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Depression and Inflammatory Changes after Cognitive-Behavioral Stress Management as Predictors of Survival and Disease Recurrence in Women with Non-Metastatic Breast Cancer

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DEPRESSION AND INFLAMMATORY CHANGES AFTER COGNITIVE-BEHAVIORAL STRESS MANAGEMENT AS PREDICTORS OF SURVIVAL AND DISEASE RECURRENCE IN WOMEN WITH NON-METASTATIC BREAST CANCER

By

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Both depression and inflammation are independently associated with breast cancer health outcomes, and multiple studies have shown that depression and inflammatory markers may be linked among women with breast cancer. Studies of cognitive-behavioral based psychosocial interventions have found beneficial intervention effects on time to survival and recurrence in breast cancer patients. However, the mechanisms through which interventions affect clinical health outcomes are less understood. It has been suggested that psychosocial interventions may affect long-term breast cancer clinical disease endpoints via effects on immune and inflammatory processes, but more research is necessary to explore these relationships. The current study examined the relationships between post-surgical and pre-adjuvant levels of depressive symptoms and pro-inflammatory cytokines with long-term clinical health outcomes, both individually and in combination, among a cohort of non-metastatic breast cancer patients. It also sought to replicate recent findings that a cognitive behavioral stress management (CBSM) psychosocial intervention predicts favorable breast cancer clinical disease endpoints, and examined possible mediators of these effects.

The present sample included 90 women with non-metastatic breast cancer and available blood data for analyses of serum pro-inflammatory cytokines from a larger clinical trial. Women were initially recruited and assessed at 2-10 weeks post-surgery

(T1). At that time, information was collected related to demographic characteristics, medical history, treatment plans, and psychosocial functioning. Women were randomized to either a 10-week group-based CBSM intervention or a 1-day psychoeducational group seminar control. Participants were re-assessed at 6 months (T2), 12 months (T3), and 5-years (T5) post-T1. Blood samples for cytokine analyses were collected at T1 and T3. At 8-15 year follow-up (11-year median; T6), a tumor registry linkage was performed and medical chart reviews were conducted to determine mortality status (including cause and date of death) and disease free status (i.e., recurrence status) of study participants.

Cox Proportional Hazards Models were conducted to assess the direct effects of baseline depressive symptoms and serum concentrations of pro-inflammatory cytokines (i.e., IL-1β, IL-6, and TNF-α) on time to clinical disease endpoints (i.e., all-cause mortality, breast cancer-specific mortality, and breast cancer recurrence) assessed at 11-year median follow-up (Aim 1a). Bootstrapped linear regression analyses were used to test indirect relationships between baseline depressive symptoms and pro-inflammatory cytokines with time to clinical disease endpoints (Aim 1b). Cox Proportional Hazards Models were conducted to assess for group differences (i.e., CBSM vs. control) in time to clinical disease endpoints (Aim 2a). Finally, bootstrapped linear regression analyses were used to test indirect effects of CBSM on time to clinical disease endpoints through 12-month changes in depressive symptoms and pro-inflammatory cytokines (Aim 2b). Unadjusted and adjusted models were conducted, which accounted for age, stage of disease, surgical procedure, hormone therapy, and smoking status. All analyses were run in the 90 women for whom blood data were available, and in a subset of 73 women who initially had invasive disease (i.e., not stage 0).

At median 11-year follow-up, 8 women (8.9%) were deceased and 6 of those deaths (75.0%) were related to breast cancer. A total of 17 women (18.9%) had experienced a breast cancer recurrence. In Aim 1a, results of Cox Proportional Hazards analyses revealed non-significant relationships between baseline variables and time to clinical disease endpoints in both the full and invasive subsamples in unadjusted and adjusted models (all *p*s > 0.10). In Aim 1b, unadjusted and adjusted linear regression analyses revealed significant associations between greater baseline depressive symptoms and concurrent greater serum concentrations of IL-1β (β = 0.29, $p = 0.007$) and TNF- α (β = 0.30, $p = 0.004$). A marginal association emerged between greater baseline depressive symptoms and concurrent greater IL-6 (β = 0.179 $p = 0.077$). These findings were retained in the invasive subsample. However, as in Aim 1a, baseline levels of depressive symptoms and pro-inflammatory cytokines did not predict time to clinical disease endpoints (all *p*s > 0.10), and thus mediation was not supported. In Aim 2a, results of Cox Proportional Hazards analyses revealed non-significant group differences in time to clinical disease endpoints in both the full and invasive subsamples in unadjusted and adjusted models (all *p*s > 0.10). In Aim 2b, results of linear regression analyses revealed non-significant group differences in 12-month changes in depressive symptoms and pro-inflammatory cytokines (all *p*s > 0.10), and mediation was therefore not supported.

The observed associations between baseline depressive symptoms and pro-inflammatory cytokines have implications for the treatment of women with breast cancer who report comorbid elevated depressive symptoms. However, the long-term implications of these findings, including the role of psychosocial interventions, are inconclusive. More research is needed, including large well-controlled trials, to further

investigate the associations between these variables to elucidate the mechanisms through which depressive symptoms, inflammation, and psychosocial interventions interact and ultimately affect long-term clinical health outcomes of breast cancer patients.

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Chapter 1: Introduction

Depression, Disease Progression, and Survival in Breast Cancer

Breast cancer patients often report elevated levels of depressive symptoms; reports of prevalence of depression range from 4.5-37% (Kissane, Maj, & Sartorious, 2011) and median estimates of approximately 20-30% of women report elevated depressive symptoms (Massie, 2004). Increasing evidence suggests that stress-related psychosocial factors, such as depression, influence mortality in cancer patients (Chida, Hamer, Wardle, & Steptoe, 2008; Cohen et al., 2012; Lutgendorf, Sood, & Antoni, 2010; Pinquart & Duberstein, 2010; Satin, Linden, & Phillips, 2009).

In breast cancer specifically, individual studies have linked elevated depressive symptoms to increased mortality in samples of women with non-metastatic disease (Antoni et al., 2017; Hjerl et al., 2003; Kanani, Davies, Hanchett, & Jack, 2016; Watson, Haviland, Greer, Davidson, & Bliss, 1999) and metastatic disease (Giese-Davis et al., 2011; Kanani et al., 2016). Meta-analyses have shown that higher levels of depressive symptoms predict elevated mortality in cancer patients (Pinquart & Duberstein, 2010; Satin et al., 2009) and in breast cancer patients specifically (Chida et al., 2008). However, some studies have found no relationship between depressive symptoms and survival among breast cancer patients (Phillips et al., 2008; Spiegel & Giese-Davis, 2003), and studies have failed to establish a relationship between depressive symptoms and breast cancer recurrence (Antoni et al., 2017; Phillips et al., 2008; Satin et al., 2009; Watson et al., 1999). These discrepancies indicate a need for further study to clarify the relationships between depressive symptoms and clinical disease endpoints of breast cancer patients.

Cancer-related mortality is likely a result of disease progression and metastasis, which involve several complex steps (Fidler, 2003). Evidence suggests that psychological factors such as depression may affect disease progression (Spiegel & Giese-Davis, 2003), and there are multiple points throughout the metastatic cascade where this may occur (Lutgendorf et al., 2010).

For instance, among women with ovarian cancer, depression has been linked to matrix metalloprotinease (MMP)-9 secretion by tumor associated macrophages (TAMs; Lutgendorf et al., 2008a), which are known to influence tumor cell migration and invasion (Coussens & Werb, 2002; Pollard, 2004). Depression has been associated with downregulation of the cellular immune response (Irwin, 2002; Zorrilla et al., 2001), which plays a role in immunosurveillance and lysis of tumor cells (Lutgendorf et al., 2010). In addition, depressive symptoms have been associated with decreased survival and increased pro-metastatic and pro-inflammatory gene expression in circulating leukocytes among individuals with metastatic renal cell carcinoma (Cohen et al., 2012), which suggests that the link between depressive symptoms and survival among cancer patients may be associated with inflammatory processes.

The Interaction of Depression and Inflammation in Breast Cancer

Pro-inflammatory cytokines are the mediating signalers of inflammatory processes (Coussens & Werb, 2002; Mantovani, 2005) and have been implicated in cancer-related depression (Lutgendorf et al., 2008b). It is largely agreed that interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) are main pro-inflammatory cytokines in inflammatory responses (Mantovani, Allavena, Sica, & Balkwell, 2008), and multiple studies have shown associations between depression and

these cytokines as well as other markers of inflammation among mixed cancer populations (Howren, Lamkin, & Suls, 2009; Jehn et al., 2006; Musselman et al., 2001; Soygur et al., 2007). Notably, one study showed that cancer patients (pancreatic, esophageal, and breast) diagnosed with major depressive disorder (MDD) had similar levels of IL-6 as healthy persons with MDD. In turn, cancer patients and healthy persons with MDD both had greater levels of IL-6 than cancer patients and healthy persons without MDD, who did not differ from each other (Musselman et al., 2001).

Among samples of women with ovarian cancer, support for the relationship between depression and inflammation is mixed. Importantly, studies finding an association between depressive symptoms and inflammation have focused on vegetative symptoms of depression, which include symptoms such as "could not get going," and "had trouble keeping my mind on tasks" (Lutgendorf et al., 2008b; Schrepf et al., 2013). In contrast, a study that failed to find an association between depressive symptoms and inflammation did not distinguish between subtypes of depressive symptoms (Costanzo et al., 2005). Thus, it may be the case that vegetative symptoms are most closely linked to inflammation among ovarian cancer patients, rather than the more general conceptualization of depression.

Similarly, the findings relating depression and inflammation in breast cancer patients are mixed. No association was found between depression and inflammation in a cross-sectional study of women with non-metastatic breast cancer assessed after recently completing primary treatment (i.e. surgery, radiation therapy, chemotherapy; Bower et al., 2011). However, two additional cross-sectional studies have found relationships

between depression/depressive symptoms and inflammation (Bouchard et al., 2016a; Soygur et al., 2007).

A study of women with non-metastatic, invasive breast cancer found that levels of IL-6 were elevated in breast cancer patients with MDD, breast cancer patients without MDD, and medically healthy women with MDD compared to medically and psychologically healthy controls (Soygur et al., 2007). Notably, breast cancer patients with MDD had higher levels of IL-6 than any other group (Soygur et al., 2007).

In our own study sample of women with non-metastatic breast cancer, we found significantly higher levels TNF-α among women with depressive symptoms above an accepted clinical cutoff compared to women whose depressive symptoms fell below the cutoff (Bouchard et al., 2016a). Women with elevated depressive symptoms had marginally higher levels of IL-1β and IL-6 than women with low depressive symptoms, but the effect was not statistically significant. Further, depressive symptoms, continuously measured, were positively correlated with IL-1β and TNF-α suggesting a linear association between increasing levels of depressive symptoms and serum pro-inflammatory cytokines after controlling for relevant demographic and prognostic covariates (Bouchard et al., 2016a).

When considering the discrepant findings among the cross-sectional studies of breast cancer patients described above, it is important to note that the time frames within which the studies assessed for relationships between depressive symptoms and inflammatory markers were not consistent. The first study described, which reported null findings, assessed women after completion of primary treatment for breast cancer, an average of almost 7 months post-diagnosis (Bower et al., 2011). Conversely, the studies

reporting significant findings assessed women post-diagnosis and surgery and prior to beginning adjuvant treatment (Bouchard et al., 2016a; Soygur et al., 2007). It is possible that the time of assessment is an important factor to consider, and the relationships between depressive symptoms and markers of inflammation may be strongest prior to onset of adjuvant treatment.

Longitudinally, a study of women with stage II and III breast cancer with clinically significant depressive symptoms showed that a 4-month psychosocial intervention significantly reduced both depressive symptoms and markers of inflammation (i.e., white blood cell count, neutrophil count, and ratio of helper T to suppressor T cells) over the first 12-months post-diagnosis for primary breast cancer (Thornton, Andersen, Schuler, & Carson III, 2009). The intervention effect on inflammation at 12 months was mediated by its effect on depressive symptoms at 8 months. Importantly, this study indicated that interventions targeting depressive symptoms may subsequently influence the reduction of inflammatory markers, showing a temporal relationship between variables (Thornton et al., 2009).

Beyond depressive symptoms, our research team has previously shown that greater negative affect (depressed mood, anxiety, anger, guilt) was associated with upregulation of pro-inflammatory and pro-metastatic leukocyte gene expression in the weeks post-diagnosis among women with primary non-metastatic breast cancer. After a 10-week psychosocial intervention, women who participated in the intervention had decreased negative affect and downregulation of pro-inflammatory and pro-metastatic leukocyte gene expression compared to women in the control group (Antoni et al., 2012). These two trials together indicate a longitudinal association between depressive

symptoms and, more generally, negative affective states and markers of inflammation (e.g., white blood cell counts, pro-inflammatory leukocyte gene expression) among women with breast cancer (Antoni et al., 2012; Thornton et al., 2009). Yet, neither study has shown that changes in depressive symptoms covary with changes in the "effectors" of inflammatory processes, circulating pro-inflammatory cytokines.

Inflammation, Disease Progression, and Survival in Cancer

The relationships between depression/depressive symptoms and inflammatory markers are particularly important among cancer patients, as cancer development and progression are closely linked to complex inflammatory processes (Mantovani, 2005). Rudolf Virchow was the first to link inflammation to cancer in the 1800's when he found leukocytes in samples of cancerous tissues (Balkwill & Mantovani, 2001). Since then, researchers have empirically established inflammation as a risk factor for cancer, and epidemiological studies estimate that approximately 15% of cancer incidence is associated with infection and subsequent inflammation (Rakoff-Nahoum, 2006).

Regardless of the trigger for cancer incidence, inflammatory cells and mediators such as chemokines and cytokines are found within most, if not all, tumors (Mantovani et al., 2008). Typically self-limiting inflammatory responses may become dysregulated allowing for an infiltration of white blood cells such as TAMs in precancerous tissues, which release inflammatory-signaling factors such as pro-inflammatory cytokines (Coussens & Werb, 2002; Mantovani, 2005). The resulting elevated inflammation in the microenvironment has many tumor-promoting effects including promotion of the proliferation and survival of malignant cells and the promotion of angiogenesis and

metastasis, which lead to neoplastic development and progression (Mantovani et al., 2008).

