programmed cell death (apoptosis).
IL6	Interleukin 6	Encodes cytokine IL-6, which is produced during inflammation and induces further inflammatory transcription.
TNFSF10	Tumor Necrosis Factor (Ligand) Superfamily, Member 10	Encodes a cytokine that induces apoptosis in tumor cells.
TNFRSF21	Tumor Necrosis Factor Receptor Superfamily, Member 21	Encodes a pro-inflammatory cytokine that induces apoptosis and regulates immune functioning.
PTGS2	Prostaglandin-Endoperoxide Synthase 2	Encodes an enzyme involved in synthesis of a prostaglandin (cyclooxygenase-2; COX-2), which acts as a hormone to stimulate inflammation and cell division.
CCL3	Chemokine (C-C motif) Ligand 3	Encodes a chemokine that signals recruitment of immune cells to sites of inflammation.
CCL7	Chemokine (C-C Motif) Ligand 7	Encodes chemokines that attract macrophages during inflammation and metastasis.
CCL20	Chemokine (C-C motif) Ligand 20	Encodes a chemokine that signals movement of white blood cells; involved in inflammation.
CCL3L1	Chemokine (C-C Motif) Ligand 3-Like 1	Encodes a pro-inflammatory chemokine that regulates immune functioning.
CCL4L2	Chemokine (C-C Motif) Ligand 4-Like 2	Encodes a pro-inflammatory chemokine involved in immune regulation.
CXCR7	C-X-C Chemokine Receptor Type 7	Encodes a pro-inflammatory chemokine receptor; regulates migration of tumor cells (Berahovich et al., 2013).

MMP9	Matrix Metallopeptidase 9	Encodes proteins that facilitate the breakdown of the extracellular matrix in the context of tissue remodeling and metastasis.
LMNA	Lamin A/C	Encodes proteins that provide structure near the inner nuclear membrane of a cell. Involved in tissue remodeling.

Table 2. Week by week cognitive behavioral stress management intervention content.

	Cognitive Behavioral Training	**Relaxation Training**
Week 1	Rational for Stress Management	7 Group PMR
Week 2	Stress and Awareness	Diaphragmatic Breathing 4 group PMR Beach Scene Imagery
Week 3	Automatic Thoughts Cognitive Distortions	Deep Breaching and Counting Passive PMR Special Place Imagery
Week 4	Rational Thought Replacement	Introduction to Autogenics
Week 5	Coping	Autogenics cont.
Week 6	Coping cont.	Light Meditation
Week 7	Social Support	Color Garden Imagery
Week 8	Anger Management	Meditation and Beach Scene Imagery
Week 9	Assertiveness Training	Mindfulness
Week 10	Review and Wrap-Up	The Enchanted Cove

Note: PMR = Progressive Muscle Relaxation.

Table 3. Demographic and medical characteristics of the sample.

Variable		Mean (SD)		
		CBSM (N=43)	Control (N=35)	Total (N=78)
Age after surgery		50.09 (7.38)	48.89 (7.71)	49.55 (7.51)
Ethnic Identification	*Non-Hispanic White*	32 (74.4%)	22 (62.9%)	54 (69.2%)
	Hispanic/Latino	7 (16.3%)	9 (25.7%)	16 (20.5%)
	African American/Black	4 (9.3%)	3 (8.6%)	7 (9.0%)
	Other	0 (0.0%)	1 (2.9%)	1 (1.3%)
Years of Education		16.19 (2.68)	15.46 (2.44)	15.86 (2.58)
Income[1]		72.78 (31.36)	80.13 (64.33)	76.19 (49.20)
Employment	*Employed full time*	36 (83.7%)	28 (80.0%)	64 (82.1%)
	Not employed full time	7 (16.3%)	7 (20.0%)	14 (17.9%)
Marital Status	*Married/Partnered*	32 (74.4%)	21 (60.0%)	53 (67.9%)
	Separated	2 (4.7%)	0 (0.0%)	2 (2.6%)
	Divorced	8 (18.6%)	11 (31.4%)	19 (24.4%)
	Widowed	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Single	1 (2.3%)	3 (8.6%)	4 (5.1%)
Children	*Yes*	12 (27.9%)	12 (34.3%)	24 (30.8%)
	No	31 (72.1%)	23 (65.7%)	54 (69.2%)
Number of Children		2.10 (0.91)	2.14 (0.77)	2.11 (0.85)
Surgery	*Lumpectomy*	17 (39.5%)	17 (48.6%)	34 (43.6%)
	Mastectomy	26 (60.5%)	18 (51.4%)	44 (56.4%)
Days since Surgery		34.42 (23.82)	43.69 (24.06)	38.58 (24.22)
Cancer Stage[2]	*Stage 0*	7 (16.3%)	3 (8.6%)	10 (12.8%)
	Stage I	17 (39.5%)	20 (57.1%)	37 (47.4%)
	Stage II	14 (32.6%)	10 (28.6%)	24 (30.8%)
	Stage III	5 (11.6%)	2 (5.7%)	7 (9.0%)
ER Status	*Positive*	21 (48.8%)	22 (62.9%)	43 (55.1%)
	Negative	6 (14.0%)	2 (5.7%)	8 (10.3%)
	Unknown	16 (37.2%)	11 (31.4%)	27 (34.6%)
PR Status	*Positive*	14 (32.6%)	14 (40.0%)	28 (35.9%)
	Negative	7 (16.3%)	4 (11.4%)	11 (14.1%)
	Unknown	22 (51.2%)	17 (48.6%)	39 (50.0%)
Her2/neu Status	*Positive*	5 (11.6%)	6 (17.1%)	11 (14.1%)
	Negative	20 (46.5%)	11 (31.4%)	31 (39.7%)
	Unknown	18 (41.9%)	18 (51.4%)	36 (46.2%)
Medication Use	*Anti-depressant*	2 (4.7%)	3 (8.6%)	5 (6.4%)
	Anti-anxiety	8 (18.6%)	5 (14.3 %)	13 (16.7 %)
	Sleep	8 (18.6%)	4 (11.4%)	12 (15.4%)
	Pain	13 (30.2%)	9 (25.7%)	22 (28.2%)
Body Mass Index		26.53 (4.98)	27.54 (8.24)	27.00 (6.49)

(kg/m2)				
	Normal Weight	16 (55.2%)	10 (47.6%)	26 (52.0%)
	Overweight	7 (24.1%)	7 (33.3%)	14 (28.0%)
	Obese	6 (20.7%)	4 (19.0%)	10 (20.0%)
Hamilton Depression T1		6.93 (5.97)	6.37 (4.97)	6.68 (5.52)
Hamilton Depression T2		4.97 (5.77)	5.39 (4.36)	5.16 (5.14)
Radiation	*Yes*	16 (37.2%)	9 (25.7%)	25 (32.1%)
	No	21 (48.8%)	15 (42.9%)	36 (46.2%)
	Unknown	6 (14.0%)	11 (31.4%)	17 (21.8%)
Chemotherapy	*Yes*	20 (46.5%)	13 (37.1%)	33 (42.3%)
	No	17 (39.5%)	11 (31.4%)	28 (35.9%)
	Unknown	6 (14.0%)	11 (31.4%)	17 (21.8%)
Hormone Therapy	*Yes*	22 (51.2%)	16 (45.7%)	38 (48.7%)
	No	15 (34.9%)	8 (22.9%)	23 (29.5%)
	Unknown	6 (14.0%)	11 (31.4%)	17 (21.8%)
Emotional Support T1	*HP*	4.08 (0.94)	4.44 (0.95)	4.24 (0.95)
	AW	4.05 (0.80)	4.28 (0.92)	4.15 (0.85)
	CMAF	3.73 (1.14)	3.90 (1.04)	3.81 (1.09)
	*FR***	4.25 (0.72)	4.64 (0.43)	4.43 (0.63)
Informational Support T1	*HP**	2.31 (1.26)	3.07 (1.30)	2.65 (1.32)
	AW	2.46 (1.30)	2.93 (1.14)	2.67 (1.25)
	CMAF	2.17 (1.23)	2.21 (1.00)	2.19 (1.12)
	*FR**	2.79 (1.24)	3.46 (1.27)	3.09 (1.29)
Instrumental Support T1	*HP*	3.60 (1.29)	4.04 (1.19)	3.79 (1.26)
	AW	2.59 (1.55)	3.27 (1.53)	2.90 (1.57)
	CMAF	2.23 (1.38)	2.50 (1.45)	2.36 (1.41)
	FR	2.64 (1.53)	3.14 (1.40)	2.87 (1.48)
Negative Support T1	*HP*	1.43 (0.88)	1.39 (0.59)	1.41 (0.77)
	AW	1.14 (0.25)	1.30 (0.45)	1.21 (0.36)
	CMAF	1.08 (0.27)	1.19 (0.44)	1.13 (0.36)
	FR	1.19 (0.58)	1.10 (0.24)	1.15 (0.46)
Emotional Support T2	*HP*	4.05 (0.95)	4.16 (1.11)	4.09 (1.00)
	*AW**	3.82 (0.96)	4.34 (0.71)	4.01 (0.90)
	*CMAF***	3.30 (1.17)	4.31 (0.59)	3.73 (1.08)
	*FR***	3.92 (0.84)	4.54 (0.64)	4.17 (0.82)
Informational Support T2	*HP**	1.79 (0.99)	2.39 (0.98)	2.00 (1.02)
	AW	2.03 (1.02)	2.05 (1.18)	2.04 (1.07)
	CMAF	1.35 (0.56)	1.68 (1.16)	1.49 (0.87)
	*FR**	2.11 (1.00)	2.71 (1.30)	2.35 (1.16)
Instrumental Support T2	*HP*	2.73 (1.42)	3.11 (1.45)	2.86 (1.43)
	AW	2.09 (1.35)	2.21 (1.18)	2.14 (1.28)