Indeed, a retrospective secondary analysis of a psychosocial intervention study for women with stage II and III breast cancer revealed an association between inflammatory status and odds of disease recurrence (Thornton, Andersen, & Carson III, 2008). For this study, women who experienced a breast cancer recurrence were case-matched to women who did not experience a recurrence in order to compare inflammatory markers at multiple time points. Participants were matched on study arm (intervention or control) and a host of demographic and prognostic factors known to influence disease progression and recurrence (e.g., menopausal status, hormone receptor status, tumor size, etc.; Thornton et al., 2008). Results revealed that elevated inflammatory markers (i.e., white blood cell, neutrophil, lymphocyte, and natural killer cell counts) were detectable in women who experienced a recurrence as early as 17 months before the event, whereas no such elevations were apparent in the non-recurring cases (Thornton et al., 2008). This study was the first of its kind to establish biobehavioral alterations more than a year before detectable breast cancer recurrence.

The Role of Specific Cytokines in Cancer Progression Processes

IL-1β. As reported above, the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α are main inflammatory cytokines related to neoplastic progression as a result of microenvironment inflammation (Mantovani et al., 2008). The IL-1 cytokine family is a group of 11 proteins including IL-1β (Dinarello, 1994), which has been implicated in tumor angiogenesis. Angiogenesis is the growth of blood vessels to a tumor, which supply oxygen and nutrients for tumor growth (Balkwill & Mantovani, 2001; Mantovani

et al., 2008). In animal models, mice deficient in IL-1β exhibited impaired tumor development and blood vessel growth compared to wild type mice (Voronov et al., 2003) and were resistant to the development of experimental metastases (Vidal-Vanaclocha et al., 2000). Further, treatment with an IL-1 receptor antagonist, which inhibits the action of IL-1α and IL-1β, significantly decreased tumor development (Vidal-Vanaclocha et al., 2000).

IL-1β has been described as an "alarm cytokine" due to its role in initiating inflammatory responses through induction of pro-inflammatory gene expression, which ultimately causes subsequent rapid generation of large amounts of IL-1β (Apte et al., 2006). Studies have shown that IL-1β is expressed in approximately 90% of invasive breast carcinomas, as well as in non-invasive ductal carcinoma in situ to a lesser extent (Jin et al., 1997). High levels of IL-1β in advanced breast carcinomas are correlated with other markers of aggressive tumors such as estrogen receptor negativity and high tumor grade (Jin et al., 1997; Miller et al., 2000).

IL-6. IL-6 is a pro-inflammatory cytokine secreted by macrophages and monocytes at sites of acute inflammation, and by T cells in chronic inflammation (Naugler & Karin, 2008). IL-6 has been implicated in tumor angiogenesis as well as tumor proliferation, migration, and anti-apoptosis (Armaiz-Pena, Cole, Lutgendorf, & Sood, 2013; Knupfer & Preib, 2007). In times of typical inflammation, apoptosis of inflammatory cells limits the effects of inflammation. However, in states of chronic inflammation this process may become dysregulated, allowing IL-6 to prevent apoptosis and thereby promote further inflammation and neoplasia (Naugler & Karin, 2008).

Studies have shown that IL-6 may promote breast cancer cell motility, suggesting a role in metastasis (Arhiro, Oda, Keneko, & Inai, 2000; Verhasselt et al., 1992), and multiple studies have indicated that high levels of serum IL-6 are a negative prognostic marker in breast cancer patients (Knupfer & Preib, 2007). Studies have shown that serum IL-6 is higher among patients with breast cancer versus healthy controls (Jiang, Yang, Elliott, & Head, 2000; Kozlowski, Zakrzewska, Tokajuk, & Wojtukiewicz, 2003), and levels of IL-6 increased with clinical stage of disease (Jablonska et al., 2001; Kozlowski et al., 2003). In addition, levels of serum IL-6 were greater among women with recurrent vs. non-recurrent breast cancer (Nishimura et al., 2000), and among patients with recurrent breast cancer resistant to treatment vs. patients with recurrent breast cancer considered stable (Yokoe, Iino, & Morishita, 2000). Finally, studies of women with metastatic breast cancer have shown a negative association between levels of serum IL-6 and survival among patients treated with chemotherapy (Bozcuk et al., 2004) and patients with untreated disease (Salgado et al., 2003).

TNF-α. The TNF family is a group of 19 cytokines including TNF-α (Sun & Fink, 2007), which is considered a major mediator of inflammation (Balkwill & Mantovani, 2001). TNF-α is implicated in both tissue destruction and recovery (Balkwill & Mantovani, 2001; Colotta, Allavena, Sica, Garlanda, & Mantovani, 2009). For example, regionally applied high-dose TNF-α may selectively destroy tumor blood vessels in advanced melanomas (Lejeune, Ruegg, & Lienard, 1998), but when chronically and systemically produced TNF-α may act as a tumor promoter by contributing to tissue remodeling necessary for tumor growth (Balkwill & Mantovani, 2001).

The role of TNF-α in cancer has been shown in animal models. Mice deficient in TNF-α are resistant to skin carcinogenesis (Moore et al., 1999). TNF-α has been detected in human breast cancer cells (Leek et al., 1998), and is often found in association with IL-1β and IL-6 (Balkwill & Mantovani, 2001). Similar to IL-1β, TNF-α has been described as an "alarm cytokine," and is involved in an amplification loop whereby elevated levels of TNF-α in response to inflammation trigger a cascade of events that ultimately lead to even greater production of TNF-α (Apte et al., 2006). In breast cancer specifically, TNF-α was negatively associated with survival among women with metastatic breast cancer treated with chemotherapy (Bozcuk et al., 2004).

Psychosocial Interventions, Disease Progression, and Survival in Breast Cancer

Psychosocial interventions focusing on behavioral methods for stress management are important for improving the quality of life of cancer patients and identifying stress-related pathways and biobehavioral mechanisms in cancer disease progression and clinical outcomes (Antoni, 2013; Lutgendorf et al., 2010). It follows that psychosocial interventions that reduce stress-related factors such as depression or depressive symptoms may affect clinical disease outcomes of breast cancer patients. However, it remains unclear whether psychosocial interventions have a real effect on the course of breast cancer progression and mortality (Andersen et al., 2008; Coyne, Stefanek & Palmer 2007; Spiegel, 2002), and whether such effects may be explained by changes in depressive symptoms and/or inflammatory processes (Antoni, 2013).

Within samples of women with metastatic breast cancer, a seminal study by Spiegel and colleagues (Spiegel, Bloom, Kraemer, & Gottheil, 1989) found that weekly group-based supportive expressive therapy with self-hypnosis administered over 12

months was associated with less anxiety, less depression, and less pain over the initial 12 month follow-up (Spiegel & Bloom, 1983). The intervention was associated with improved survival at 10-year follow-up compared to a treatment as usual control condition (Spiegel et al., 1989). However, subsequent efforts to replicate these findings have been mixed.

A study among women with metastatic breast cancer found that weekly group-based supportive expressive therapy over 12 months was associated with improvements in pain and psychological symptoms compared to a treatment as usual control group, but survival did not differ between study conditions (Goodwin et al., 2001). Similarly, in another study among women with metastatic breast cancer, weekly group-based supportive expressive therapy plus three classes of relaxation therapy over 12 months was not associated with a survival advantage compared to a control group who received treatment as usual plus three classes of relaxation therapy (Kissane et al., 2007). Notably, Spiegel and colleagues (2007) were themselves unable to replicate their original survival findings among women with metastatic breast cancer, except in a small subsample of women with estrogen receptor (ER) negative tumor types who showed longer survival in post-hoc analyses (Spiegel et al., 2007). Thus it remains unclear whether psychosocial interventions, specifically supportive expressive group therapy, are associated with survival advantages among metastatic breast cancer patients.

However, two randomized controlled trials of women with non-metastatic breast cancer have demonstrated beneficial effects of a cognitive-behavioral intervention on recurrence and survival (Andersen et al., 2008; Stagl et al., 2015). Andersen and colleagues (2004; 2008) tested a weekly group-based cognitive-behavioral therapy

intervention designed to lower emotional distress, reduce stress, and improve quality of life over 4 months among women with stage II and III non-metastatic breast cancer initiated in the weeks following surgery. The intervention aimed at improving QOL, reducing distress, improving health behaviors, and enhancing treatment and medical compliance, and was compared to a treatment as usual control group. The intervention was shown to improve psychological symptoms and immune functioning over the initial 4 months of follow-up (Andersen et al., 2004). At 7-13 year follow up (11-year median), women in the intervention group had significantly lower risk of breast cancer recurrence (HR = 0.55, 95% Confidence Interval [CI] [0.32-0.96], $p = 0.034$), breast cancer specific mortality (HR = 0.44, 95% CI [0.22, 0.86], $p = 0.016$) and all-cause mortality (HR = 0.51, 95% CI [0.28-0.93], $p = 0.028$) compared to women in the control group (Andersen et al., 2008).

These findings were recently replicated by our research team (Stagl et al., 2015), who tested a weekly group-based cognitive-behavioral stress management (CBSM) therapy intervention over 10-weeks aimed at improving coping and psychological adaptation and reducing stress and negative mood vs. a 1-day psychoeducation seminar control group among women with stage 0-IIIb non-metastatic breast cancer recruited in the weeks following surgery. This intervention was previously shown to improve psychological outcomes, immune system functioning, and inflammatory signaling over the initial year of follow-up (Antoni et al., 2006a; Antoni et al., 2006c; Antoni et al., 2012). At 8-15 year follow up (11-year median), women in the intervention group had marginally lower risk of breast cancer recurrence (HR = 0.45, 95% CI [0.17, 1.18], $p = 0.083$) and breast cancer specific mortality (HR = 0.25, 95% CI [0.05, 1.11], $p = 0.068$),

and significantly lower risk of all-cause mortality (HR = 0.21, 95% CI [0.05, 0.93], p = 0.040) compared to women in the control group. When analyses were restricted to women with invasive breast cancer (stage I-IIIb), who more closely resembled the Andersen and colleagues (2008) cohort, all findings became statistically significant (Stagl et al., 2015). Women with invasive disease in the intervention group had significantly lower risk of breast cancer recurrence (HR = 0.24, 95% CI [0.07, 0.82], p = 0.011) and breast cancer specific mortality (HR = 0.08, 95% CI [0.01, 0.49], p = 0.006) compared to women with invasive disease in the control group.

Potential mechanisms by which psychosocial interventions reduced recurrence and improved survival in the studies reported above (Andersen et al., 2008; Spiegel et al., 1989; Stagl et al., 2015) have been proposed but have yet to be thoroughly investigated in clinical trials (Antoni, 2013; Lutgendorf et al., 2010). Among many potential mechanisms to pursue are those associated with depressive symptoms and inflammation, specifically pro-inflammatory cytokines. These mechanisms were the focus of the study reported here.

Study Objectives

Depression (Giese-Davis et al., 2011; Pinquart & Duberstein, 2010) and inflammation (Bozcuk et al., 2004; Salgado et al., 2003; Thornton et al., 2008) have independently been linked to breast cancer health outcomes, and multiple studies have shown that depression and inflammation may themselves be linked among women with breast cancer (Bouchard et al., 2016a; Soygur et al., 2007; Thornton et al., 2009). Investigators have begun to elucidate the relationships between depressive symptoms, inflammatory markers, psychosocial interventions, and breast cancer disease outcomes

(Thornton et al., 2008; Thornton et al., 2009), but additional research is necessary to clarify relationships among these variables.

The study reported here aimed to replicate and build upon the existing literature by examining whether depressive symptoms and levels of three serum pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) prior to adjuvant treatment for primary non-metastatic breast cancer predict long-term clinical health outcomes (all-cause mortality, breast cancer specific mortality, and breast cancer recurrence) individually and in combination. The study also tested whether recent findings that a CBSM psychosocial intervention is associated with breast cancer health outcomes (Stagl et al., 2015) was replicated in a smaller sample that underwent testing for pro-inflammatory cytokines. Changes in depressive symptoms and levels of pro-inflammatory cytokines after one year of treatment were analyzed as mediators of these associations.

Specific Study Aims

This study's specific aims are represented graphically in Figure 1 (Aim 1) and Figure 2 (Aim 2), and are described below.

1a. Examined whether baseline levels of depressive symptoms and pro-inflammatory cytokines were related to time to clinical disease endpoints (i.e., all-cause mortality, breast cancer mortality, and breast cancer recurrence) at 8-15 year (11-year median) follow-up.

1b. Examined whether baseline levels of pro-inflammatory cytokines mediated the effect of baseline depressive symptoms on time to clinical disease endpoints at 11-year median follow-up. Examined whether baseline levels of depressive symptoms mediated the effects of baseline pro-inflammatory cytokines on time to

clinical disease endpoints at 11-year median follow-up.

2a. Aimed to confirm prior findings (Stagl et al., 2015) that women with breast cancer assigned to the CBSM group differed from those in the 1-day psychoeducational control group on time to clinical disease endpoints at 11-year median follow-up in the subsample of women who provided blood samples.

2b. Examined whether changes in levels of depressive symptoms and pro-inflammatory cytokines (levels at baseline minus 12-months) mediated the effect of study condition (CBSM vs. control) on time to clinical disease endpoints individually and above and beyond baseline values at 11-year median follow-up.

Chapter 2: Methods

Participants

Two hundred and forty women with non-metastatic stage 0-IIIb breast cancer were enrolled in this study between 1998 and 2005. The study was approved by the Human Subjects Research Office (HRSO) of the University of Miami (UM) Institutional Review Board (IRB) in 1998. Women were recruited through physician referrals and community advertising from a public hospital, a university-based cancer center, and surgical oncology practices in South Florida. Potential participants received personalized letters from their breast surgical oncologist or from the American Cancer Society Reach to Recovery Program via flyers referring them to the study as an opportunity to learn stress management techniques. Exclusion criteria included a prior cancer diagnosis and treatment, prior psychiatric treatment for a serious mental disorder, and lack of English language fluency.

In total, 502 potential participants were referred and screened for inclusion in this study. Of women screened, 156 passively declined enrollment due to lack of interest, 106 women did not meet inclusion criteria, and 240 participants were enrolled. Baseline assessments were conducted approximately 2-10 weeks post-surgery and prior to onset of adjuvant treatment. Following the baseline assessment, women were randomized to either a 10-week group based cognitive-behavioral stress management (CBSM) intervention group, or a 1-day psychoeducation (PE) seminar control group.

Intervention

Participants randomized to the group-based CBSM intervention met for 10 consecutive weekly group sessions lasting approximately 2 hours per session. The

structured, manualized psychosocial intervention (Antoni, 2003) combined cognitive behavioral therapy (CBT) and relaxation techniques. CBT techniques included cognitive appraisal and reframing (Beck & Emery, 1985), coping effectiveness training, assertiveness training (Fensterheim & Baer, 1975), and anger management skills. Relaxation techniques included diaphragmatic breathing, progressive muscle relaxation, guided visual imagery, and meditation (Bernstein & Borkovec, 1973). Women in the CBSM intervention were assigned weekly at-home exercises to facilitate mastery of intervention strategies.

The intervention aimed to decrease perceived stress and negative mood states; become aware of, challenge, and replace cognitive distortions with accurate appraisals using rational thought replacement; enhance coping strategies using coping effectiveness training; and enhance social support networks using assertiveness training and anger management (Antoni, 2003). Concurrently, the intervention aimed to decrease neuroendocrine markers of stress and modulate immune biomarkers to optimize health outcomes.

Intervention components were tailored specifically to cancer diagnosis and treatment-related issues. Two interventionists were assigned per group; the primary interventionist held a Ph.D. in Clinical Psychology, and co-interventionists were master's level students in a Clinical Psychology Ph.D. program at UM. Interventionists were trained in the protocol, and face-to-face supervision was provided throughout the course of the study. Two clinical psychologists monitored videotapes of the group sessions to ensure protocol fidelity and standardization.

Psychoeducation Seminar Control

Women in the control group participated in a 1-day psychoeducation seminar held in a classroom setting designed to emulate a self-help seminar. The seminar occurred on a weekend day that fell within the corresponding 10-week CBSM intervention period for that cohort. The seminar included general information related to breast cancer and cancer care as well as condensed written information related to stress management elements of the intervention. However, women in the control group lacked the opportunity to practice and integrate the CBSM techniques presented and were not assigned at-home exercises to facilitate mastery of intervention strategies.

Assessments

Initial baseline assessments at study entry (T1) were conducted approximately 2-10 weeks post-surgery and pre-adjuvant therapy. Data regarding sociodemographic information were collected, self-report psychosocial and QOL questionnaires were administered, depressive symptoms were assessed using a clinical interview, and blood samples were collected. Women were followed post-intervention and assessed at 4 subsequent time points; approximately 6 months post-enrollment (T2), 12 months post-enrollment (T3), 5 years post-enrollment (T5), and 8-15 years post-enrollment (11-year median; T6). An additional assessment took place approximately 1.5 years post-enrollment (T4), but was not used for the present analyses due to the extent of missing data.

The T1-T3 assessments consisted of psychosocial and QOL questionnaires, interview-based assessment of depressive symptoms, and collection of blood samples.

Details of the parent study are described in the original report of study results (Antoni et al., 2006a).

The T5 assessment included psychosocial questionnaires and self-report of participants' breast cancer status. Women were asked to indicate if they had experienced a breast cancer recurrence, a new cancer occurrence, were unsure if their new cancer was a recurrence or new primary, or had not experienced a second cancer diagnosis. In the case of a breast cancer recurrence or new cancer, participants were asked to report the date of diagnosis.

The T6 assessment was conducted in 2012 and included brief psychosocial questionnaires as well as data collection regarding health outcomes (mortality and breast cancer recurrence). For mortality data, a linkage study was performed with the Florida Cancer Data System (FCDS) of the Florida Department of Health in which identifiable information (first name, last name, gender, social security number [SSN], race, street address) was linked to the registry to determine cause of death for study participants who had passed away since study enrollment. At the time of the search in 2012, the FCDS was current through the year 2012 and consistent with the National Death Index through the year 2011. Further, the online search engines ancestry.com and archives.com were searched using participants' first name, last name, date of birth, and SSN to verify linkage results. Information on mortality status was obtained for all 240 participants.

For information on disease recurrence at T6, new data was collected using three approaches: participant self-report via phone screen, participant self-report via questionnaire, and medical chart review conducted by study personnel. The UM IRB approved a protocol to re-contact study participants and collect self-report data related to

contact information, breast cancer status, and the name and contact information of their current physician/oncologist. In addition, consenting participants were sent an updated IRB-approved consent for medical chart review with a pre-stamped and pre-addressed return envelope to ensure convenience of study participation. This new data were added to existing data on disease recurrence collected at the T5 assessment.

Recurrence status was available for 199 women, and for most cases a combination of data collection approaches was used. Recurrence data were collected from T5 assessment information only (N = 7), from T6 phone screen only (N = 9), from T6 packet only (N = 1), and from T6 chart review only (N = 34). Recurrence data were collected from two or three sources for 91 participants, and from all four sources for 57 participants.

Measures

Demographics. Information related to *demographics* (age, race/ethnicity, menopausal status), *socioeconomics* (education, income), *cancer diagnosis and treatment-related factors* (time from surgery to T1 assessment, stage of disease, positive lymph nodes removed during surgery, estrogen receptor [ER] status, progesterone receptor [PR] status, HER-2/neu receptor status, surgery type, chemotherapy, radiation therapy, hormone therapy, psychiatric and pain medication use), *and health behavior characteristics* (physical activity, sleep, Body Mass Index [BMI]) was collected via self-report at the initial assessment prior to study randomization, and data were verified by medical chart review. New information related to breast cancer recurrence treatment was also collected at subsequent assessments (e.g., additional surgeries and treatments).

Depressive symptoms. The 17-item interview-based Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) was used to assess presence and severity of depressive symptoms over the past week at assessments T1-T3 (see Appendix A). High inter-rater reliability, internal consistency, and discriminant validity have been shown for this scale previously (Miller, Bishop, Norman, & Maddever, 1985). A clinical psychologist with extensive training in use of the HRSD trained study assessors based on the structured interview guide (Williams, 1989). The HRSD has previously been used in samples of women with breast cancer (Poleshuck et al. 2006; Soygur et al., 2007).

Pro-inflammatory cytokines. Analyses focused on serum concentrations of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α measured using ultrasensitive ELISA kits from Life Technologies (USA). The lowest level of detection for cytokines was 0.06 pg/ml, 0.09 pg/ml, and 0.10 pg/ml for IL-1β, IL-6, and TNF-α respectively. Assays were performed according to manufacturer's instructions and yielded the following intra- and inter-assay coefficients of variability (%), respectively: IL-1β (6.4, 7.2), IL-6 (8.3, 10.0), and TNF-α (6.7, 8.2). For participants with cytokine levels below the level detectable by ELISA kit, the lowest level detectable was substituted as the participant's cytokine value in order to maximize cytokine data available. At T1 there were 5 participants with cytokine values below the detectable level (4 for IL-1β, 0 for IL-6, and 1 for TNF-α). At T3 there were 4 participants with cytokine values below the detectable level (3 for IL-1β, 0 for IL-6, and 1 for TNF-α).

Analytic Strategy

Statistical Program for the Social Sciences (SPSS) version 19.0 was used for all analyses. Data collected across time points were merged to create a single database

inclusive of time points T1-T3, T5, and T6. Status variables were created to indicate participant experience of an event of interest (1 = yes; 0 = no), and time to event variables were created for each event of interest (i.e., time from date of randomization to date of event). Time was measured in days, months, and years for ease of interpretation. There were three events of interest: all-cause mortality, breast cancer-specific mortality, and breast cancer recurrence. Analyses were restricted to a subsample of participants who provided blood samples for pro-inflammatory cytokine studies at the T1 and T3 assessment time points in order to maintain a common sample across study analyses (N = 90).

Censoring. Censoring is a practice implemented when the total time to a given event cannot be determined (Rich et al., 2010). In the present study, data were censored at T6 in four instances: for participants who did not experience an event (i.e., were alive and/or did not have a breast cancer recurrence), participants who were lost to follow-up, participants who had previously dropped out of the study, and participants whose cancer status could not be obtained.

Data met the assumption of non-informative censoring, which assumes that the reasons for participant drop out are unrelated to the study or study treatment. This assumption is often determined by study design; for example, if participants were lost to follow-up for unforeseen circumstances or dropped out of the study for a variety of reasons, as was the case in the present study, one may assume that censoring was non-informative (Allison, 2010; Prinja, Gupta & Verma, 2010).

Data were right censored, meaning it is known that the event of interest had not yet occurred at time of follow-up. Participants alive at time of T6 follow-up were right-

censored with the date they were last reported alive, and women with no reported breast cancer recurrence or for whom data were unavailable were right-censored with the last known date of disease free status.

Covariates. All analyses were run first unadjusted, and again with chosen covariates. Two criteria were used to determine candidate confounders to be considered in the analyses as covariates. First, any variables that were significantly different between the CBSM and control group at baseline were considered as covariates in models with CBSM as a predictor. Second, prognostic risk factors and adjuvant treatments known to affect the clinical outcomes of interest were considered *a priori* as potential covariates based on proposed guidelines set forth by researchers in order to avoid model overfit (Babyak, 2004; Harrell, 2001). According to these guidelines, researchers ideally create an *a priori* list of covariates based on theory and empirical evidence and retain these covariates in the final model. However, when the number of predictors is too large, the number of covariates should be reduced to avoid model overfit (Babyak, 2004). One suggested strategy is to examine the correlations between predictors and eliminate all but one of the closely correlated predictors (Babyak, 2004).

Given these suggestions, the current study selected an *a priori* list of covariates that either differed by group assignment at baseline or were prognostic risk factors and adjuvant treatments known to affect the clinical outcomes of interest. The following demographic, prognostic, and treatment-related variables were considered for inclusion as covariates in controlled analyses: age (Anders et al., 2008; Han et al., 2004; O'Connor et al., 2009), menopausal status (Carlson et al., 2009), time elapsed from surgery to baseline (Carlson et al., 2009), stage of disease (Carlson et al., 2009; Galea, Blamey,

Elston, & Ellis, 1992), tumor size (Soerjomataram, Louwman, Ribot, Roukema, & Coebergh, 2008), number of positive lymph nodes removed during surgery (Soerjomataram et al., 2008), procedure type (Carlson et al., 2009), ER and PR status (Allred et al., 2009; O'Connor et al., 2009), HER2-neu receptor status (Carlson et al., 2009; Ross & Fletcher, 1998; Soerjomataram et al., 2008), chemotherapy received (Chia, Bryce, & Gelmon, 2005; Clark et al., 2005b), radiation therapy received (Clarke et al., 2005a), hormone therapy received (Chia et al., 2005; Clarke et al., 2005b), smoking status (O'Connor et al., 2009), BMI (O'Connor et al, 2009), and use of anti-depressant medications (Hamer, Batty, Marmot, Singh-Manoux, & Kivimaki, 2011; O'Connor et al., 2009).

Covariates were narrowed down after conducting Pearson's correlation and Spearman's rho analyses to determine degree of collinearity among the candidate covariates (Babyak, 2004). For any predictor variables that were highly correlated ($r \geq 0.40$), a choice was made between the two regarding which variable would be retained in the final model. Chi-square and one-way ANOVAs were conducted to determine group differences at baseline among demographic, medical, treatment-related, and psychosocial variables. Candidate covariates that were significantly different between study groups at were either retained or accounted for in the final model.

The final covariates retained in the model were: *age* (highly correlated with menopausal status), *stage of disease* (highly correlated with tumor size, number of positive lymph nodes removed during surgery, and chemotherapy received [which differed by group]), *surgical procedure type* (highly correlated with radiation therapy

received), *hormone therapy received* (highly correlated with ER and PR statuses), and *smoking status* (significantly differed between study groups).

BMI was not highly correlated with other covariates, but was unavailable for 28.9% of the sample. Thus to include BMI in analyses without sacrificing sample size, controlled analyses were run first with the final covariates listed above (age, stage of disease, procedure type, hormone therapy received, and smoking status) and again with BMI as an additional covariate in "fully adjusted" models. Notably, there was only 1 death among participants with BMI data available; thus analyses of time to all-cause mortality and breast cancer-specific mortality were not possible. Analyses of disease free interval were run in fully adjusted models.

In order to avoid model over-fit (Babyak, 2004), not all proposed covariates were included or accounted for by highly correlated covariates in the final model. Specifically, time elapsed from surgery to baseline was not highly correlated with other covariates, but was unlikely to influence long-term health outcomes. HER2/neu status was not accounted for by highly correlated covariates, but was unavailable for the majority (51.1%) of the study sample. Finally, use of anti-depressant medications was not accounted for by highly correlated covariates, but was equal between study groups and low in frequency (10.0% of total participants reported use of anti-depressant medications). Thus, these variables were not included as covariates in the final model.

Invasive subsample. It was observed in the larger parent sample that the CBSM intervention was more strongly related to long term breast cancer health outcomes when analyses are restricted to women with invasive disease (i.e., stage I-III; Stagl et al., 2015). Thus all analyses were first conducted in the subsample of participants who provided

blood samples for pro-inflammatory cytokine studies at the T1 and T3 assessments regardless of stage of disease (N = 90). Analyses were then restricted to participants in this subsample with invasive disease (stage I-IIIb; n = 73).

Aim 1. Baseline variable effects on clinical disease endpoints. The first aim was to examine the relationships between baseline levels of depressive symptoms and pro-inflammatory cytokines with time to clinical disease endpoints (i.e., all-cause mortality, breast cancer-specific mortality, and breast cancer recurrence) at 8-15 year (11-year median) follow-up (Figure 1).

Aim 1a. The direct effect of baseline variables on time to clinical disease endpoints was examined using unadjusted Cox Proportional Hazard Ratios (Cox, 1972). In addition, adjusted models were examined to assess the effects of baseline variables on time to clinical disease endpoint above and beyond the effect of demographic, prognostic, and treatment variables (see section Covariates). Models indicated the relative risk of an event per unit change in the predicting variable. A hazard ratio of 1 indicated no increased risk of event per unit change in the predictor, whereas a ratio of < 1 indicated a lower risk of event per unit change in the predictor, and a ratio of > 1 indicated an increased risk of event per unit change in the predictor. Hazard ratio estimates were interpreted at a two-tailed significance level of $p < 0.05$. Confidence intervals at 95% were obtained for each hazard ratio estimate; estimates with lower and upper confidence interval limits that did not contain the value 1.0 were considered meaningful predictors of the outcome.

Aim 1b. The indirect effects of baseline levels of depressive symptoms and pro-inflammatory cytokines on time to clinical disease endpoints were examined in mediation

models. For example, the indirect effect of baseline depressive symptoms on time to all-cause mortality was assessed with each baseline pro-inflammatory cytokine as a mediating variable. Alternatively, the indirect effect of a pro-inflammatory cytokine on time to all-cause mortality was assessed with baseline depressive symptoms as a mediating variable. Mediation models were assessed using bootstrapping methods within an SPSS macro program (Hayes, 2009; MacKinnon, Lockwood & Williams, 2004; Preacher & Hayes, 2004), and extended from the traditional Baron and Kenny (1986) approach to mediation.