	CMAF	1.88 (1.05)	2.56 (1.50)	2.16 (1.29)
	*FR**	1.78 (0.99)	2.54 (1.59)	1.33 (0.93)
Negative Support T2	*HP*	1.24 (0.57)	1.25 (0.39)	1.25 (0.51)
	*AW**	1.18 (0.39)	1.03 (0.11)	1.13 (0.33)
	CMAF	1.08 (0.27)	1.00 (0.00)	1.04 (0.21)
	FR	1.10 (0.45)	1.04 (0.14)	1.08 (0.29)

[1]Income in thousands of US dollars
[2]TNM staging system
HP, husband/partner; AW, adult women; CMAF, children and male adult family; and FR, friends.
Note: Significance of CBSM versus control group differences are denoted as follows:
*p < .05 **p < .01

Table 4. Two-tailed paired samples t-tests comparing levels of social support from different sources at T1 and T2.

Time	Support Type	Source 1	Source 2	Source 1 - Source 2	SD	*t*	df	*p* (two-tailed)
T1	Emotional	HP	AW	0.006	1.080	-0.043	51	.966
		HP	CMAF	0.458	1.062	2.864	43	.006**
		HP	FR	-0.175	0.913	-1.508	61	.137
		AW	CMAF	0.336	0.802	3.053	52	.004**
		AW	FR	-0.224	0.788	-2.326	66	.023*
		CMAF	FR	-0.617	0.990	-4.707	56	.000**
T1	Negative	HP	AW	0.173	0.593	2.104	51	.040*
		HP	CMAF	0.239	0.555	2.852	43	.007**
		HP	FR	0.282	0.618	3.595	61	.001**
		AW	CMAF	0.057	0.349	1.181	52	.243
		AW	FR	0.090	0.313	2.342	66	.022*
		CMAF	FR	0.018	0.283	0.468	56	.641
T1	Informational	HP	AW	-0.154	1.460	-0.760	51	.451
		HP	CMAF	0.622	1.319	3.164	44	.003**
		HP	FR	-0.500	1.617	-2.435	61	.018*
		AW	CMAF	0.407	1.325	2.260	53	.028*
		AW	FR	-0.388	1.314	-2.418	66	.018*
		CMAF	FR	-0.983	1.249	-5.990	57	.000**
T1	Instrumental	HP	AW	0.788	2.071	2.746	51	.008**
		HP	CMAF	1.489	1.646	6.067	44	.000**
		HP	FR	0.968	1.774	4.296	61	.000**
		AW	CMAF	0.407	1.486	2.015	53	.049*
		AW	FR	0.194	2.017	0.787	66	.434
		CMAF	FR	-0.569	1.788	-2.423	57	.019*
T2	Emotional	HP	AW	0.015	1.107	0.087	42	.931
		HP	CMAF	0.303	1.394	1.359	38	.182
		HP	FR	-0.107	1.061	-0.711	49	.480
		AW	CMAF	0.317	0.838	2.390	39	.022*
		AW	FR	-0.146	0.775	-1.349	50	.183
		CMAF	FR	-0.526	0.918	-3.842	44	.000**
T2	Negative	HP	AW	0.128	0.451	1.859	42	.070
		HP	CMAF	0.205	0.425	3.015	38	.005**
		HP	FR	0.180	0.438	2.909	49	.005**
		AW	CMAF	0.088	0.275	2.014	39	.051
		AW	FR	0.088	0.239	2.638	50	.011*
		CMAF	FR	-0.011	0.075	-1.000	44	.323
T2	Informational	HP	AW	-0.186	1.547	-0.789	42	.435

		HP	CMAF	0.513	1.295	2.473	38	.018*
		HP	FR	-0.440	1.402	-2.219	49	.031*
		AW	CMAF	0.600	0.871	4.356	39	.000**
		AW	FR	-0.294	1.006	2.088	50	.042*
		CMAF	FR	-0.911	0.900	-6.791	44	.000**
T2	Instrumental	HP	AW	0.595	1.849	2.087	41	.043*
		HP	CMAF	0.605	2.047	1.822	37	.076
		HP	FR	0.680	1.834	2.621	49	.012*
		AW	CMAF	0.105	1.269	0.511	37	.612
		AW	FR	0.080	1.441	0.393	49	.696
		CMAF	FR	0.070	1.100	0.416	42	.680

Note: SD, standard deviation; df, degrees of freedom; HP, husband/partner; AW, adult women; CMAF, children and male adult family; and FR, friends.
*p < .05 **p < .01

Table 5. Means and standard deviations of key study variables for participants in the CBSM condition, in the control condition, and in the total sample.

Variable	Timepoint	Mean (SD)		
		CBSM (N=43)	Control (N=35)	Total (N=78)
Social Well-Being	*T1***	21.34 (5.33)	24.06 (3.31)	22.56 (4.71)
	*T2***	19.72 (6.08)	23.33 (3.51)	21.14 (5.48)
Negative Affect	*T1*	41.49 (10.78)	39.11 (11.44)	40.42 (11.07)
	T2	38.30 (8.05)	36.54 (11.30)	37.61 (9.41)
IL1A	*T1**	9.78 (1.80)	8.91 (1.78)	9.39 (1.83)
	T2	9.92 (1.74)	10.00 (1.29)	9.96 (1.54)
IL1B	*T1***	13.52 (1.18)	12.47 (1.70)	13.05 (1.52)
	T2	13.50 (1.25)	13.65 (0.81)	13.57 (1.07)
IL6	*T1*	10.57 (1.87)	10.09 (2.22)	10.36 (2.03)
	T2	10.76 (2.01)	10.88 (1.47)	10.82 (1.77)
TNFSF10	*T1*	9.41 (1.05)	9.70 (1.25)	9.54 (1.15)
	T2	9.75 (1.07)	9.32 (0.91)	9.56 (1.01)
TNFRSF21	*T1**	10.44 (0.91)	10.00 (0.84)	10.25 (0.90)
	T2	10.39 (0.91)	10.56 (0.72)	10.46 (0.83)
CCL3	*T1**	13.25 (1.25)	12.31 (1.74)	12.83 (1.55)
	T2	13.40 (1.29)	13.23 (0.87)	13.32 (1.11)
CCL7	*T1*	10.47 (1.56)	9.92 (1.49)	10.22 (1.54)
	T2	10.35 (1.52)	10.26 (1.15)	10.31 (1.35)
CCL20	*T1**	11.10 (1.83)	9.95 (2.09)	10.58 (2.02)
	T2	11.15 (1.77)	11.27 (1.54)	11.20 (1.65)
CCL3L1	*T1**	12.47 (1.39)	11.67 (1.75)	12.11 (1.60)
	T2	12.64 (1.41)	12.60 (0.89)	12.62 (1.19)
CCL4L2	*T1**	11.66 (1.34)	10.98 (1.63)	11.35 (1.51)
	T2	11.91 (1.37)	11.90 (1.00)	11.91 (1.20)
CXCR7	*T1***	8.30 (0.87)	7.83 (0.56)	8.09 (0.78)
	T2	8.11 (0.68)	8.41 (0.62)	8.24 (0.67)
PTGS2	*T1**	11.78 (1.22)	11.04 (1.34)	11.45 (1.32)
	T2	11.73 (1.19)	11.95 (0.94)	11.83 (1.08)
MMP9	*T1*	9.40 (1.14)	8.96 (0.85)	9.20 (1.04)
	T2	9.31 (1.06)	9.42 (0.86)	9.36 (0.96)
LMNA	*T1***	10.25 (0.80)	9.90 (0.75)	9.96 (0.84)
	T2	10.02 (0.91)	9.88 (0.61)	9.96 (0.78)
Cytokine Composite	*T1**	10.92 (1.11)	10.37 (1.27)	10.67 (1.21)
	T2	11.01 (1.06)	11.06 (0.78)	11.03 (0.93)
Chemokine Composite	*T1***	11.21 (1.16)	10.45 (1.34)	10.87 (1.29)
	T2	11.26 (1.16)	11.28 (0.84)	11.27 (1.02)
Pro-Metastatic Composite	*T1***	9.82 (0.89)	9.28 (0.73)	9.58 (0.86)

	T2	9.67 (0.90)	9.65 (0.59)	9.66 (0.77)
Serum IL-6 (log transformed)	*T1*	1.55 (1.20)	1.74 (1.13)	1.63 (1.16)
Serum IL-1β (log transformed)	*T1*	0.13 (1.27)	0.64 (0.94)	0.10 (1.13)
Serum TNF-α (log transformed)	*T1*	0.60 (1.00)	0.70 (1.02)	0.65 (1.00)

Note: Gene expression reported in RNA expression units (log2).
Significance of CBSM versus control group differences are denoted as follows:
*p < .05 **p < .01

Table 6. Correlations between expression of genes for pro-inflammatory cytokines, genes for pro-inflammatory chemokines, and pro-metastatic genes at T1 and T2.