Tests of mediation were interpreted by examining multiple paths within each model: the effect of the independent variable on the mediator (path A), the effect of the mediator on the dependent variable while controlling for the independent variable (path B), the total effect of the independent variable on the dependent variable (path C; tested in aim 1a), and finally the effect of the independent variable on the dependent variable while controlling for the mediator (path C'). Mediation models that meet Baron and Kenny (1986) criteria will have significant paths A and B, and a non-significant path C'. Path C is not required to be significant (Hayes, 2009). The significance of the indirect effect (path A x Path B) was tested using the Sobel test (Preacher & Hayes, 2004), and a significant indirect effect implies mediation, such that the relationship between the independent variable and the dependent variable was mediated by the proposed mediator variable (Hayes, 2009; MacKinnon et al., 2004; Preacher & Hayes, 2004).

Aim 2. Intervention effects on clinical disease endpoints. The second aim was to examine whether women with breast cancer assigned to the CBSM group differed from those in the 1-day PE control group on time to clinical disease endpoints at 11-year

median follow up, and whether such effects were mediated by changes in depressive symptoms and pro-inflammatory cytokines over the first year of study follow-up (Figure 2).

Aim 2a. The effect of study condition (CBSM = 1; PE = 0) on time to clinical disease endpoints was examined using unadjusted Cox Proportional Hazard Ratios (Cox, 1972). In addition, adjusted models were examined to assess intervention effects on time to clinical disease endpoint above and beyond the effect of demographic, prognostic, and treatment variables (see section Covariates). As before, hazard ratio estimates were interpreted at a two-tailed significance level of $p < 0.05$. Confidence intervals at 95% were obtained for each hazard ratio estimate; estimates with lower and upper confidence interval limits that did not contain the value 1.0 were considered meaningful predictors of the outcome.

Aim 2b. Intervention effects on time to clinical disease endpoints were examined in mediation models. Change scores from T1-T3 were computed to represent changes in levels of depressive symptoms and pro-inflammatory cytokines across the first year of study participation. These change scores served as mediators for the present mediation analyses. Models were assessed with change scores included as mediators independently and also with baseline values of the mediator included as a covariate to assess for the mediator's association with time to clinical disease endpoints above and beyond baseline values. As described above, mediation models were assessed using bootstrapping methods within an SPSS macro program (Hayes, 2009; MacKinnon et al., 2004; Preacher & Hayes, 2004).

Chapter 3: Results

Patient Sample Characteristics

The Consolidated Standards of Reporting Trials (CONSORT) diagram of study enrollment and retention is shown in Figure 3. Women who provided blood data for cytokine analyses at T1 and T3 (N = 90) were mostly similar to women who did not provide blood samples at these time points (N = 150). For full descriptive information by group (did vs. did not provide blood data) on demographic, medical, treatment-related, and psychosocial variables, see Table 1.

Women who provided blood data were significantly different from women who did not provide blood data with regard to stage of disease ($p = 0.049$). The majority of women who provided blood data had stage I disease (41.1%) followed by stage II (36.7%), stage 0 (18.9%) and stage III disease (3.3%). The majority of women who did not provide blood data had stage II disease (38.9%) followed by stage I (30.9%), stage 0 (16.8%), and stage III disease (13.4%). It is notable that women who did and did not provide blood data did not differ with regard to the proportion of cases with invasive vs. non-invasive disease ($p > 0.10$).

Women who provided blood data had significantly fewer lymph nodes removed during surgery ($M = 0.81$, $SD = 2.41$) than women who did not provide blood data ($M = 1.92$, $SD = 3.67$; $p = 0.011$). Notably, the standard deviation of positive lymph nodes among women who did not provide blood data was large, and indicates a potential difference in disease severity between women who did and did not provide blood samples. Women who provided blood data also significantly differed from women who did not provide blood data with regard to receipt of chemotherapy ($p = 0.037$); of the

women who provided blood data, 46.7% had received chemotherapy compared to 60.7% of women who did not provide blood data. Finally, women who provided blood data had marginally longer time from study entry to death (M = 3158.43, SD = 1221.88) than women who did not provide blood data (M = 2845.20, SD = 1418.85, p = 0.083). Beyond these significant and marginally significant differences, women who did and did not provide blood data did not differ on any other study variables.

At the 11-year median follow-up, women who provided blood data for cytokine analyses at T1 and T3 were an average of 60.77 (SD = 7.95) years old. For full descriptive information by group (CBSM vs. control) on demographic, medical, treatment-related, and psychosocial variables, see Table 2. Study groups differed with regard to receipt of chemotherapy (p = 0.011). In the control group, 33.3% of women had received chemotherapy, whereas 60.0% of women in the CBSM group had received chemotherapy. In addition, study groups differed with regard to smoking status (p = 0.021), with 5 reported smokers in the control group (11.1%), and no reported smokers in the CBSM group. Study groups differed marginally with regard to surgical procedure type (p = 0.090). In the control group, 64.4% of women underwent a lumpectomy and 35.6% underwent a mastectomy. In the CBSM group 46.7% of women underwent a lumpectomy and 53.3% underwent a mastectomy. The study groups did not differ on any other study variables.

Of the women who provided blood data at T1 and T3, a total of 8 women (8.9%) were deceased at T6 follow-up. Of those 8 deaths, 6 (75.0%) were related to breast cancer, and 2 (25.0%) were not related to breast cancer. Of the non-breast cancer related deaths, 1 death was due to a malignant neoplasm without site specification, and 1 death

was due to an unknown cause. Average time to death was 3158.43 days (*SD* = 1221.88), or 103.29 months (*SD* = 40.17), or 8.12 years (*SD* = 3.46). Women who were still alive at the time of follow-up (82 women, 91.1%) were censored using the last date they were documented alive.

Of the women who provided blood data at T1 and T3, a total of 17 women (18.9%) experienced a breast cancer recurrence. Caution was taken in determining whether the documented recurrence was indeed a breast cancer recurrence rather than a new primary cancer occurrence. Average disease free interval was 2392.54 days (*SD* = 1349.42), or 78.12 months (*SD* = 44.31), or 6.06 years (*SD* = 3.75). Women who did not experience a breast cancer recurrence (73 women, 81.1%) were censored using the date they were last documented to be disease free.

Aim 1a: Direct Effects of Baseline Variables on Time to Clinical Disease Endpoints

Cox Proportional Hazards were conducted to assess the direct relationships between baseline variables (i.e., depressive symptoms and serum concentrations of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α) and time to clinical disease endpoints (i.e., all-cause mortality, breast cancer-specific mortality, and disease free interval) in separate models (Figure 1).

Unadjusted models. Unadjusted Cox Proportional Hazards models revealed non-significant findings in the full study sample (all *p*s > 0.10; Table 3), and null findings were also obtained when analyses were restricted to women with invasive disease (all *p*s > 0.10; Table 4).

Adjusted models. Adjusted Cox Proportional Hazards models controlled for age, stage, procedure, hormone therapy, and smoking status. Findings were all non-significant

in the full study sample (all *p*s > 0.10; Table 5), and null findings were also obtained when analyses were restricted to women with invasive disease (all *p*s > 0.10; Table 6).

Fully adjusted Cox Proportional Hazards models were conducted, which included BMI as an additional covariate when predicting disease free interval. The fully adjusted models also revealed non-significant results in both the full study sample and the invasive sub-sample (all *p*s > 0.10 Table 7).

Aim 1b: Indirect Effects of Baseline Variables on Time to Clinical Disease Endpoints

Regression analyses were used to test whether baseline variables (i.e., depressive symptoms and serum concentrations of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α) were indirectly related to time to clinical disease endpoints (i.e., all-cause mortality, breast cancer-specific mortality, disease free interval). Six models were tested for each clinical disease endpoint. In each model, path A was the effect of the independent variable on the mediator variable. Path B was the effect of the mediator variable on time to the clinical disease endpoint while controlling for the independent variable.

The models are as follows: Model 1 was the indirect effect of depressive symptoms on time to the clinical disease endpoint through serum concentration of IL-1β; Model 2 was the indirect effect of depressive symptoms on time to the clinical disease endpoint through serum concentration of IL-6; Model 3 was the indirect effect of depressive symptoms on time to the clinical disease endpoint through serum concentration of TNF-α; Model 4 was the indirect effect of serum concentration of IL-1β on time to the clinical disease endpoint through depressive symptoms; Model 5 was the

indirect effect of serum concentration of IL-6 on time to the clinical disease endpoint through depressive symptoms; Model 6 was the indirect effect of serum concentration of TNF-α on time to the clinical disease endpoint through depressive symptoms.

Unadjusted models. Paths A for Models 1-6 were identical for all clinical disease endpoints (i.e., relationships among baseline depressive symptoms and serum pro-inflammatory cytokines). Full path A results are detailed in Table 8 (full study sample) and Table 9 (invasive sub-sample). Full path B results are detailed in Table 10 (full study sample) and Table 11 (invasive sub-sample).

Model 1 path A was significant in the full study sample, with greater levels of baseline depressive symptoms concurrently associated with greater serum concentration of IL-1β ($p = 0.013$). This finding was retained in the invasive sub-sample ($p = 0.030$). All paths B were non-significant ($ps > 0.10$), indicating no relationship between baseline serum concentration of IL-1β and time to clinical disease endpoints (assessed in separate models) when controlling for baseline depressive symptoms. Therefore mediation was not supported.

Model 2 path A was marginally significant in the full study sample, with greater baseline levels of depressive symptoms marginally associated with concurrent greater serum concentration of IL-6 ($p = 0.064$). This finding became non-significant in the invasive sub-sample ($p > 0.10$). All paths B were non-significant in the full study sample ($ps > 0.10$), indicating no relationship between baseline serum concentration of IL-6 and time to clinical disease endpoints (assessed in separate models) when controlling for baseline depressive symptoms. Therefore mediation was not supported. Paths B were not

assessed in the invasive sub-sample because path A was non-significant, and mediation was therefore not supported.

Model 3 path A was significant in the full study sample, with greater levels of baseline depressive symptoms concurrently associated with greater serum concentration of TNF-α ($p = 0.031$). This finding was retained in the invasive sub-sample ($p = 0.036$). All paths B were non-significant ($ps > 0.10$), indicating no relationship between serum concentration of TNF-α and time to clinical disease endpoints (assessed in separate models) when controlling for baseline depressive symptoms. Therefore mediation was not supported.

Model 4 path A was significant in the full study sample, with greater baseline serum concentration of IL-1β concurrently associated with greater levels of depressive symptoms ($p = 0.013$). This finding was retained in the invasive sub-sample ($p = 0.030$). All paths B were non-significant ($ps > 0.10$), indicating no relationship between baseline depressive symptoms and time to clinical disease endpoints (assessed in separate models) when controlling for baseline serum concentration of IL-1β. Therefore mediation was not supported.

Model 5 path A was marginally significant in the full study sample, with greater baseline serum concentration of IL-6 marginally associated with concurrent greater levels of depressive symptoms ($p = 0.064$). This finding became non-significant in the invasive sub-sample ($p > 0.10$). All paths B were non-significant in the full study sample ($ps > 0.10$), indicating no relationship between baseline depressive symptoms and time to clinical disease endpoints (assessed in separate models) when controlling for baseline serum concentration of IL-6. Therefore mediation was not supported. Paths B were not

assessed in the invasive sub-sample because path A was non-significant, and mediation was therefore not supported.

Model 6 path A was significant in the full study sample, with greater baseline serum concentration of TNF-α concurrently associated with greater levels of depressive symptoms ($p = 0.031$). This finding was retained in the invasive sub-sample ($p = 0.036$). All paths B were non-significant ($ps > 0.10$), indicating no relationship between baseline depressive symptoms and time to clinical disease endpoints (assessed in separate models) when controlling for baseline serum concentration of TNF-α. Therefore mediation was not supported.

Adjusted models. Adjusted regression analyses controlled for age, stage, procedure, hormone therapy, and smoking status. Again, paths A for Models 1-6 were identical for all clinical disease endpoints. Full path A results are detailed in Table 12 (full study sample) and Table 13 (invasive sub-sample). Full path B results are detailed in Table 14 (full study sample) and Table 15 (invasive sub-sample).

Model 1 path A was significant in the full study sample, with greater levels of baseline depressive symptoms concurrently associated with greater serum concentration of IL-1β ($p = 0.007$). This finding was retained in the invasive sub-sample ($p = 0.012$). All paths B were non-significant ($ps > 0.10$), indicating no relationship between baseline serum concentration of IL-1β and time to clinical disease endpoints (assessed in separate models) when additionally controlling for baseline depressive symptoms. Therefore mediation was not supported.

Model 2 path A was marginally significant in the full study sample, with greater baseline levels of depressive symptoms marginally associated with concurrent greater

serum concentration of IL-6 ($p = 0.077$). This finding became non-significant in the invasive sub-sample ($p > 0.10$). All paths B were non-significant in the full study sample ($ps > 0.10$), indicating no relationship between baseline serum concentration of IL-6 and time to clinical disease endpoints (assessed in separate models) when additionally controlling for baseline depressive symptoms. Therefore mediation was not supported. Paths B were not assessed in the invasive sub-sample because path A was non-significant, and mediation was therefore not supported.

Model 3 path A was significant in the full study sample, with greater levels of baseline depressive symptoms concurrently associated with greater serum concentration of TNF-α ($p = 0.004$). This finding was retained in the invasive sub-sample ($p = 0.013$). All paths B were non-significant ($ps > 0.10$), indicating no relationship between serum concentration of TNF-α and time to clinical disease endpoints (assessed in separate models) when additionally controlling for baseline depressive symptoms. Therefore mediation was not supported.

Model 4 path A was significant in the full study sample, with greater baseline serum concentration of IL-1β concurrently associated with greater levels of depressive symptoms ($p = 0.007$). This finding was retained in the invasive sub-sample ($p = 0.012$). All paths B were non-significant ($ps > 0.10$), indicating no relationship between baseline depressive symptoms and time to clinical disease endpoints (assessed in separate models) when additionally controlling for baseline serum concentration of IL-1β. Therefore mediation was not supported.

Model 5 path A was marginally significant in the full study sample, with greater baseline serum concentration of IL-6 marginally associated with concurrent greater levels

of depressive symptoms ($p = 0.077$). This finding became non-significant in the invasive sub-sample ($p > 0.10$). All paths B were non-significant in the full study sample ($ps > 0.10$), indicating no relationship between baseline depressive symptoms and time to clinical disease endpoints (assessed in separate models) when additionally controlling for baseline serum concentration of IL-6. Therefore mediation was not supported. Paths B were not assessed in the invasive sub-sample because path A was non-significant, and mediation was therefore not supported.

Model 6 path A was significant in the full study sample, with greater baseline serum concentration of TNF-α concurrently associated with greater levels of depressive symptoms ($p = 0.004$). This finding was retained in the invasive sub-sample ($p = 0.013$). All paths B were non-significant ($ps > 0.10$), indicating no relationship between baseline depressive symptoms and time to clinical disease endpoints (assessed in separate models) when controlling for baseline serum concentration of TNF-α. Therefore mediation was not supported.

Fully adjusted disease free interval. Fully adjusted Cox Proportional Hazards models including BMI as an additional covariate were run in the full study sample and in the invasive sub-sample with disease free survival as the outcome variable. Full path A results are detailed in Table 16 (full study sample) and Table 17 (invasive sub-sample). Full path B results are detailed in Table 18 (full study sample) and Table 19 (invasive sub-sample).

Model 1 path A was significant in the full study sample, with greater levels of baseline depressive symptoms concurrently associated with greater serum concentration of IL-1β ($p = 0.015$). This finding was retained in the invasive sub-sample ($p = 0.007$).

All paths B were non-significant (*p*s > 0.10), indicating no relationship between baseline serum concentration of IL-1β and time to breast cancer recurrence when additionally controlling for baseline depressive symptoms. Therefore mediation was not supported.

Model 2 path A was non-significant in the full study sample, indicating no relationship between baseline depressive symptoms and concurrent serum concentration of IL-6 ($p > 0.10$). Therefore mediation was not supported. Path A was marginally significant in the invasive sub-sample ($p = 0.062$), but path B was non-significant ($p > 0.10$), indicating no relationship between baseline serum concentration of IL-6 and time to breast cancer recurrence when additionally controlling for baseline depressive symptoms. Mediation was therefore not supported.

Model 3 path A was significant in the full study sample, with greater levels of baseline depressive symptoms concurrently associated with greater serum concentration of TNF-α ($p = 0.017$). This finding was retained in the invasive sub-sample ($p = 0.011$). All paths B were non-significant (*p*s > 0.10), indicating no relationship between serum concentration of TNF-α and time to breast cancer recurrence when additionally controlling for baseline depressive symptoms. Therefore mediation was not supported.

Model 4 path A was significant in the full study sample, with greater baseline serum concentration of IL-1β concurrently associated with greater levels of depressive symptoms ($p = 0.015$). This finding was retained in the invasive sub-sample ($p = 0.007$). All paths B were non-significant (*p*s > 0.10), indicating no relationship between baseline depressive symptoms and time to breast cancer recurrence when additionally controlling for baseline serum concentration of IL-1β. Therefore mediation was not supported.

Model 5 path A was non-significant in the full study sample, indicating no relationship between baseline depressive symptoms and concurrent serum concentration of IL-6 ($p > 0.10$). Therefore mediation was not supported. Path A was marginally significant in the invasive sub-sample ($p = 0.062$), but path B was non-significant ($p > 0.10$), indicating no relationship between baseline serum concentration of IL-6 and time to breast cancer recurrence when additionally controlling for baseline depressives symptoms. Mediation was therefore not supported.

Model 6 path A was significant in the full study sample, with greater baseline serum concentration of TNF-α concurrently associated with greater levels of depressive symptoms ($p = 0.017$). This finding was retained in the invasive sub-sample ($p = 0.011$). All paths B were not significant ($ps > 0.10$), indicating no relationship between baseline depressive symptoms and time to breast cancer recurrence when additionally controlling for serum concentration of TNF-α. Mediation was therefore not supported.

Aim 2a: Direct Effect of Intervention on Time to Clinical Disease Endpoints

Cox Proportional Hazards were conducted to assess group differences (i.e., CBSM vs. control) on time to clinical disease outcomes (i.e., all-cause mortality, breast cancer mortality, breast cancer recurrence) in separate models (Figure 2).

Unadjusted models. Unadjusted Cox Proportional Hazards models revealed non-significant findings in the full study sample (all $ps > 0.10$; Table 20), and null findings were also obtained when analyses were restricted to women with invasive disease (all $ps > 0.10$; Table 20, bottom half).

Adjusted models. Adjusted Cox Proportional Hazards models controlled for age, stage, procedure, hormone therapy, and smoking status. Findings were all non-significant

in the full study sample (all *p*s > 0.10; Table 21), and null findings were also obtained when analyses were restricted to women with invasive disease (all *p*s > 0.10; Table 21, bottom half).

Fully adjusted Cox Proportional Hazards models were conducted, which included BMI as an additional covariate when predicting disease free interval. The fully adjusted models also revealed non-significant results in both the full study sample and the invasive sub-sample (*p*s > 0.10; Table 22).

Aim 2b: Indirect Effect of Intervention on Time to Clinical Disease Endpoints

Regression analyses were used to test whether study condition (i.e., CBSM vs. control) related to clinical disease endpoints (i.e., all-cause mortality, breast cancer-specific mortality, disease free interval) indirectly through 12-month changes in depressive symptoms or serum concentrations of IL-1β, IL-6, or TNF-α. Four models were assessed for each clinical disease endpoint. In each model, path A was the effect of the independent variable on the mediator variable. Path B was the effect of the mediator variable on time to the clinical disease endpoint while controlling for the independent variable.

The models are as follows: Model 1 was the indirect effect of study condition on time to the clinical disease endpoint through 12-month change in depressive symptoms; Model 2 was the indirect effect of study condition on time to the clinical disease endpoint through 12-month change in serum concentration of IL-1β; Model 3 was the indirect effect of study condition on time to the clinical disease endpoint through 12-month change in serum concentration of IL-6; Model 4 was the indirect effect of study condition

on time to the clinical disease endpoint through 12-month change in serum concentration of TNF-α.

Paths A for Models 1-4 were identical for all clinical disease endpoints (i.e., study condition predicting 12-month change in depressive symptoms, serum concentration of IL-1 β, IL-6, and TNF-α, respectively).

Unadjusted models. Unadjusted regression analyses revealed non-significant findings for all paths A in the full study sample (all *p*s > 0.10; Table 23). Women in the intervention group had an average decrease in depressive symptoms of 1.98 points on the HRSD (*SE* = 0.81) compared to an average decrease of 0.50 points (*SD* = 0.81) in the control group. Women in the intervention group had an average increase in IL-1β of 0.06 log transformed pg/µl (*SE* = 0.15) compared to an average increase of 0.12 log transformed pg/µl (*SE* = 0.15) in the control group. Women in the intervention group had an average increase in IL-6 of 0.01 log transformed pg/µl (*SE* = 0.19) compared to an average increase of 0.06 log transformed pg/µl (*SE* = 0.19) in the control group. Finally, women in the intervention group had an average increase in TNF-α of 0.13 log transformed pg/µl (*SE* = 0.13) compared to an average increase of 0.05 log transformed pg/µl (*SE* = 0.13) in the control group.

Null findings were also obtained when analyses were restricted to women with invasive disease (all *p*s > 0.10; Table 23, bottom half). Findings remained non-significant when analyses included baseline values of the mediating variable as a covariate (all *p*s > 0.10; Table 24). As all paths A were non-significant, mediation was not supported. Therefore, further tests of the bootstrapped indirect effects were not computed.

Adjusted models. Adjusted regression analyses were conducted controlling for age, stage, procedure, hormone therapy, and smoking status. Findings were non-significant for all paths A in the full study sample (all *p*s > 0.10; Table 25). Women in the intervention group had an average decrease in depressive symptoms of 2.17 points on the HRSD (*SE* = 0.85) compared to an average decrease of 0.31 points (*SE* = 0.85) in the control group. Women in the intervention group had an average increase in IL-1β of 0.08 log transformed pg/µl (*SE* = 0.15) compared to an average increase of 0.10 log transformed pg/µl (*SE* = 0.15) in the control group. Women in the intervention group had an average increase in IL-6 of 0.03 log transformed pg/µl (*SE* = 0.20) compared to an average increase of 0.04 log transformed pg/µl (*SE* = 0.20) in the control group. Finally, women in the intervention group had an average increase in TNF-α of 0.17 log transformed pg/µl (*SE* = 0.13) compared to an average increase of 0.01 log transformed pg/µl (*SE* = 0.13) in the control group.

Null findings were also obtained when analyses were restricted to women with invasive disease (all *p*s > 0.10; Table 25, bottom half). Findings remained non-significant when analyses included baseline values of the mediating variable as a covariate (all *p*s > 0.10; Table 26). Finally, null findings were retained in the fully adjusted models, which included BMI as an additional covariate (all *p*s > 0.10; Table 27). As all paths A were non-significant, mediation was not supported. Therefore, further tests of the bootstrapped indirect effects were not computed.

Chapter 4: Discussion

The study reported here followed women with primary non-metastatic breast cancer from the weeks post-surgery, through participation in a manualized, group-based psychosocial intervention (Antoni, 2003), and out to 8-15 years (11-year median) into survivorship to examine possible predictors of long-term clinical health outcomes. Previous research has shown that depression (Giese-Davis et al., 2011; Pinquart & Duberstein, 2010) and inflammation (Bozcuk et al., 2004; Salgado et al., 2003; Thornton et al., 2008) are independently associated with breast cancer health outcomes, and are related to one another (Soygur et al., 2007; Thornton et al., 2009). Studies of cognitive-behavioral based psychosocial interventions have found beneficial intervention effects on both survival and recurrence in breast cancer patients (Andersen et al., 2008; Stagl et al., 2015). The mechanisms through which interventions affect clinical health outcomes are less understood.

The current study sought to replicate and extend the extant literature. It examined the relationships between post-surgical and pre-adjuvant levels of depressive symptoms and pro-inflammatory cytokines with long-term clinical health outcomes, both individually and in combination, among a cohort of non-metastatic breast cancer patients. It also sought to replicate recent findings that a CBSM psychosocial intervention predicts favorable breast cancer health outcomes (Stagl et al., 2015), and examined possible mediators of these effects.

Effects of Baseline Variables on Time to Clinical Disease Endpoints

Aim 1a. Aim 1a of the reported study examined whether baseline levels of depressive symptoms and pro-inflammatory cytokines (i.e., IL-1β, IL-6, and TNF-α)

were related to time to clinical disease endpoints (i.e., all-cause mortality, breast cancer mortality, and breast cancer recurrence) at 11-year median follow-up. Findings revealed non-significant relationships between baseline variables and time to clinical disease endpoints in both the full sample (stage 0 – III) and invasive subsample (stage I – III) in unadjusted, adjusted, and fully adjusted models.

In this study, baseline depressive symptoms were unrelated to time to all-cause mortality. Although many previous studies and meta-analyses have found a relationship between greater depressive symptoms and greater all-cause mortality in breast cancer patients (e.g., Chida et al., 2008; Giese-Davis et al., 2011), other studies have found no relationship (Phillips et al., 2008; Spiegel & Giese-Davis, 2003). Thus, the null finding in this study appears to question the notion of a relationship between depressive symptoms and overall survival among breast cancer patients. However, in our own full parent study sample, we found that greater depressive symptoms predicted shorter all-cause survival in unadjusted and adjusted models (Antoni et al., 2017).

The lack of confirmatory findings in this study could represent a lack of statistical power to detect these associations. In survival analyses, the number of events determines power, rather than the overall sample size (Bradburn, Clark, Love, & Altman, 2003). Ad-hoc analyses were conducted using an approach designed specifically for calculation of estimated sample size needs for clinical trials (Browner, Newman, & Hulley, 2013a; Browner, Newman, & Hulley, 2013b; Schoenfeld, 1983) in order to determine the estimated number of events needed to detect an effect of baseline depressive symptoms on time to all-cause mortality based on previous research (Kohn, Jarrett, & Senyak, 2016).

In the full parent study sample (N = 240) reported by Antoni and colleagues (2017), 28 of the women who had baseline depressive symptom data were deceased due to all causes at 11-year median follow-up (12.1%). Having mild to moderate baseline levels of depressive symptoms significantly predicted shorter time to all-cause mortality (compared to low levels of depressive symptoms; HR = 2.58). In order to detect a comparable effect size, a study would require approximately 36 deaths due to all causes. In this study, there were 8 all-cause deaths (8.9%), indicating a lack of power to detect an effect of baseline depressive symptoms on time to all-cause mortality, even if such an effect were present.

This study also found no relationship between baseline depressive symptoms and time to breast-cancer specific mortality. Virtually all previous studies of the relationship between depressive symptoms and mortality in breast cancer patients have focused on all-cause mortality and have not reported on breast cancer-specific mortality (Giese-Davis et al., 2011; Hjerl et al., 2003; Kanani et al., 2016; Phillips et al., 2008; Pinquart & Duberstein, 2010; Satin et al., 2009; Watson et al., 1999). This could reflect a lack of studies that have empirically investigated this relationship. In our own full parent study sample, we found no relationship between magnitude of depressive symptoms and breast cancer-specific survival (unpublished data). Thus, the null finding in this study confirms our prior null finding.

Depressive symptoms were also unrelated to time to breast cancer recurrence in this study. This is consistent with previous literature that has failed to find an association between depressive symptoms and breast cancer recurrence (Phillips et al., 2008; Satin et al., 2009; Watson et al., 1999) including our own full study sample (Antoni et al., 2017).

It is possible that behavioral and/or psychosocial factors that were not measured in this study could influence detection of disease recurrence and ultimately breast cancer-specific mortality (e.g., communication between patient and physician, compliance with or accessibility of follow-up care; DiMatteo, Lepper, & Croghan, 2000). Thus, future research should take variables such as these into account.

This was the first study of its kind to examine relationships between baseline levels of serum pro-inflammatory cytokines (i.e., IL-1β, IL-6, and TNF-α) and time to clinical disease endpoints among non-metastatic breast cancer patients. Results were contrary to expectations, with all relationships being non-significant. It was hypothesized that elevated levels of IL-1β, IL-6, and TNF-α would be related to shorter time to clinical disease endpoints at 11-year median follow-up, based on a body of literature showing that each of these pro-inflammatory cytokines is associated with tumor progression and poor prognosis in animal and human models of metastatic disease (e.g., Arhiro et al., 2000; Bozcuk et al., 2004; Jin et al., 1997; Vidal-Valaclocha et al., 2000).

Similarly, Aim 2b investigated changes in pro-inflammatory cytokines from baseline to 12-months as mediators of intervention effects on time to clinical disease endpoints. Since all paths A were non-significant (group differences in time to clinical disease endpoints, discussed below), mediation was not possible, and paths B were not reported (change in pro-inflammatory cytokines predicting time to clinical disease endpoints while controlling for study condition). However, ad hoc analyses revealed that all paths B were non-significant (*p*s > 0.10), and changes in pro-inflammatory cytokines did not predict clinical endpoints.