T1 Pro-Inflammatory Cytokines	**1**	**2**	**3**	**4**	**5**	**6**
1. *IL1A*	--	--	--	--	--	--
2. *ILIB*	0.837**	--	--	--	--	--
3. *IL6*	0.859**	0.754**	--	--	--	--
4. *TNFSF10*	0.312**	0.111	0.573**	--	--	--
5. *TNFRSF21*	0.541**	0.429**	0.444**	0.236*	--	--
6. *PTGS2*	0.891**	0.824**	0.797**	0.225*	0.414**	--
T2 Pro-Inflammatory Cytokines	**1**	**2**	**3**	**4**	**5**	**6**
1. *IL1A*	--	--	--	--	--	--
2. *ILIB*	0.818**	--	--	--	--	--
3. *IL6*	0.838**	0.717**	--	--	--	--
4. *TNFSF10*	0.043	0.029	0.446**	--	--	--
5. *TNFRSF21*	0.377*	0.368*	0.184	-0.171	--	--
6. *PTGS2*	0.897**	0.826**	0.775**	-0.035	0.344*	--
T1 Pro-Inflammatory Chemokines	**1**	**2**	**3**	**4**	**5**	**6**
1. *CCL3*	--	--	--	--	--	--
2. *CCL7*	0.455**	--	--	--	--	--
3. *CCL20*	0.849**	0.509**	--	--	--	--
4. *CCL3L1*	0.983**	0.482**	0.838**	--	--	--
5. *CCL4L2*	0.935**	0.511**	0.886**	0.941**	--	--
6. *CXCR7*	0.391**	0.505**	0.585**	0.362**	0.443**	--
T2 Pro-Inflammatory Chemokines	**1**	**2**	**3**	**4**	**5**	**6**
1. *CCL3*	--	--	--	--	--	--
2. *CCL7*	0.468**	--	--	--	--	--
3. *CCL20*	0.755**	0.641**	--	--	--	--
4. *CCL3L1*	0.969**	0.500**	0.736**	--	--	--
5. *CCL4L2*	0.944**	0.579**	0.845**	0.947**	--	--
6. *CXCR7*	0.208	0.617**	0.550**	0.237	0.331*	--
T1 Pro-Metastatic Factors	**1**	**2**				
1. *MMP9*	--	--				
2. *LMNA*	0.685**	--				
T2 Pro-Metastatic Factors	**1**	**2**				
1. *MMP9*	--	--				
2. *LMNA*	0.544**	--				

*p < .05 **p < .01

Table 7. Aim 1.1 and 1.2 (BMI-adjusted) cross-sectional baseline regression analyses relating leukocyte pro-inflammatory and pro-metastatic gene expression and social well-being in multivariable analyses.

Aim	Independent Variable	Dependent Variable	N	β (SE)	t	p	R^2 Change
1.1	Social Well-Being	Negative Affect**†	78	-0.432 (0.238)	-4.186	.000	0.183
1.2	Social Well-Being	Negative Affect**†	50	-0.589 (0.279)	-4.641	.000	0.286
1.1	Social Well-Being	*IL1A*†*	78	-0.224 (0.043)	-2.038	.045	0.049
1.2	Social Well-Being	*IL1A*†*	50	-0.397 (0.059)	-2.624	.012	0.130
1.1	Social Well-Being	*ILIB*	78	-0.124 (0.036)	-1.107	.272	0.015
1.2	Social Well-Being	*ILIB*	50	-0.216 (0.047)	-1.378	.175	0.038
1.1	Social Well-Being	*IL6*	78	-0.152 (0.049)	-1.334	.186	0.023
1.2	Social Well-Being	*IL6*†	50	-0.242 (0.071)	-1.535	.132	0.048
1.1	Social Well-Being	*TNFSF10*	78	-0.019 (0.028)	-0.162	.872	0.000
1.2	Social Well-Being	*TNFSF10*	50	-0.117 (0.041)	-0.719	.476	0.011
1.1	Social Well-Being	*TNFRSF21*	78	-0.138 (0.021)	-1.269	.209	0.019
1.2	Social Well-Being	*TNFRSF21*†	50	-0.302 (0.026)	-2.006	.051	0.075
1.1	Social Well-Being	*CCL3*	78	-0.126 (0.037)	-1.125	.264	0.016
1.2	Social Well-Being	*CCL3*	50	-0.251 (0.048)	-1.639	.109	0.052
1.1	Social Well-Being	*CCL7*	78	-0.099 (0.036)	-0.895	.374	0.010
1.2	Social Well-Being	*CCL7*	50	-0.188 (0.046)	-1.207	.234	0.029
1.1	Social Well-Being	*CCL20*	78	-0.170 (0.048)	-1.512	.135	0.028
1.2	Social Well-Being	*CCL20*†*	50	-0.332 (0.065)	-2.158	.037	0.091
1.1	Social Well-Being	*CCL3L1*	78	-0.134 (0.038)	-1.204	.232	0.018
1.2	Social Well-Being	*CCL3L1*	50	-0.245 (0.050)	-1.593	.118	0.049
1.1	Social Well-Being	*CCL4L2*	78	-0.146 (0.036)	-1.292	.200	0.021
1.2	Social Well-Being	*CCL4L2*	50	-0.273 (0.050)	-1.767	.084	0.062
1.1	Social Well-Being	*CXCR7*	78	-0.178 (0.018)	-1.692	.095	0.031
1.2	Social Well-Being	*CXCR7*†	50	-0.280 (0.023)	-1.976	.055	0.065
1.1	Social Well-Being	*PTGS2*	78	-0.146 (0.032)	-1.308	.195	0.021
1.2	Social Well-Being	*PTGS2*†*	50	-0.353 (0.042)	-2.313	.026	0.103
1.1	Social Well-Being	*MMP9*†*	78	-0.239 (0.023)	-2.301	.024	0.056
1.2	Social Well-Being	*MMP9*†*	50	-0.353 (0.032)	-2.338	.024	0.102
1.1	Social Well-Being	*LMNA*†*	78	-0.273 (0.020)	-2.478	.016	0.073
1.2	Social Well-Being	*LMNA*†**	50	-0.504 (0.024)	-3.531	.001	0.210
1.1	Social Well-Being	Cytokine Composite	78	-0.172 (0.029)	-1.554	.124	0.029
1.2	Social Well-Being	Cytokine Composite*†	50	-0.328 (0.040)	-2.127	.039	0.089
1.1	Social Well-Being	Chemokine Composite	78	-0.163 (0.030)	-1.480	.143	0.026
1.2	Social Well-Being	Chemokine Composite*†	50	-0.311 (0.040)	-2.032	.048	0.080
1.1	Social Well-Being	Pro-Metastatic	78	-0.277 (0.019)	-2.620	.011	0.075

1.2	Social Well-Being	Composite*† Pro-Metastatic Composite**†	50	-0.458 (0.026)	-3.081	.004	0.173
1.1	Social Well-Being	Serum IL-6**†	51	-0.410 (0.035)	-3.240	.002	0.159
1.2	Social Well-Being	Serum IL-6*	36	-0.382 (0.047)	-2.322	.027	0.126
1.1	Social Well-Being	Serum IL-1β*†	51	-0.318 (0.037)	-2.319	.025	0.096
1.2	Social Well-Being	Serum IL-1β	36	-0.325 (0.053)	-1.836	.077	0.091
1.1	Social Well-Being	Serum TNF-α*†	51	-0.330 (0.033)	-2.382	.022	0.103
1.2	Social Well-Being	Serum TNF-α	36	-0.279 (0.050)	-1.507	.143	0.067

Note: Aim 1.1 analyses control for age, stage of disease, days since surgery, and education. Aim 1.2 analyses control for age, stage of disease, days since surgery, education, and BMI.

*p < .05 **p < .01

†Statistically significant after application of the Benjamini-Hochberg procedure at a false discovery rate of 0.10.

Table 8. Aim 2.1 and 2.2 (BMI-adjusted) cross-sectional baseline regression analyses relating leukocyte pro-inflammatory and pro-metastatic gene expression to negative affect in multivariable analyses.