This is in contrast with recent findings from our own parent study. Previously, logistic regression analyses revealed that decreases in specific pro-inflammatory leukocyte gene expression predicted odds of survival at 11-year median follow-up after controlling for relevant covariates (Bouchard et al., 2016b). Specifically, a significant association emerged between decreased *TNFSF10* and greater odds of survival ($p < 0.05$), and marginal associations emerged between decreases in *TNFRSF21* and *IL6* and greater odds of survival ($ps < 0.10$). While the outcome of interest in the previous study differs from that of the current study (odds of survival vs. time to clinical event), the associations observed between change in leukocyte pro-inflammatory gene expression and survival indicate a role for inflammatory markers as predictors of long-term health outcomes in breast cancer patients. Notably, the sample of participants in which these findings emerged (n = 80) is a subset of this dissertation's sample (N = 90).

Further, we recently found evidence of an intervention effect on change in the leukocyte gene expression of a composite representing a leukocyte conserved transcriptional response to adversity (CTRA). This CTRA composite is characterized by up-regulated inflammatory production signaling (including *IL1B*, *IL6*, and *TNF* genes), among other processes (i.e., down-regulated anti-viral and antibody production signaling; Antoni et al., 2016). Women in the CBSM intervention expressed an attenuated CTRA response post-intervention compared to women in the control group, who showed an increased CTRA response. The attenuated CTRA response was associated, in turn, with greater disease free interval at 11-year median follow-up (Antoni et al., 2016). As before, the association observed between attenuated CTRA response and greater disease free

interval indicates a role for inflammatory markers as predictors of clinical disease endpoints.

Finally, another research team found that elevated inflammatory markers (i.e., white blood cell, neutrophil, lymphocyte, and natural killer cell counts) were detectable in women who experienced a breast cancer recurrence as early as 17 months before the event (Thornton et al., 2008). These results extend the associations between inflammatory markers and clinical endpoints to also include biological markers such as specific cell counts.

Taking all of these studies together, the relationship between inflammatory markers and long-term clinical disease endpoints among breast cancer patients remains unclear. There are methodological differences among the studies described, which make close comparison with the current study difficult. Most notable is the difference in measurement of inflammation. It could be the case that more distal markers of inflammation (i.e., leukocyte gene expression) do not covary with more proximal markers (i.e., serum concentrations of corresponding pro-inflammatory cytokines). Future research would benefit from assessing multiple markers of inflammation simultaneously in order to clarify whether associations between inflammation and breast cancer clinical health outcomes are significant, and if so, with which markers (e.g., serum pro-inflammatory cytokines, leukocyte pro-inflammatory gene expression, white blood cell, neutrophil, lymphocyte, and natural killer cell counts.)

Aim 1b. Aim 1b examined the indirect relationships between baseline levels of depressive symptoms and pro-inflammatory cytokines on time to clinical disease endpoints at 11-year median follow-up. All models revealed non-significant indirect

effects, due to the absence of associations between baseline mediating variables and long-term clinical outcomes while controlling for the corresponding baseline independent variable (paths B). This was unsurprising given the lack of associations between baseline variables and clinical outcomes seen in Aim 1a. However, several significant concurrent relationships emerged between baseline depressive symptoms and pro-inflammatory cytokines (paths A).

In uncontrolled models, greater levels of baseline depressive symptoms were significantly and concurrently related to greater serum concentrations of IL-1β and TNF-α, and these relationships were retained in the subset of women with invasive disease. Greater baseline depressive symptoms were also marginally related to greater concentration of IL-6, although this relationship became non-significant in the invasive sub-sample. The same pattern of results was found when regressions were reversed (i.e., cytokines predicting depressive symptoms). All of these findings were retained in adjusted models (which controlled for age, stage, procedure, hormone therapy, and smoking status) and fully adjusted models (which additionally controlled for BMI using the cases for which this information was available) with the exception of relationships between depressive symptoms and IL-6. In the fully adjusted models, baseline depressive symptoms were unrelated to concentration of IL-6, although this relationship was marginally significant in the invasive sub-sample. The same pattern was observed when regressions were reversed.

Research relating depressive symptoms and pro-inflammatory cytokines among breast cancer patients has been mixed (Bouchard et al., 2016a; Bower et al., 2011; Soygur et al., 2007), and discrepant findings could potentially be explained by differences in

study design. Specifically, a study that reported null findings assessed women after they had completed primary treatment for breast cancer, which was an average of 7 months post-diagnosis (Bower et al., 2011). On the other hand, a study that reported significant associations between depression and cytokine levels assessed women much earlier in the treatment trajectory – post-breast cancer diagnosis and surgery, and before beginning adjuvant treatment (Soygur et al., 2007).

The findings reported by Soygur and colleagues (2007) provide a close source of comparison for the results of the present study (which are reported in Bouchard et al., 2016a), since the time at which breast cancer patients were assessed is similar. The present findings contribute to the literature supporting relationships between poor psychological adaptation (e.g., depressed mood) and biobehavioral processes (e.g., inflammation; Armaiz-Pena et al., 2013; Thornton et al., 2009) through signaling of the sympathetic nervous system and HPA axis (Antoni et al., 2006b; Cole et al., 2015; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Lutgendorf et al., 2010). These biological alterations may affect tumor growth (Lutgendorf et al., 2002), invasion (Sood et al., 2006) and metastatic signaling (Sloan et al., 2010; Yang et al., 2009) through interactions with the tumor microenvironment.

These findings also extend the extant literature to include a lower range of depressive symptoms than would be observed in a clinically defined depressed sample, such as that of Soygur and colleagues (2007). The findings reported here suggest that depressive symptoms are related to inflammatory processes above and beyond the effect of demographic and medical covariates, even within a lower range of symptomatology. These findings have implications for the clinical treatment of women with breast cancer

who report comorbid elevated depressive symptoms. For example, it may be possible to reduce depressive symptoms through interventions (psychological or pharmacological) early in treatment, and concurrently modulate biological mechanisms related to depressive symptoms, on the one hand, and disease progression on the other (Antoni, 2013).

Effects of Intervention on Time to Clinical Disease Endpoints

Aim 2a. Aim 2a of the reported study sought to confirm prior findings (Stagl et al., 2015) that women with breast cancer assigned to the CBSM group differed from those in the 1-day psychoeducational control group on time to clinical disease endpoints at 11-year median follow-up in the subsample of women who provided blood samples. Findings revealed non-significant relationships between study condition and time to clinical disease endpoints in both the full and invasive subsample in unadjusted, adjusted, and fully adjusted models. Similar to above (effect of baseline depressive symptoms on all-cause mortality), ad-hoc analyses were conducted to determine the estimated number of events needed to detect intervention effects on clinical disease endpoints based on published data, which are described below (Kohn et al., 2016; Schoenfeld, 1983).

In the full parent study sample (N = 240) reported by Stagl and colleagues (2015), 30 women were deceased due to all causes at 11-year median follow-up (12.5%), and an intervention effect was found for all-cause mortality (HR = 0.21). In order to detect a comparable intervention effect size, a study would require approximately 13 deaths due to all causes. Using a different comparison point, that of Andersen and colleagues (2008) who also reported an intervention effect on all-cause mortality (HR = 0.51), a study would require approximately 70 deaths due to all causes. Thus, the range of events

necessary to detect an intervention effect comparable to those found in previously published studies ($0.21 \leq HR \leq 0.51$) is approximately 13-70 deaths due to all causes. In this study, there were 8 all-cause deaths (8.9%), indicating a lack of power to detect an intervention effect on time to all-cause mortality, even if such an effect were present.

In the full parent study sample (N = 240) reported by Stagl and colleagues (2015), 22 women had passed away due to breast cancer-related factors (9.2% of sample). A marginal intervention effect was found for breast-cancer specific mortality when all cases were analyzed (HR = 0.25), and the effect became significant when analyses were restricted to women with invasive disease (HR = 0.08). In order to detect a comparable significant effect size seen in the invasive subsample, a study would require approximately 6 breast cancer-related deaths. Andersen and colleagues (2008) also reported an intervention effect on breast cancer-mortality (HR = 0.44), and a study would require approximately 47 deaths to detect a comparable effect. Thus, the range of events necessary to detect an intervention effect comparable to previously published studies ($0.08 \leq HR \leq 0.44$) is approximately 6-47 deaths due to breast cancer-related causes. In this study, there were exactly 6 breast cancer-related deaths (6.7%), all of which were retained in the invasive sub-sample. However, this represents the smallest possible number of events necessary to obtain the strongest intervention effect seen in previous studies (Stagl et al., 2015). Thus, it is possible that a weaker intervention effect on breast cancer-related mortality was present in this subset of women with blood samples, but was not detectable.

In the full parent study sample (N = 240) reported by Stagl and colleagues (2015), 47 women had experienced a confirmed breast cancer recurrence (19.6% of sample). A

marginal intervention effect was found for breast cancer recurrence when all cases were analyzed (HR = 0.45), and the effect became significant when analyses were restricted to women with invasive disease (HR = 0.24). In order to detect a comparable significant effect size seen in the invasive subsample, a study would require approximately15 breast cancer recurrences. Andersen and colleagues (2008) also reported an intervention effect on breast cancer recurrence (HR = 0.55), and a study would require approximately 88 breast cancer recurrences to detect a comparable effect. Thus, the range of events necessary to detect an intervention effect comparable to previously published studies ($0.24 \leq HR \leq 0.55$) is approximately 15-88 breast cancer recurrences. In this study, 17 women experienced a breast cancer recurrence (18.9%), and all events were retained in the invasive subsample. Thus, one could expect an intervention effect to be detected if one were present. However, similar to breast cancer-related mortality, 17 breast cancer recurrences falls at the lower end of the range of events necessary to obtain a stronger intervention effect similar to previous studies (Stagl et al., 2015). Thus, it is possible that a weaker intervention effect on breast cancer recurrence was present in this subset of women with blood samples, but was not detectable.

The lack of significant intervention effects on clinical disease endpoints in this study are difficult to fit into the extant literature, given the observation that intervention effects were significant in the larger parent study (Stagl et al., 2015). The current literature examining whether psychosocial interventions influence disease outcomes is controversial, with studies reporting mixed results. A study of supportive expressive group therapy found an intervention effect on improved 10-year survival in metastatic breast cancer patients vs. a treatment as usual control group (Spiegel et al., 1989), but

efforts to replicate this finding have been mixed (Goodwin et al., 2001; Kissane et al., 2007; Spiegel et al., 2007). Two randomized controlled trials of women with non-metastatic breast cancer have found intervention effects of cognitive-behavioral based interventions on disease outcomes, including results from this study's larger parent trial (Andersen et al., 2008; Stagl et al., 2015). The findings reported here must be interpreted with caution, and do not necessary indicate that no intervention effects were present. Rather, in the context of the broader study (Stagl et al., 2015), it appears that there was simply not enough statistical power to detect the previously observed intervention effects in the subsample of women who provided blood samples.

Aim 2b. Aim 2b of this study examined the indirect relationships of study condition (CBSM vs. control) on time to clinical disease endpoints through changes in levels of depressive symptoms and pro-inflammatory cytokines (levels at baseline minus 12-months). All models revealed non-significant indirect effects due to the absence of study condition differences regarding 12-month changes in depressive symptoms and pro-inflammatory cytokines (paths A). Because paths A were non-significant and indirect effects were therefore not supported, paths B were not reported (for discussion of post-hoc analyses of paths B, see above).

A meta-analysis concluded that CBT can reduce depression in the short term (i.e., less than 8 months) among cancer survivors (Osborn, Demoncada, & Feuerstein, 2006), and previous trials have reported that psychosocial interventions result in decreased depression/depressive symptoms relative to controls (e.g., Goodwin et al., 2001; Kissane et al., 2007; Spiegel & Bloom, 1983). In our own parent study, CBSM reduced negative affect (Antoni et al., 2006c) and social disruption, and increased benefit finding, positive

affect, emotional well-being, positive life style change, and positive states of mind up to 12-months after enrollment compared to the psychoeducational control group (Antoni et al., 2006a). A previous trial by our research group also found that the CBSM intervention reduced the prevalence of moderate depression, as defined by an accepted clinical cutoff for the outcome measure, compared to a control group seminar (Antoni et al., 2001).

Although the study condition difference in 12-month change in depressive symptoms did not reach significance in the present study, it is notable that the changes in depressive symptoms observed were in the hypothesized direction with women in the CBSM group reporting larger decreases in depressive symptoms than women in the control group. In the unadjusted model, the corresponding *r* was 0.14, which is equivalent to a Cohen's *d* effect size of 0.28 and represents a small effect (Cohen, 1988; Rosenthal, 1994). This is similar to the effect previously reported in the larger parent study, Cohen's *d* = 0.33 (Antoni et al., 2006a). Further, in the present adjusted model (controlling for age, stage, procedure, hormone therapy, and smoking status), the corresponding *r* was 0.25, which is equivalent to a Cohen's *d* effect size of 0.53 and represents a medium effect (Cohen, 1988). Thus, the non-significant effect of the intervention on change in depressive symptoms observed in the reported study is comparable to and potentially larger than the intervention effect on negative affect observed in the larger study sample. This indicates that statistical power was lacking to detect the relationship among women with available blood samples.

Previous research has also shown that cognitive-behavioral interventions are associated with improved immune functioning. For example, Andersen and colleagues (2004) found that a CBT-based intervention resulted in stable or increased T-cell

blastogenesis in women with stage II and III breast cancer, whereas this response was decreased for women in the control group. In this same cohort of women, the intervention was related to decreased markers of inflammation (i.e., white blood cell count, neutrophil count, and ratio of helper T to suppressor T cells) over the first 12-months post-diagnosis for primary breast cancer, and the intervention effect on decreased inflammation was mediated by 8-month decreases in depressives symptoms (Thornton et al., 2009).

In a subsample (n = 80) of this dissertation's sample (N = 90), we found that the CBSM intervention reversed the up-regulation of negative affect-associated pro-inflammatory and pro-metastatic leukocyte gene expression compared to women in the control group (Antoni et al., 2012). As discussed above, we also recently found that CBSM was associated with an attenuated CTRA gene expression composite, which includes up-regulated inflammatory production signaling (as well as down-regulated anti-viral and antibody production signaling; Antoni et al., 2016). Thus, the current non-significant relationships between CBSM and changes in pro-inflammatory cytokines are in contrast with other findings from the larger study, and suggest a need for further investigation and clarification.