Aim	Independent Variable	Dependent Variable	N	β (SE)	t	p
2.1	Negative Affect	*IL1A*	78	0.236 (0.021)	1.916	.059
2.2	Negative Affect	*IL1A*	50	0.153 (0.033)	0.838	.407
2.1	Negative Affect	*TNFRSF21*	78	0.098 (0.010)	0.784	.436
2.2	Negative Affect	*TNFRSF21*	50	0.078 (0.014)	0.430	.670
2.1	Negative Affect	*CCL20*	78	0.236 (0.024)	1.872	.065
2.2	Negative Affect	*CCL20*	50	0.119 (0.036)	0.640	.526
2.1	Negative Affect	*CXCR7*	78	0.184 (0.009)	1.544	.127
2.2	Negative Affect	*CXCR7*	50	0.250 (0.013)	1.487	.145
2.1	Negative Affect	*PTGS2*	78	0.240 (0.015)	1.914	.060
2.2	Negative Affect	*PTGS2*	50	0.191 (0.023)	1.041	.304
2.1	Negative Affect	*MMP9*	78	0.058 (0.012)	0.484	.630
2.2	Negative Affect	*MMP9*	50	0.184 (0.018)	1.016	.315
2.1	Negative Affect	*LMNA*	78	0.145 (0.010)	1.158	.251
2.2	Negative Affect	*LMNA*	50	0.193 (0.013)	1.130	.265
2.1	Negative Affect	Cytokine Composite	78	0.157 (0.014)	1.246	.217
2.2	Negative Affect	Cytokine Composite	50	0.052 (0.022)	0.277	.783
2.1	Negative Affect	Chemokine Composite	78	0.106 (0.015)	0.845	.401
2.2	Negative Affect	Chemokine Composite	50	0.022 (0.022)	0.117	.908
2.1	Negative Affect	Pro-Metastatic Composite	78	0.105 (0.010)	0.873	.386
2.2	Negative Affect	Pro-Metastatic Composite	50	0.206 (0.014)	1.155	.225
2.1	Negative Affect	Serum IL-6	51	-0.104 (0.016)	-0.721	.474
2.2	Negative Affect	Serum IL-6	36	-0.066 (0.022)	-0.309	.760
2.1	Negative Affect	Serum IL-1β	51	-0.020 (0.017)	-0.128	.899
2.2	Negative Affect	Serum IL-1β	36	0.113 (0.025)	0.495	.625
2.1	Negative Affect	Serum TNF-α	51	-0.103 (0.015)	-0.648	.521
2.2	Negative Affect	Serum TNF-α	36	-0.070 (0.023)	-0.292	.772

Note: Aim 2.1 analyses control for age, days since surgery, and baseline levels of the dependent variable. Aim 2.2 analyses control for age, days since surgery, BMI, and baseline levels of the dependent variable.

*p < .05 **p < .01

Table 9. Aim 3 regression analyses predicting social well-being, negative affect, and markers of inflammation and metastasis from study condition in multivariable analyses controlling for age, days since surgery, radiation, chemotherapy, hormone therapy, and baseline levels of the dependent variable.

Independent Variable	Dependent Variable	N	R^2 Change	β (SE)	t	p
Condition	Social Well-Being	60	0.001	-0.035 (0.931)	-0.422	.675
Condition	Negative Affect	60	0.010	0.104 (2.342)	0.816	.418
Condition	*IL1A*	36	0.009	0.106 (0.582)	0.580	.566
Condition	*IL1B*	36	0.002	0.047 (0.320)	0.333	.741
Condition	*IL6*	36	0.006	0.087 (0.639)	0.506	.617
Condition	*TNFSF10*	36	0.050	0.250 (0.344)	1.543	.134
Condition	*TNFRSF21*	36	0.037	-0.212 (0.266)	-1.397	.174
Condition	*CCL3*	36	0.036	0.208 (0.365)	1.299	.204
Condition	*CCL7*	36	0.003	-0.064 (0.449)	-0.407	.687
Condition	*CCL20*	36	0.003	0.062 (0.582)	0.366	.717
Condition	*CCL3L1*	36	0.032	0.196 (0.402)	1.199	.241
Condition	*CCL4L2*	36	0.021	0.159 (0.420)	0.940	.355
Condition	*CXCR7*	36	0.058	-0.266 (0.252)	-1.474	.152
Condition	*PTGS2*	36	0.000	0.012 (0.378)	0.074	.942
Condition	*MMP9*	36	0.002	-0.049 (0.310)	-0.319	.752
Condition	*LMNA*	36	0.000	0.024 (0.294)	0.136	.893
Condition	Cytokine Composite	36	0.007	0.092 (0.323)	0.562	.579
Condition	Chemokine Composite	36	0.006	0.083 (0.350)	0.499	.622
Condition	Pro-Metastatic Composite	36	0.001	-0.028 (0.261)	-0.175	.863

Note: Aim 3 analyses control for age, days since surgery, radiation treatment, chemotherapy, hormone treatment, and baseline levels of the dependent variable.
*p < .05 **p < .01

FIGURES

Figure 1. Theoretical model of CBSM effects on social well-being, negative affect, and inflammation after surgery for breast cancer.

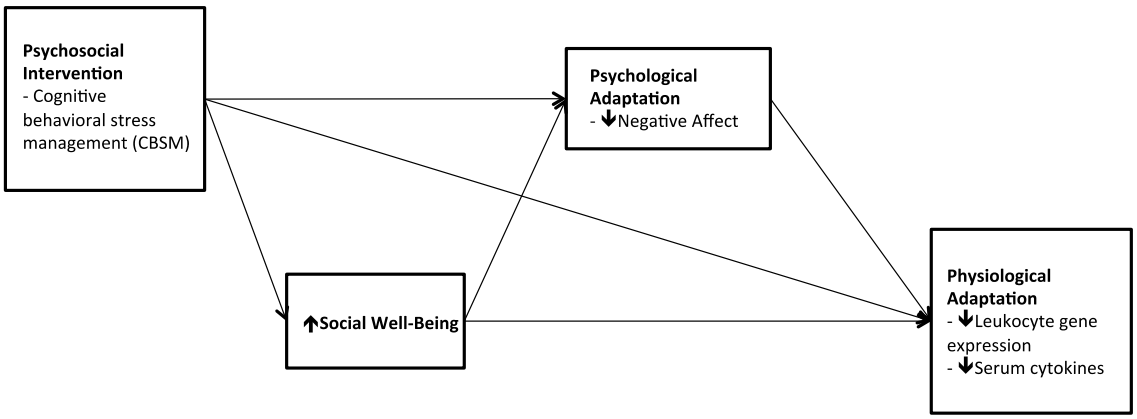


Figure 2. CONSORT flow diagram.

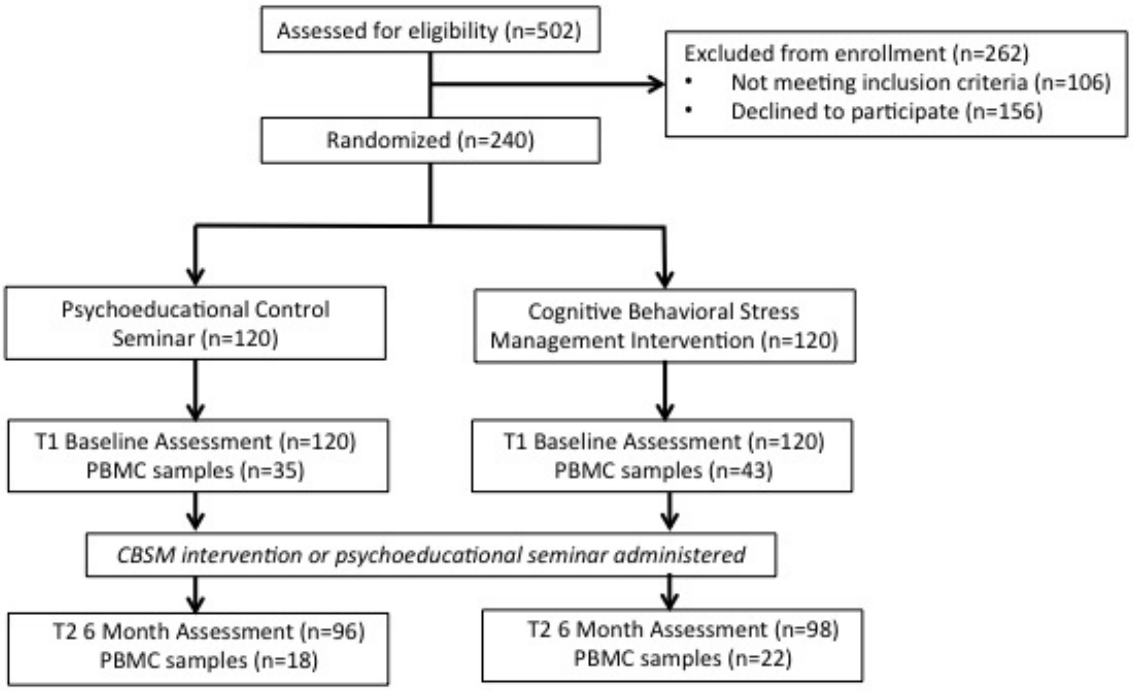
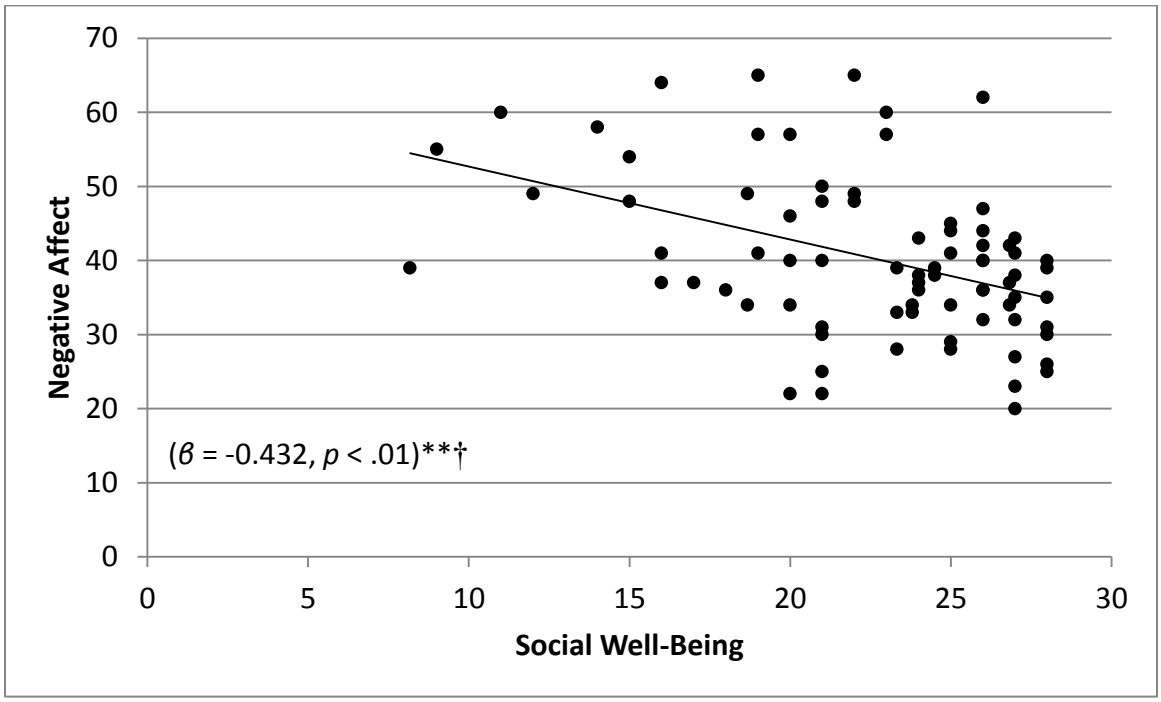
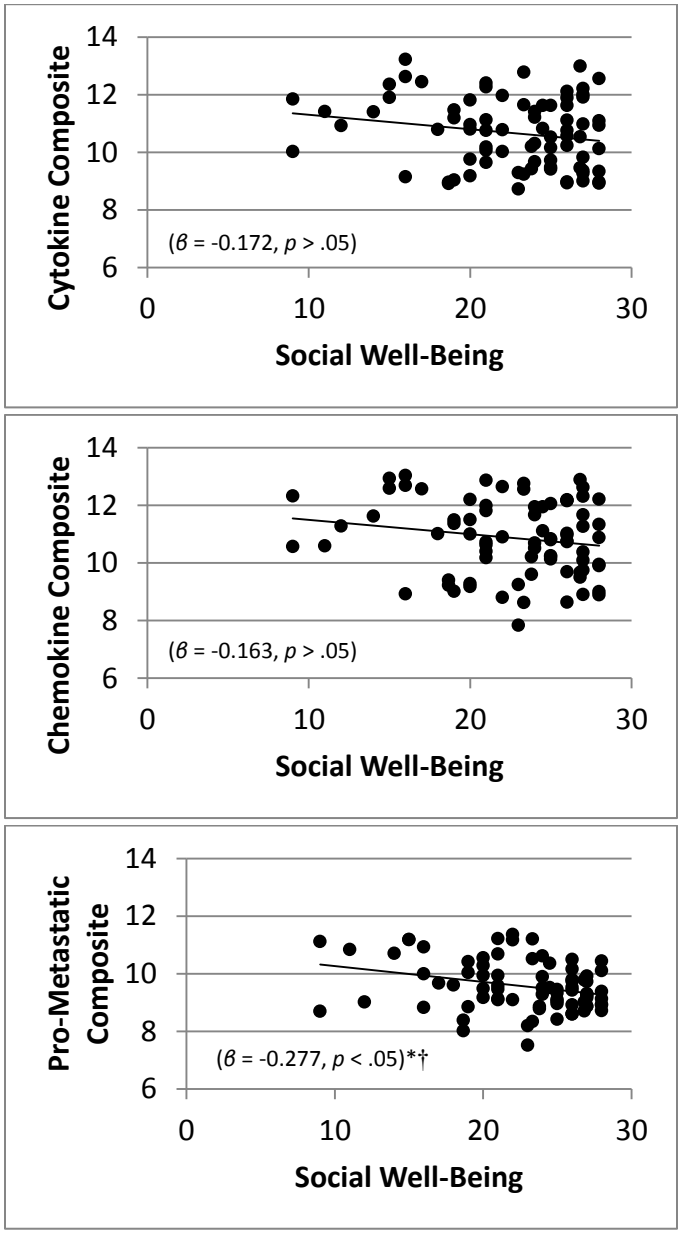


Figure 3. Scatterplot depicting the Aim 1.1 association between social well-being and negative affect after surgery for breast cancer.



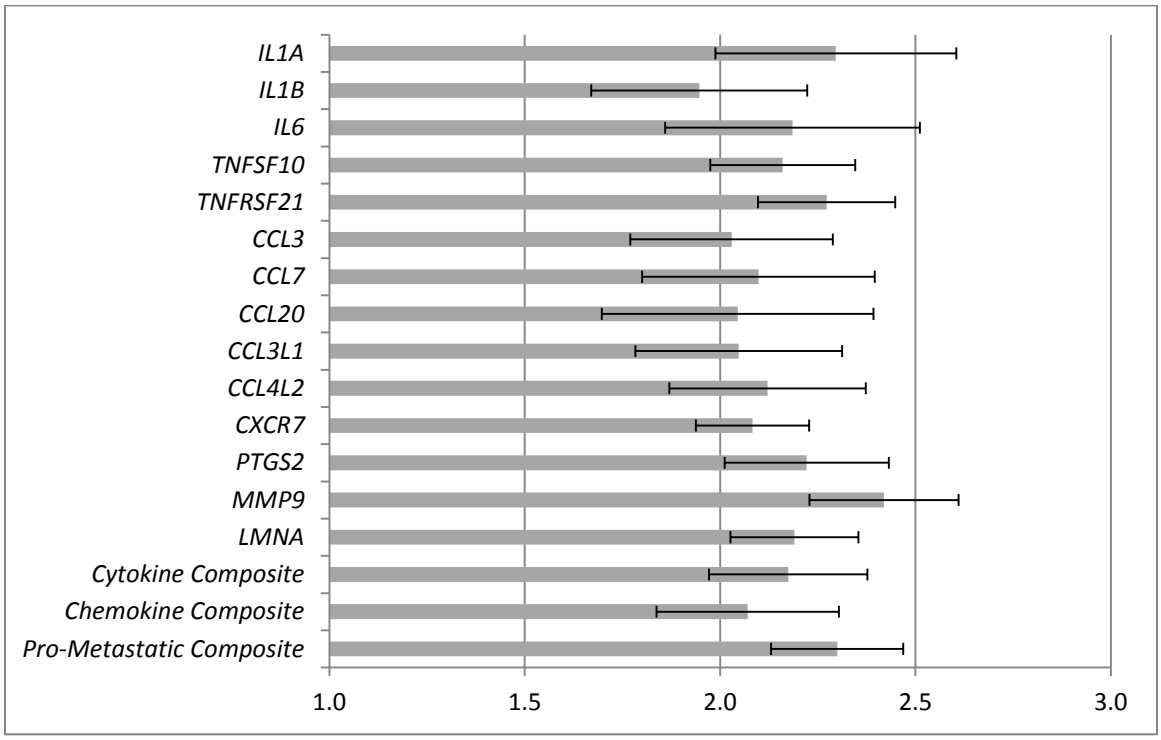
Note: Scatterplot depicts data after winsorization.
*p < .05 **p < .01
†Statistically significant after application of the Benjamini-Hochberg procedure at a false discovery rate of 0.10.

Figure 4. Scatterplots depicting the Aim 1.1 association between social well-being and pro-inflammatory and pro-metastatic gene expression composites after surgery for breast cancer.