The study reported here was the first study to specifically test for CBSM effects on changes in serum levels of pro-inflammatory cytokines among women with breast cancer, making it a unique contribution to the extant literature. The closest points of comparison come from studies of other interventions that included pro-inflammatory cytokines as outcome measures. For example, mindfulness-based stress management (MBSR) is a program modeled after that of Kabat-Zinn (Kabat-Zinn, 1990; Kabat-Zinn, Lipworth, & Burney, 1985) and focuses on mindfulness through awareness of breath,

walking and sitting meditations, and mindful yoga. Carlson and colleagues (2007) tested an 8-week MBSR program for breast and prostate cancer survivors, and found decreased T-cell production of pro-inflammatory cytokines (TNF, IL-4, and IL-10) at 6- and 12-months post-intervention. However, that study did not include a control group, which makes it impossible to infer that the intervention caused the immune changes. In addition, Carlson and colleagues (2007) used stimulated production of cytokines, whereas the present study used serum concentrations. Finally, they included breast and prostate cancer survivors if they had a history of disease at any time in the past with a minimum of 3 months since surgery (Carlson et al., 2007), making comparison to this study difficult.

Recently, Campo and colleagues (2015) tested a 12-week Tai chi chih (TCC) intervention among older female cancer survivors (age ≥ 55) with limitations in physical functioning. TCC is a form of meditative movement that consists of a specified order of fluid and focused physical movements coordinated with breathing and imagery (Rogers, Larkey, & Keller, 2009). The majority of participants in the study had a history of breast cancer, and were approximately 8-9 years post-diagnosis and 6-8.5 years post treatment (Campo et al., 2015). Results revealed no intervention effects on pro-inflammatory cytokines (IL-10, IL-4, IL-12, IL-6, and TNF-α), although intervention effects were found for systolic blood pressure and cortisol (Campo et al., 2015). The findings reported in the present study are consistent with those reported by Campo and colleagues (2015) in that there were no intervention effects for IL-6 and TNF-α. However, it is difficult to compare the study reported here to the study reported by Campo and colleagues (2015) given the differences in the time at which patients participated in the studies (early in

treatment vs. 6-8.5 years post-treatment, respectively), the age of participants (M = 50.48 vs. M = 66.54, respectively), and the interventions used (psychologically vs. physically-based, respectively).

Possibly the best source of comparison for the study reported here is that by Witek-Janusek and colleagues (2008). These researchers tested an 8-week MBSR program, and compared it to an assessment-only control group among women with stage 0-II breast cancer who did not receive chemotherapy. Similar to the present study, women were recruited a minimum of 10 days post-surgery and before initiating adjuvant therapies. Notably, women self-selected into study condition. At the end of the MBSR program, women in the intervention showed decreased levels of IL-4 and IL-10 (but not IL-6) compared to the assessment-only condition, and these decreases were maintained at 1-month post-intervention. Both the study reported here and the study by Witek-Janusek and colleagues (2008) exclusively included breast cancer patients at similar stages of disease (stage 0-III vs. stage 0-II, respectively). Interestingly, although Witek-Janusek and colleagues (2008) found an intervention effect for some pro-inflammatory cytokines, they did not find an effect on IL-6. Thus, the present study's lack of intervention effect on IL-6 is consistent with this report.

Strengths and Limitations

Strengths. A strength of the present study was the homogenous sample of women with non-metastatic breast cancer and use of theoretically supported covariates. Study analyses were conducted in all women for whom blood samples were available, regardless of stage of disease. While stage 0 cancers are generally associated with positive prognosis, they still pose a risk of breast cancer recurrence for approximately 7%

of women (Sue, Killelea, Horowitz, Lannin & Chagpar, 2012). Since some women with stage 0 breast cancer will experience a recurrence, the main study analyses included women with stage 0 disease. However, stronger intervention effects on clinical disease endpoints were found in the larger parent study when restricting analyses to women with invasive disease (Stagl et al., 2015). Thus, supplemental analyses were conducted in the subset of women who had invasive disease (i.e., stage I-III) in order to fully evaluate relationships among depressive symptoms, pro-inflammatory cytokines, and the CBSM intervention and long-term clinical disease endpoints in this study.

This study used a manualized, structured CBSM intervention (Antoni, 2003), which allows for more reliable replication of this study's procedures. Women were enrolled and initially assessed during a distinct time in the breast cancer treatment trajectory (i.e., 2-10 weeks post-surgery and pre-adjuvant treatment), which allowed for specific analyses of relationships among baseline variables similar to those of previous research (Soygur et al., 2007). This is also a unique time at which to provide a psychosocial intervention. It's possible that the favorable intervention effects on long-term clinical outcomes seen in the parent study (Stagl et al., 2015) may have been affected by women's ability to better cope with and adapt to treatment demands early in the medical treatment process after honing the stress management skills taught in the intervention.

Limitations. Several limitations must be noted. First, survival and recurrence were not primary endpoints in the original study's design. As was discussed above, analyses within the subset of parent study participants for whom blood data were available limited the number of observed events (i.e., deaths and recurrences), and

possibly reduced the statistical power to detect intervention effects on clinical disease endpoints, even if such effects were present. There was a lack of data in this study pertaining to additional clinicopathological variables potentially related to clinical endpoints (e.g., postsurgical residual disease and complications, surgical margins, luminal a, luminal b), and information on use of inflammatory medications was not available. Data were incomplete pertaining to BMI and HER2/neu, which limited the use of these variables in study models. It would be beneficial for future work to consider these variables, as they may affect relationships between depressive symptoms, inflammatory markers, and long-term clinical disease endpoints.

This study took place in a university-based setting and women self-selected into the program. Women in this study were motivated to participate in research, agreeable to the weekly time commitment for the intervention, and had a high average annual household income. It is possible that women in this study do not represent all breast cancer patients seen in hospitals and community clinics. Further, women with stage IV metastatic disease were excluded from this study in order to maintain a homogenous sample of early stage breast cancer patients. Thus, study findings may not be generalizable to women with advanced disease. Women self-reported all demographic and psychosocial measures, which allows for the possibility of inaccurate reports. However, medical and treatment information was verified via medical chart review, which increases the reliability of biomedical covariates used in the analyses.

Clinical Implications

The relationships observed between baseline depressive symptoms and concurrent pro-inflammatory cytokines have implications for the treatment of breast cancer patients,

particularly patients who report elevated depressive symptoms (as discussed in Bouchard et al., 2016a). It may be possible to target biological mechanisms related to depressive symptoms in an effort to reduce the possibility of disease progression. Recent work has shown that pharmacological interventions for depressive symptoms affect levels of inflammation (Tuglu, Hakan Kara, Caliyurt, Vardar, & Abay, 2003), and assessing this possibility among breast cancer patients would be beneficial. Alternatively, it is possible that treatments targeting inflammatory processes may subsequently affect depressive symptoms. One study showed, in a cohort of medically healthy individuals with treatment-resistant MDD, that a TNF antagonist was associated with decreased depressive symptoms (Raison et al., 2013). Expanding this research would be very beneficial for the treatment of the general population as well as breast cancer patients (for a review see Miller, Maletic, & Raison, 2009).

As was discussed above, the null relationships observed in this study between the CBSM intervention and time to clinical disease endpoints are not necessarily indicative of a lack of relationships. Rather, there was likely too little statistical power to detect these associations. CBSM was significantly associated with time to all-cause mortality, breast-cancer specific mortality, and breast cancer recurrence in the larger parent study (Stagl et al., 2015) and other trials (Andersen et al., 2008), and indicate that attending to psychological processes early in treatment for breast cancer may be protective for long-term clinical disease outcomes.

Future Research

Future research would benefit from further investigation of the relationships between depressive symptoms, pro-inflammatory cytokines, and CBSM with long-term

health outcomes among breast cancer patients. Specifically, there is a need for larger trials in which long-term follow-up of clinical disease endpoints is included in the original study design. Further, including multiple markers of inflammation such as pro-inflammatory cytokines (Bouchard et al., 2016; Soygur et al., 2007), leukocyte gene expression of pro-inflammatory signaling (Antoni et al., 2012; Antoni et al., 2016), and specific cell counts (Thornton et al., 2009) would be beneficial to clarify associations between inflammatory processes and clinical health outcomes of breast cancer patients.

One noted limitation of this study was the lack of data pertaining to additional clinicopathological variables potentially related to clinical endpoints. Although efforts were made to collect data on as many relevant biomedical variables as possible, future research should attempt to collect more complete data regarding variables such as BMI, HER2/neu status, surgical margins, etc. Breast cancer is a heterogeneous disease, with various diagnostic indicators resulting in a wide range of presentation. Previous research has shown that histological grade, tumor node metastasis (TNM) staging, and hormone receptor status are particular important to consider when estimating survival and recurrence among breast cancer patients (Rakha et al., 2010). Thus, these are indicated as particularly important variables to consider in future research.

Finally, the current study did not account for adherence to medical treatments such as hormone therapy. Women with positive ER or PR status are often prescribed hormone therapy such as tamoxifen for 5-10 years post-treatment. Despite reducing rates of recurrence and mortality (Early Breast Cancer Trialists' Collaborative Group, 2005; Winer et al., 2005) not all women are adherent to hormone therapy regimens (Murphy, Bartholomew, Carpentier, Bluethmann, & Vernon, 2012). Previous research has shown

that up to 51% of breast cancer patients with hormone sensitive disease do not adhere to hormone therapy for the full duration (Hershman et al., 2010), and this non-adherence was associated with increased mortality (Hershman et al., 2011). Thus, adherence to hormone therapy is indicated as an important factor to consider when conducting future research on predictors of long-term clinical disease endpoints among women with breast cancer.

Conclusion

Women with early stage breast cancer with greater depressive symptoms after surgery showed greater concurrent inflammation revealed in higher serum concentrations of IL-1β and TNF-α, and marginally higher levels of IL-6. However, this sample did not reveal associations of post-surgical levels of depressive symptoms and serum pro-inflammatory cytokines (i.e., IL-1β, IL-6, and TNF-α) with time to clinical disease endpoints (i.e., all-cause mortality, breast cancer mortality, and breast cancer recurrence) at 11-year median follow-up, individually or in combination. A cognitive behavioral stress management (CBSM) intervention was unrelated to favorable breast cancer health outcomes compared to a 1-day psychoeducational seminar control. CBSM was also unrelated to 12-month changes in depressive symptoms and serum pro-inflammatory cytokines. The observed associations between baseline depressive symptoms and pro-inflammatory cytokines have implications for the treatment of women with breast cancer who report comorbid elevated depressive symptoms. However, the long-term implications of these findings, including the role of psychosocial interventions, are inconclusive and indicate a need for more research to further investigate the associations between these variables.

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APPENDIX A

PSYCHOSOCIAL MEASURE

Hamilton Rating Scale for Depression (HRSD)

PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW

Instructions: For each item select the one "cue" which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).

1 DEPRESSED MOOD (*sadness, hopeless, helpless, worthless)*

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/her spontaneous verbal and non-verbal communication.

2 FEELINGS OF GUILT

0 [ ] Absent.
1 [ ] Self reproach, feels he/she 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.

3 SUICIDE

0 [ ] Absent.
1 [ ] Feels life is not worth living.
2 [ ] Wishes he/she were dead or any thoughts of possible death to self.
3 [ ] Ideas or gestures of suicide.
4 [ ] Attempts at suicide (any serious attempt rate 4).

4 INSOMNIA: EARLY IN THE NIGHT

0 [ ] No difficulty falling asleep.
1 [ ] Complains of occasional difficulty falling asleep, i.e. more than ½ hour.
2 [ ] Complains of nightly difficulty falling asleep.

5 INSOMNIA: MIDDLE OF THE NIGHT

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).

6 INSOMNIA: EARLY HOURS OF THE MORNING

0 [ ] No difficulty.
1 [ ] Waking in early hours of the morning but goes back to sleep.
2 [ ] Unable to fall asleep again if he/she gets out of bed.

7 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 the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
3 [ ] Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
4 [ ] Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores or if patient fails to perform routine chores unassisted.

8 RETARDATION (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)

0 [ ] Normal speech and thought.
1 [ ] Slight retardation during the interview.
2 [ ] Obvious retardation during the interview.
3 [ ] Interview difficult.
4 [ ] Complete stupor.

9 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.

10 ANXIETY PSYCHIC

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.

11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:
gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching
cardio-vascular – palpitations, headaches
respiratory – hyperventilation, sighing

urinary frequency
sweating

0 [ ] Absent.
1 [ ] Mild.
2 [ ] Moderate.
3 [ ] Severe.
4 [ ] Incapacitating.

12 SOMATIC SYMPTOMS GASTRO-INTESTINAL

0 [ ] None.
1 [ ] Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
2 [ ] Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13 GENERAL SOMATIC SYMPTOMS

0 [ ] None.
1 [ ] Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
2 [ ] Any clear-cut symptom rates 2.

14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances)

0 [ ] Absent.
1 [ ] Mild.
2 [ ] Severe.

15 HYPOCHONDRIASIS

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

16 LOSS OF WEIGHT *(RATE EITHER a OR b)*

a) According to the patient:

0 [ ] No weight loss.
1 [ ] Probable weight loss associated with present illness.
2 [ ] Definite (according to patient) weight loss.
3 [ ] Not assessed.

b) According to weekly measurements:

0 [ ] Less than 1 lb weight loss in week.
1 [ ] Greater than 1 lb weight loss in week.
2 [ ] Greater than 2 lb weight loss in week.
3 [ ] Not assessed.

17 INSIGHT

0 [ ]	Acknowledges being depressed and ill.
1 [ ]	Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc..
2 [ ]	Denies being ill at all.