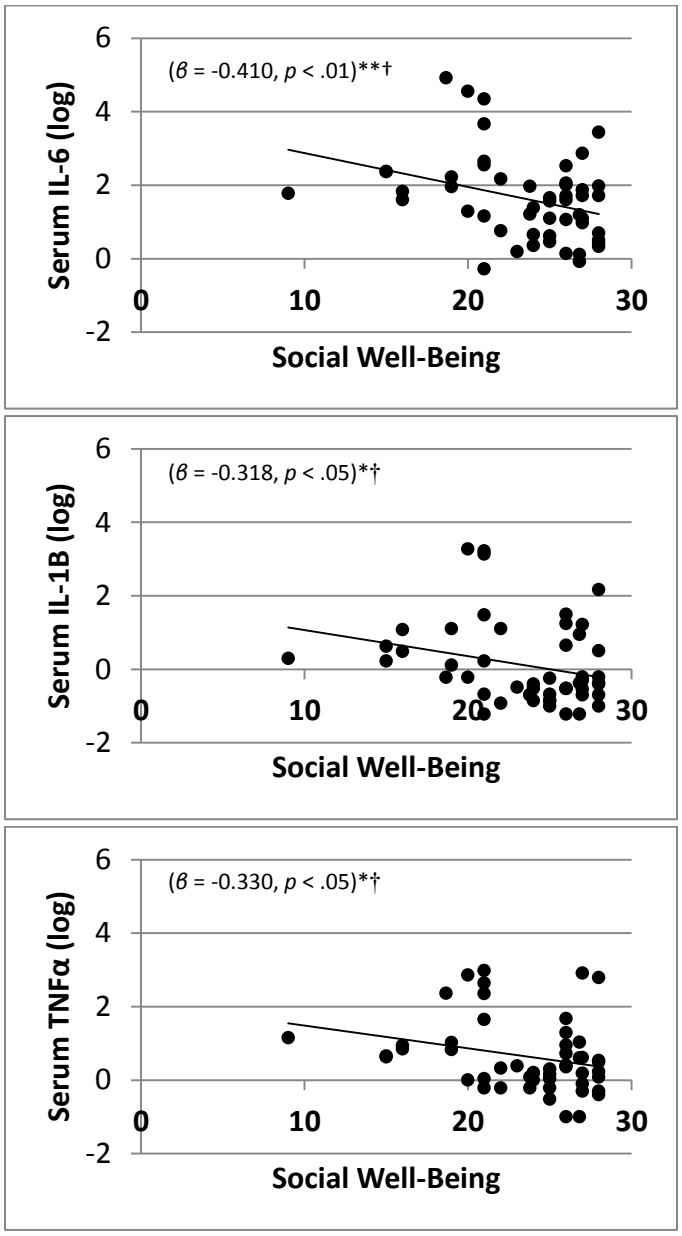
Note: Scatterplots depict data after winsorization. Gene expression reported in RNA expression units (log2).
*p < .05 **p < .01
†Statistically significant after application of the Benjamini-Hochberg procedure at a false discovery rate of 0.10.

Figure 5. Fold differences in pro-inflammatory and pro-metastatic gene expression in participants with low versus high social well-being determined by median split.



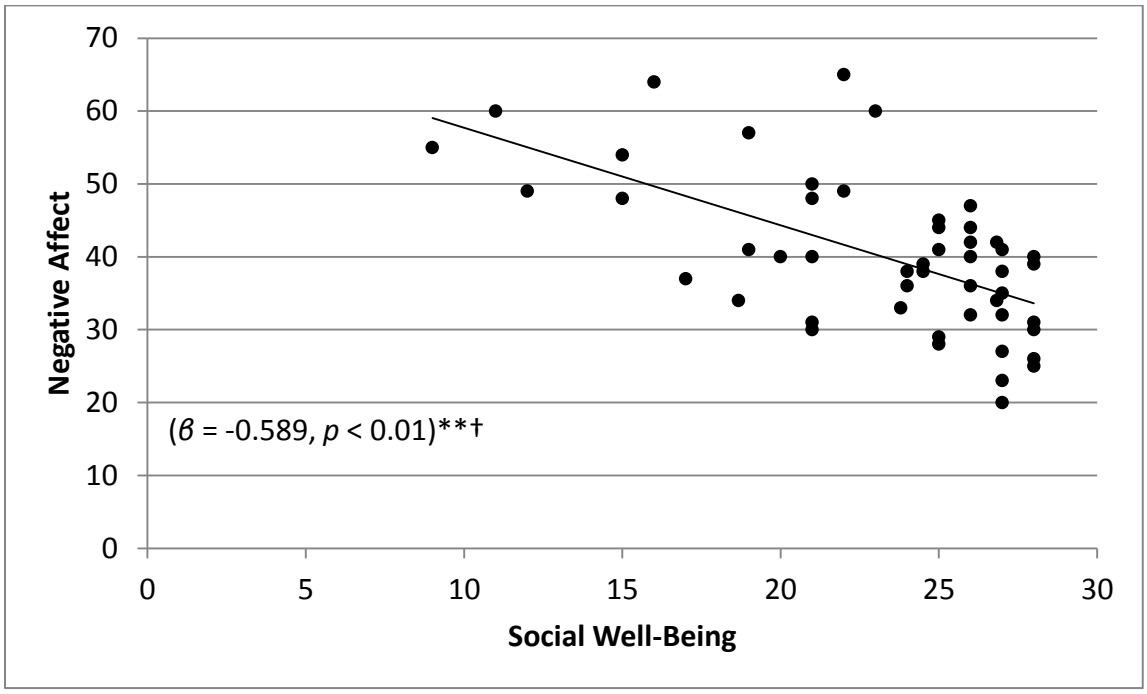
Note: Cytokine Composite consisted of *IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21*, and *PTGS2*. Chemokine composite consisted of *CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*. Pro-metastatic composite consisted of *MMP9* and *LMNA*. Gene expression reported in RNA expression units (log2).

Figure 6. Scatterplots depicting the Aim 1.1 association between social well-being and serum pro-inflammatory cytokines after surgery for breast cancer.



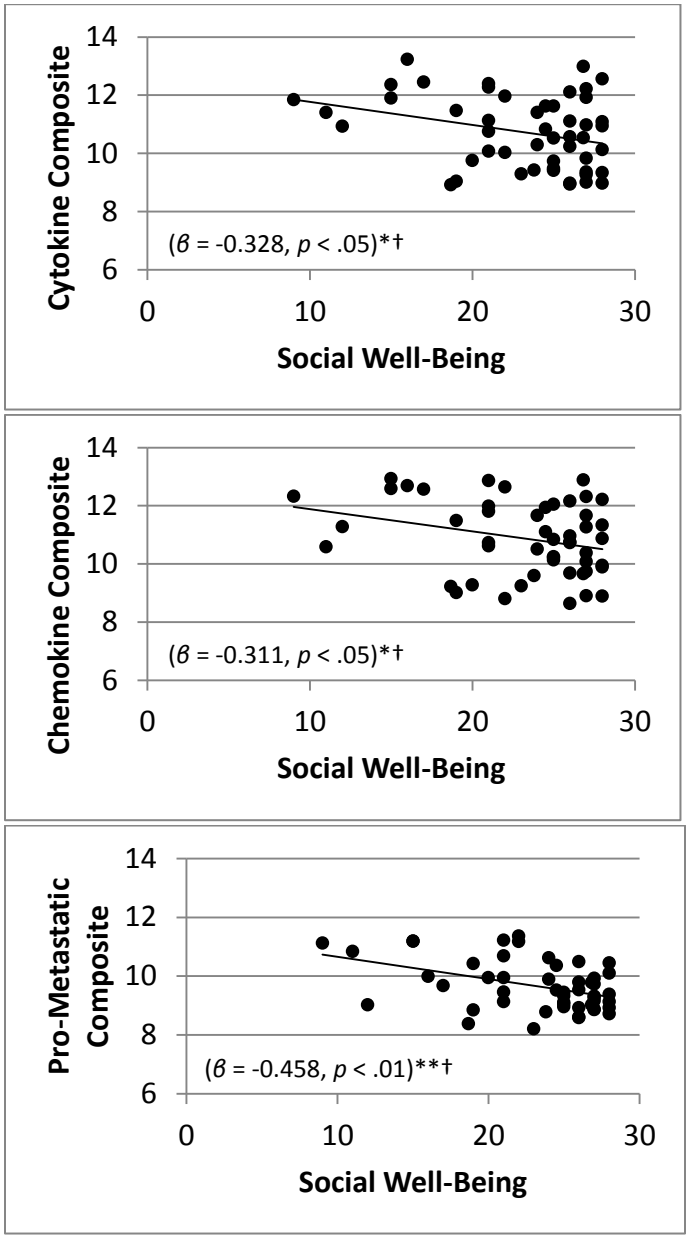
Note: Scatterplot depicts data after winsorization.
*p < .05 **p < .01
†Statistically significant after application of the Benjamini-Hochberg procedure at a false discovery rate of 0.10.

Figure 7. Scatterplot depicting the Aim 1.2 association between social well-being and negative affect after surgery for breast cancer, controlling for BMI.



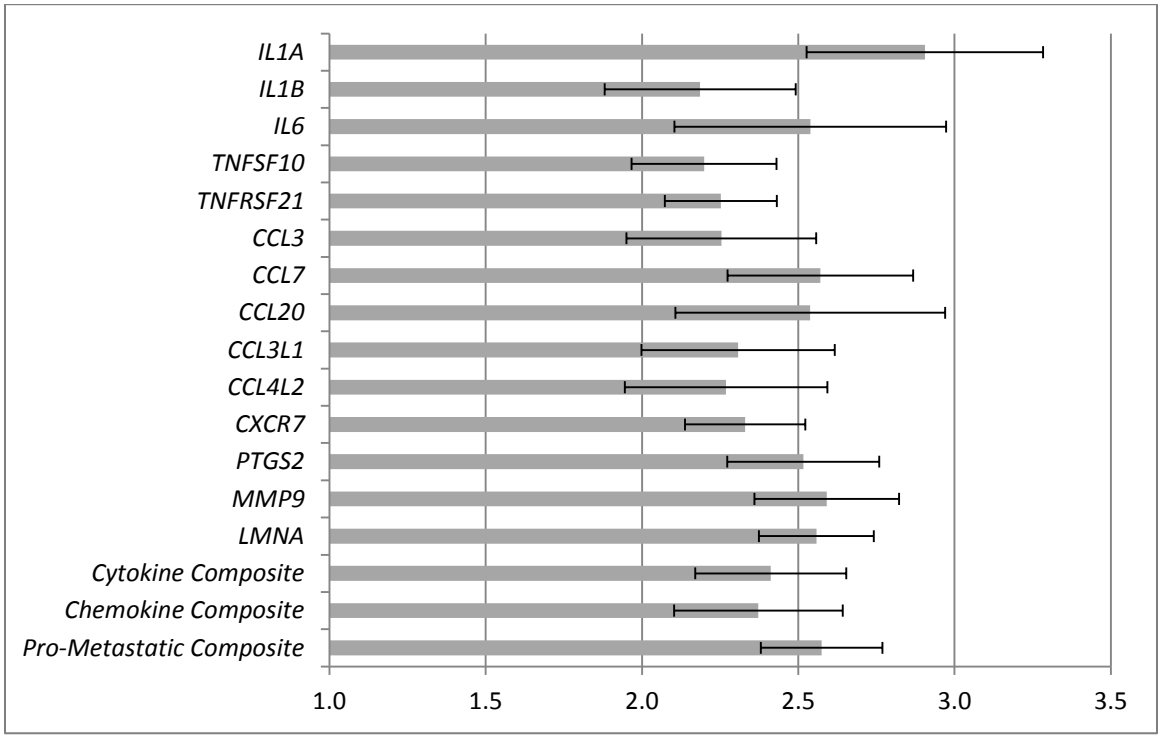
Note: Scatterplot depicts data after winsorization.
*p < .05 **p < .01
†Statistically significant after application of the Benjamini-Hochberg procedure at a false discovery rate of 0.10.

Figure 8. Scatterplots depicting the Aim 1.2 association between social well-being and pro-inflammatory and pro-metastatic gene expression composites after surgery for breast cancer, controlling for BMI.



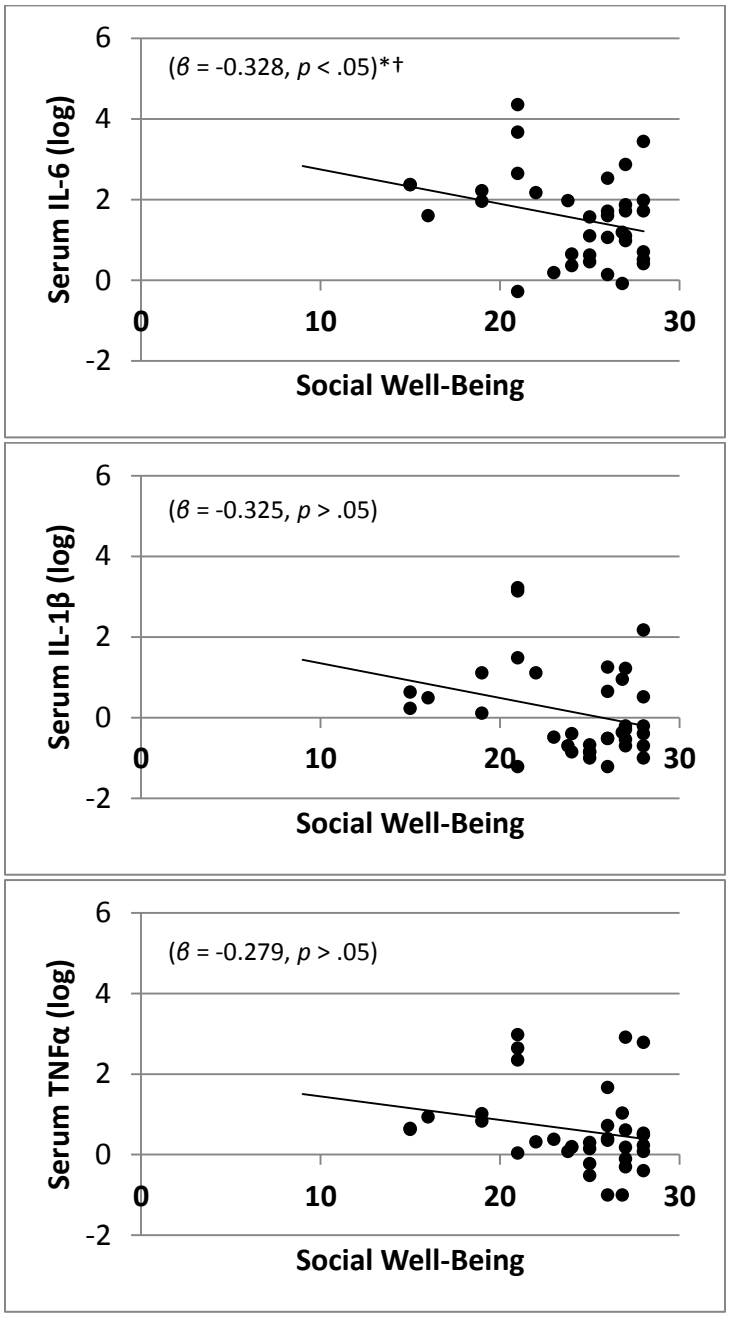
Note: Scatterplot depicts data after winsorization. Gene expression reported in RNA expression units (log2).
*p < .05 **p < .01
†Statistically significant after application of the Benjamini-Hochberg procedure at a false discovery rate of 0.10.

Figure 9. Fold differences in pro-inflammatory and pro-metastatic gene expression in participants with low versus high social well-being determined by median split, controlling for BMI.



Note: Cytokine Composite consisted of *IL1A*, *IL1B*, *IL6*, *TNFSF10*, *TNFRSF21*, and *PTGS2*. Chemokine composite consisted of *CCL3*, *CCL7*, *CCL20*, *CCL3L1*, *CCL4L2*, and *CXCR7*. Pro-metastatic composite consisted of *MMP9* and *LMNA*.

Figure 10. Scatterplots depicting the Aim 1.2 association between social well-being and serum pro-inflammatory cytokines after surgery for breast cancer, controlling for BMI.



Note: Scatterplot depicts data after winsorization.
*p < .05 **p < .01
†Statistically significant after application of the Benjamini-Hochberg procedure at a false discovery rate of 0.10.

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APPENDIX A: Affects Balance Scale (ABS)

Instructions: 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:

Please write your answer on the line.

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

1. Nervous
2. Sad
3. Regretful
4. Irritable
5. Happy
6. Pleased
7. Excited
8. Passionate
9. Timid
10. Hopeless
11. Blameworthy
12. Resentful
13. Glad
14. Calm
15. Energetic
16. Loving
17. Tense
18. Worthless
19. Ashamed
20. Angry
21. Cheerful
22. Satisfied
23. Active
24. Friendly
25. Anxious
26. Miserable
27. Guilty
28. Enraged
29. Delighted
30. Relaxed
31. Vigorous
32. Affectionate
33. Afraid
34. Unhappy
35. Remorseful
36. Bitter
37. Joyous
38. Contented
39. Lively
40. Warm

APPENDIX B: Functional Assessment of Cancer Therapy – Breast Cancer

(FACT-B)

Below is a list of statements that other women with breast cancer have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

1 = Not at all.
2 = A little bit.
3 = Somewhat.
4 = Quite a bit.
5 = Very much.

Physical Well-Being

1. I have a lack of energy.
2. I have nausea.
3. Because of my physical condition, I have trouble meeting the needs of my family.
4. I have pain.
5. I am bothered by side effects of treatment.
6. I feel ill.
7. I am forced to spend time in bed.

Social/Family Well-Being

1. I feel close to my friends.
2. I get emotional support from my family.
3. I get support from my friends.
4. My family has accepted my illness.
5. I am satisfied with family communication about my illness.
6. I feel close to my partner (or the person who is my main support).
   Regardless of your current level of sexual activity, please, answer the following question. If you prefer not to answer it, please check this box [ ] and go to the next section.
7. I am satisfied with my sex life.

Emotional Well-Being

1. I feel sad.
2. I am satisfied with how I am coping with my illness.
3. I am losing hope in the fight against my illness.
4. I feel nervous.
5. I worry about dying.
6. I worry that my condition will get worse.

Functional Well-Being

1. I am able to work (include work at home).
2. My work (include work at home) is fulfilling.

3. I am able to enjoy life.
4. I have accepted my illness.
5. I am sleeping well.
6. I am enjoying the things I usually do for fun.
7. I am content with the quality of my life right now.

Additional Concerns

1. I have been short of breath.
2. I am self-conscious about the way I dress.
3. One or both of my arms are swollen or tender.
4. I feel sexually attractive.
5. I am bothered by hair loss.
6. I worry that other members of my family might someday get the same illness I have.
7. I worry about the effect of stress on my illness.
8. I am bothered by a change in weight.
9. I am able to feel like a woman.

APPENDIX C: Hamilton Rating Scale for Depression (HRSD)

1. **Depressed Mood** (Sadness, hopelessness, helplessness, worthlessness)
   - 0 = Absent
   - 1 = These feeling states indicated only on questioning
   - 2 = These feeling states spontaneously reported verbally
   - 3 = Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
   - 4 = Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **Somatic Symptoms: General**
   - 0 = None
   - 1 = Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
   - 2 = Any clear-cut symptom rates 2

3. **Insomnia: Early**
   - 0 = No difficulty falling asleep
   - 1 = Complains of occasional difficulty falling asleep — i.e., more than 1/2 hour
   - 2 = Complains of nightly difficulty falling asleep

4. **Insomnia: Middle**
   - 0 = No difficulty
   - 1 = Patient complains of being restless and disturbed during the night
   - 2 = Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

5. **Insomnia: Late**
   - 0 = No difficulty
   - 1 = Waking in early hours of the morning but goes back to sleep
   - 2 = Unable to fall asleep again if he gets out of bed

6. **Work and Activities**
   - 0 = No difficulty
   - 1 = Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
   - 2 = Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
   - 3 = Decrease in actual time spent in activities or decrease in productivity
   - 4 = Stopped working because of present illness

7. **Genital Symptoms** (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)
   - 0 = Absent
   - 1 = Mild
   - 2 = Severe

8. **Somatic Symptoms: Gastrointestinal**
   - 0 = None
   - 1 = Loss of appetite but eating without encouragement from others. Food intake about normal
   - 2 = Difficulty eating without urging from others. Marked reduction of appetite and food intake

9. **Loss of Weight** (When rating by history)
   - 0 = No weight loss
   - 1 = Probably weight loss associated with present illness
   - 2 = Definite (according to patient) weight loss
   - 3 = Not assessed

10. **Feelings of Guilt**
   - 0 = Absent
   - 1 = Self reproach, feels he has let people down
   - 2 = Ideas of guilt or rumination over past errors or sinful deeds
   - 3 = Present illness is a punishment. Delusions of guilt
   - 4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

11. **Suicide**
   - 0 = Absent
   - 1 = Feels life is not worth living
   - 2 = Wishes he were dead or any thoughts of possible death to self
   - 3 = Suicidal ideas or gesture
   - 4 = Attempts at suicide (any serious attempt rates 4)

12. **Anxiety: Psychological**
   - 0 = No difficulty
   - 1 = Subjective tension and irritability
   - 2 = Worrying about minor matters
   - 3 = Apprehensive attitude apparent in face or speech
   - 4 = Fears expressed without questioning

13. **Anxiety: Somatic** [Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)]
    0 = Absent
    1 = Mild
    2 = Moderate
    3 = Severe
    4 = Incapacitating

14. **Hypochondriasis**
    0 = Not present
    1 = Self-absorption (bodily)
    2 = Preoccupation with health
    3 = Frequent complaints, requests for help, etc.
    4 = Hypochondriacal delusions

15. **Insight**
    0 = Acknowledges being depressed and ill
    1 = Acknowledges illness but attributes cause to bad food, climate, over work, virus, need for rest, etc.
    2 = Denies being ill at all

16. **Agitation**
    0 = None
    1 = Fidgetiness
    2 = Playing with hands, hair, etc.
    3 = Moving about, can't sit still
    4 = Hand wringing, nail biting, hair-pulling, biting of lips

17. **Retardation: Psychomotor** (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
    0 = Normal speech and thought
    1 = Slight retardation at interview
    2 = Obvious retardation at interview
    3 = Interview difficult
    4 = Complete stupor

APPENDIX D: Sources of Social Support Scale (SSSS)

The next sets of items concern the kinds of help and support you get from various people regarding your illness. The items ask about several different sets of people, but apply the same questions to each. Use the following choices for these items:

1 = Not at all.
2 = A little.
3 = A moderate amount.
4 = A pretty large amount.
5 = A lot.

A. The first items concern your **husband/partner**. [*If you do not have a husband/partner, **leave these items blank** and skip to section B, number 11*].

1. How much does your husband/partner give you **advice or information** about your breast cancer (whether you want it or not)?
2. How much does your husband/partner give you **assistance** with things related to your breast cancer (for example, helping you with daily chores, driving you places, dealing with bills and paperwork)?
3. How much does your husband/partner give you **reassurance**, **encouragement**, and **emotional support** (affection) concerning your breast cancer?
4. How much does your husband/partner **listen to and try to understand** your worries about your breast cancer?
5. How much can you relax and be yourself around your husband/partner?
6. How much can you **open up to** your husband/partner if you need to talk about your worries about your cancer?
7. How often does your husband/partner **argue** with you relating to your cancer?
8. How often does your husband/partner **criticize** you relating to your cancer?
9. How often does your husband/partner **let you down** when you are counting on him?
10. How often does your husband/partner **withdraw from discussions** about your illness or try to **change the topic** away from your illness?

B. The next items concern **adult women in your family** (sisters, mother, aunts, or adult daughters). [*If you do not have adult women in your family, **leave these items blank** and skip to section C, number 21*].

11. How much do these women give you **advice or information** about your breast cancer (whether you want it or not)?
12. How much do these women give you **assistance** with things related to your breast cancer (for example, helping you with daily chores, driving you places, dealing with bills and paperwork)?
13. How much do these women give you **reassurance**, **encouragement**, and **emotional support** (affection) concerning your breast cancer?
14. How much do these women **listen to and try to understand** your worries about your breast cancer?
15. How much can you relax and be yourself around these women?

16. How much can you **open up to** these women if you need to talk about your worries about your cancer?
17. How often do these women **argue** with you relating to your cancer?
18. How often do these women **criticize** you relating to your cancer?
19. How often do these women **let you down** when you are counting on him?
20. How often do these women **withdraw from discussions** about your illness or try to **change the topic** away from your illness?

C. The next items concern ***other*** **family members.** [*If you do not have other family besides those mentioned above, **leave these items blank** and skip to section D, number 31*].

21. How much do these people give you **advice or information** about your breast cancer (whether you want it or not)?
22. How much do these people give you **assistance** with things related to your breast cancer (for example, helping you with daily chores, driving you places, dealing with bills and paperwork)?
23. How much do these people give you **reassurance**, **encouragement**, and **emotional support** (affection) concerning your breast cancer?
24. How much do these people **listen to and try to understand** your worries about your breast cancer?
25. How much can you relax and be yourself around these people?
26. How much can you **open up to** these people if you need to talk about your worries about your cancer?
27. How often do these people **argue** with you relating to your cancer?
28. How often do these people **criticize** you relating to your cancer?
29. How often do these people **let you down** when you are counting on him?
30. How often do these people **withdraw from discussions** about your illness or try to **change the topic** away from your illness?

D. The next items concern **your friends**.

31. How much do your friends give you **advice or information** about your breast cancer (whether you want it or not)?
32. How much do your friends give you **assistance** with things related to your breast cancer (for example, helping you with daily chores, driving you places, dealing with bills and paperwork)?
33. How much do your friends give you **reassurance**, **encouragement**, and **emotional support** (affection) concerning your breast cancer?
34. How much do your friends **listen to and try to understand** your worries about your breast cancer?
35. How much can you relax and be yourself around your friends?
36. How much can you **open up to** your friends if you need to talk about your worries about your cancer?
37. How often do your friends **argue** with you relating to your cancer?
38. How often do your friends **criticize** you relating to your cancer?
39. How often do your friends **let you down** when you are counting on him?

40. How often do your friends **withdraw from discussions** about your illness or try to **change the topic** away from your illness?

E. The next items concern your **health care providers**.

1. How much do your health care providers give you **advice or information** about your breast cancer (whether you want it or not)?
2. How much do your health care providers give you **assistance** with things related to your breast cancer (for example, helping you with daily chores, driving you places, dealing with bills and paperwork)?
3. How much do your health care providers give you **reassurance**, **encouragement**, and **emotional support** (affection) concerning your breast cancer?
4. How much do your health care providers **listen to and try to understand** your worries about your breast cancer?
5. How much can you relax and be yourself around your health care providers?
6. How much can you **open up to** your health care providers if you need to talk about your worries about your cancer?
7. How often do your health care providers **argue** with you relating to your cancer?
8. How often do your health care providers **criticize** you relating to your cancer?
9. How often do your health care providers **let you down** when you are counting on him?
10. How often do your health care providers **withdraw from discussions** about your illness or try to **change the topic** away from your illness?