Tables

Table 1

Means, Standard Deviations, and Frequencies of Study Variables by Study Inclusion

Variable	Blood Data (N = 90)	No Blood Data (N = 150)	Statistic	*p*
Condition			$\chi^2(1) = 0.00$	1.000
CBSM	45 (50.0%)	75 (50.0%)		
Control	45 (50.0%)	75 (50.0%)		
Age at baseline (years)	50.48 (7.68)	50.26 (9.77)	$F(1, 237) = 0.03$	0.857
Age at T6 (years)	60.77 (7.95)	60.19 (10.29)	$F(1, 237) = 0.21$	0.651
Race/Ethnicity			$\chi^2(3) = 5.69$	0.128
White non-Hispanic	63 (70.8%)	89 (59.3%)		
Hispanic	18 (20.2%)	43 (28.7%)		
Black	8 (9.0%)	13 (8.7%)		
Asian	0 (0.0%)	5 (3.3%)		
Education (years)	15.42 (2.54)	15.67 (2.29)	$F(1, 237) = 0.62$	0.430
Menopausal Status			$\chi^2(1) = 0.60$	0.441
Premenopausal	43 (47.8%)	64 (42.7%)		
Postmenopausal	47 (52.2%)	86 (57.3%)		
Employment Status			$\chi^2(1) = 1.68$	0.195
Not Employed	19 (21.1%)	43 (28.7%)		
Employed	71 (78.9%)	107 (71.3%)		
Income (thousands of dollars)	77.22 (50.94)	81.13 (75.60)	$F(1, 210) = 0.17$	0.680
Time Since Surgery (days)	37.94 (22.51)	42.25 (23.25)	$F(1, 237) = 1.98$	0.161
Stage			$\chi^2(3) = 7.85$	0.049*
0	17 (18.9%)	25 (16.8%)		
I	37 (41.1%)	46 (30.9%)		
II	33 (36.7%)	58 (38.9%)		
III	3 (3.3%)	20 (13.4%)		
Invasive vs. Non-Invasive			$\chi^2(1) = 0.17$	0.678
0	17 (18.9%)	25 (16.8%)		
I-III	73 (81.1%)	124 (83.2%)		

Size of Tumor (cm)	1.81 (1.33)	1.85 (1.38)	$F(1, 119) = 0.03$	0.862
Positive Lymph Nodes	0.81 (2.41)	1.92 (3.67)	$F(1, 236) = 6.51$	0.011*
Procedure Type			$\chi^2(1) = 1.29$	0.257
Lumpectomy	50 (55.6%)	72 (48.0%)		
Mastectomy	40 (44.4%)	78 (52.0%)		
Estrogen Receptor Status			$\chi^2(1) = 1.76$	0.185
Positive	58 (84.9%)	98 (76.0%)		
Negative	11 (15.9%)	31 (24.0%)		
Progesterone Receptor Status			$\chi^2(1) = 0.92$	0.338
Positive	41 (68.3%)	72 (61.0%)		
Negative	19 (31.7%)	46 (39.0%)		
HER2/neu Status			$\chi^2(1) = 0.08$	0.778
Positive	9 (20.5%)	17 (22.7%)		
Negative	35 (79.5%)	58 (77.3%)		
Received Chemotherapy			$\chi^2(1) = 4.37$	0.037*
Yes	42 (46.7%)	85 (60.7%)		
No	48 (53.3%)	55 (39.3%)		
Received Radiation Therapy			$\chi^2(1) = 0.59$	0.443
Yes	50 (56.2%)	84 (61.3%)		
No	39 (43.8%)	53 (38.7%)		
Received Hormone Therapy			$\chi^2(1) = 2.63$	0.105
Yes	69 (76.7%)	92 (66.7%)		
No	21 (23.3%)	46 (33.3%)		
Smoking Status			$\chi^2(1) = 0.12$	0.731
Smoker	5 (5.6%)	10 (6.7%)		
Non-Smoker	85 (94.4%)	140 (93.3%)		
Body Mass Index	26.27 (5.21)	26.42 (5.89)	$F(1, 146) = 0.03$	0.868
Body Mass Categories			$\chi^2(3) = 0.84$	0.840
Underweight	0 (0.0%)	1 (1.2%)		
Normal	32 (50.0%)	40 (47.1%)		
Overweight	21 (32.8%)	29 (34.1%)		
Obese	11 (17.2%)	15 (17.6%)		

Anti-Depressant Use T1			$\chi^2(1) = 0.10$	0.748
Yes	9 (10.0%)	17 (11.3%)		
No	81 (90.0%)	133 (88.7%)		
HRSD T1	7.26 (5.52)	7.69 (5.43)	$F(1, 228) = 0.34$	0.558
HRSD T3	6.10 (5.02)	5.82 (5.04)	$F(1, 177) = 0.15$	0.702
Time to Death (days)	3158.43 (1221.88)	2845.20 (1418.85)	$F(1, 237) = 3.04$	0.083∞
Disease Free Interval (days)	2392.54 (1349.42)	2317.00 (1481.08)	$F(1, 237) = 0.16$	0.693
All-Cause Mortality			$\chi^2(1) = 1.72$	0.190
Yes	8 (8.9%)	22 (14.7%)		
No	82 (91.1%)	128 (85.3%)		
Breast Cancer Mortality			$\chi^2(1) = 1.08$	0.298
Yes	6 (6.7%)	16 (10.7%)		
No	84 (93.3%)	134 (89.3%)		
Breast Cancer Recurrence			$\chi^2(1) = 0.04$	0.834
Yes	17 (18.9%)	30 (20.0%)		
No	73 (81.1%)	120 (80.0%)		

Note. ∞$p < 0.100$; *$p < 0.050$; HRSD = Hamilton Rating Scale for Depression.

Table 2

Means, Standard Deviations, and Frequencies of All Study Variables within Study Conditions

Variable	Control (n = 45)	CBSM (n = 45)	Statistic	*p*
Age at baseline (years)	50.56 (8.00)	50.40 (7.43)	$F(1, 88) = 0.01$	0.924
Age at T6 (years)	60.82 (8.09)	60.71 (7.90)	$F(1, 88) = 0.00$	0.948
Race/Ethnicity			$\chi^2(2) = 0.23$	0.893
White non-Hispanic	32 (72.7%)	31 (68.9%)		
Hispanic	8 (18.2%)	10 (22.2%)		
Black	4 (9.1%)	4 (8.9%)		
Asian	0 (0.0%)	0 (0.0%)		
Education (years)	15.16 (2.58)	15.69 (2.49)	$F(1, 88) = 1.00$	0.321
Menopausal Status			$\chi^2(1) = 0.05$	0.833
Premenopausal	21 (46.7%)	22 (48.9%)		
Postmenopausal	24 (53.3%)	23 (50.1%)		
Employment Status			$\chi^2(1) = 0.60$	0.438
Not Employed	8 (17.8%)	11 (24.4%)		
Employed	37 (82.2%)	34 (75.6%)		
Income (thousands of dollars)	79.49 (60.87)	74.72 (37.72)	$F(1, 81) = 0.18$	0.675
Time Since Surgery (days)	40.00 (21.93)	35.89 (23.15)	$F(1, 88) = 0.75$	0.389
Stage			$\chi^2(3) = 4.05$	0.257
0	10 (22.2%)	7 (15.6%)		
I	17 (37.8%)	20 (44.4%)		
II	18 (40.0%)	15 (33.3%)		
III	0 (0.0%)	3 (6.7%)		
Invasive vs. Non-Invasive			$\chi^2(1) = 0.65$	0.419
0	10 (22.2%)	7 (15.6%)		
I-III	35 (77.8%)	38 (84.4%)		
Size of Tumor (cm)	1.69 (1.27)	1.95 (1.41)	$F(1, 42) = 0.40$	0.528
Positive Lymph Nodes	0.42 (0.97)	1.20 (3.24)	$F(1, 88) = 2.39$	0.126
Procedure Type			$\chi^2(1) = 2.88$	0.090∞
Lumpectomy	29 (64.4%)	21 (46.7%)		
Mastectomy	16 (35.6%)	24 (53.3%)		
Estrogen Receptor Status			$\chi^2(1) = 0.87$	0.350
Positive	30 (88.2%)	28 (80.0%)		
Negative	4 (11.8%)	7 (20.0%)		

Progesterone Receptor Status			$\chi^2(1) = 0.21$	0.650
Positive	19 (65.5%)	22 (71.0%)		
Negative	10 (34.5%)	9 (29.0%)		
HER2/neu Status			$\chi^2(1) = 0.14$	0.709
Positive	4 (18.2%)	5 (22.7%)		
Negative	18 (81.8%)	17 (77.3%)		
Received Chemotherapy			$\chi^2(1) = 6.43$	0.011*
Yes	15 (33.3%)	27 (60.0%)		
No	30 (66.7%)	18 (40.0%)		
Received Radiation Therapy			$\chi^2(1) = 0.01$	0.904
Yes	25 (56.8%)	25 (55.6%)		
No	19 (43.2%)	20 (44.4%)		
Received Hormone Therapy			$\chi^2(1) = 0.06$	0.803
Yes	34 (75.6%)	35 (77.8%)		
No	11 (24.4%)	10 (22.2%)		
Smoking Status			$\chi^2(1) = 5.29$	0.021*
Smoker	5 (11.1%)	0 (0.0%)		
Non-Smoker	40 (88.9%)	45 (100.0%)		
Body Mass Index	26.82 (5.82)	25.72 (4.55)	$F(1, 63) = 0.70$	0.407
Body Mass Categories			$\chi^2(2) = 2.37$	0.305
Underweight	0 (0.0%)	0 (0.0%)		
Normal	13 (40.6%)	19 (59.4%)		
Overweight	12 (37.5%)	9 (28.1%)		
Obese	7 (21.9%)	4 (12.5%)		
Anti-Depressant Use T1			$\chi^2(1) = 0.12$	0.725
Yes	5 (11.1%)	4 (8.9%)		
No	40 (88.9%)	41 (91.1%)		
HRSD T1	7.22 (5.08)	7.29 (5.99)	$F(1, 88) = 0.00$	0.955
HRSD T3	6.80 (5.05)	5.41 (4.95)	$F(1, 86) = 1.69$	0.197
IL-1β T1	0.83 (0.88)	0.95 (1.06)	$F(1, 88) = 0.33$	0.567
IL-1β T3	0.95 (0.84)	1.00 (0.81)	$F(1, 88) = 0.09$	0.769
IL-6 T1	1.85 (1.25)	1.87 (1.23)	$F(1, 88) = 0.01$	0.937
IL-6 T3	1.91 (1.01)	1.88 (1.19)	$F(1, 88) = 0.02$	0.895
TNF-α T1	1.05 (0.86)	1.06 (0.89)	$F(1, 87) = 0.00$	0.970
TNF-α T3	1.10 (0.74)	1.19 (0.90)	$F(1, 87) = 0.25$	0.622
Time to Death (days)	3183.73 (1125.24)	3133.13 (1323.80)	$F(1, 88) = 0.04$	0.846

Disease Free Interval (days)	2223.78 (1336.47)	2561.31 (1356.50)	$F(1, 88) = 1.41$	0.238
All-Cause Mortality			$\chi^2(1) = 0.00$	1.000
Yes	4 (8.9%)	4 (8.9%)		
No	41 (91.1%)	41 (91.1%)		
Breast Cancer Mortality			$\chi^2(1) = 0.71$	0.398
Yes	2 (4.4%)	4 (8.9%)		
No	43 (95.6%)	41 (91.1%)		
Breast Cancer Recurrence			$\chi^2(1) = 0.07$	0.788
Yes	8 (17.8%)	9 (20.0%)		
No	37 (82.2%)	36 (80.0%)		

Note. $\infty p < 0.100$; $^*p < 0.050$; HRSD = Hamilton Rating Scale for Depression; IL-1β = interleukin 1 beta; IL-6 = interleukin 6; TNF-α = tumor necrosis factor alpha.

Table 3

Unadjusted Cox Proportional Hazards Regressions Showing Effects of Baseline Depressive Symptoms and Pro-Inflammatory Cytokines on Time to Clinical Outcomes at 8-15 Year Follow-up in Full Study Sample (Aim 1a)

Outcome	Predictor	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
All-Cause Mortality	HRSD	0.06	0.06	0.306	1.06	0.95	1.19
	IL-1β	-0.19	0.43	0.664	0.83	0.35	1.94
	IL-6	0.14	0.30	0.644	1.15	0.64	2.05
	TNF-α	0.25	0.39	0.529	1.28	0.59	2.76
Breast Cancer Specific Mortality	HRSD	0.01	0.08	0.934	1.01	0.87	1.17
	IL-1β	-0.06	0.43	0.895	0.95	0.40	2.21
	IL-6	0.26	0.32	0.410	1.30	0.70	2.42
	TNF-α	0.38	0.41	0.354	1.46	0.66	3.24
All-Cause Mortality	HRSD	0.03	0.04	0.555	1.03	0.94	1.12
	IL-1β	-0.27	0.28	0.328	0.76	0.44	1.32
	IL-6	-0.11	0.21	0.616	0.90	0.59	1.37
	TNF-α	-0.07	0.30	0.810	0.93	0.52	1.68

Note. N = 90; *B* = Unstandardized Coefficient; *SE* = Standard Error; CI = Confidence Interval; HR = Hazard Ratio; LL = Lower Limit; UL = Upper Limit; HRSD = Hamilton Rating Scale for Depression.

Table 4

Unadjusted Cox Proportional Hazards Regressions Showing Effects of Baseline Depressive Symptoms and Pro-Inflammatory Cytokines on Time to Clinical Outcomes at 8-15 Year Follow-up in Invasive Sub-Sample (Aim 1a)

Outcome	Predictor	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
All-Cause Mortality	HRSD	0.07	0.06	0.254	1.07	0.95	1.20
	IL-1β	-0.17	0.42	0.686	0.84	0.37	1.93
	IL-6	0.11	0.30	0.714	1.12	0.62	2.02
	TNF-α	0.18	0.39	0.652	1.19	0.56	2.55
Breast Cancer Specific Mortality	HRSD	0.01	0.07	0.847	1.01	0.88	1.17
	IL-1β	-0.05	0.42	0.916	0.96	0.42	2.19
	IL-6	0.24	0.32	0.454	1.28	0.68	2.41
	TNF-α	0.30	0.40	0.453	1.35	0.62	2.97
Breast Cancer Recurrence	HRSD	0.03	0.04	0.439	1.03	0.95	1.13
	IL-1β	-0.26	0.28	0.351	0.77	0.45	1.33
	IL-6	-0.15	0.22	0.495	0.86	0.56	1.33
	TNF-α	-0.12	0.29	0.682	0.89	0.45	1.58

Note. N = 73; *B* = Unstandardized Coefficient; *SE* = Standard Error; CI = Confidence Interval; HR = Hazard Ratio; LL = Lower Limit; UL = Upper Limit; HRSD = Hamilton Rating Scale for Depression.

Table 5

Adjusted Cox Proportional Hazards Regressions Showing Effects of Baseline Depressive Symptoms and Pro-Inflammatory Cytokines on Time to Clinical Outcomes at 8-15 Year Follow-up in Full Study Sample (Aim 1a)

Outcome	Predictor	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
All-Cause Mortality	HRSD	0.01	0.07	0.909	1.01	0.88	1.16
	IL-1β	-0.24	0.48	0.619	0.79	0.31	2.00
	IL-6	0.00	0.39	0.999	1.00	0.46	2.17
	TNF-α	0.37	0.50	0.457	1.45	0.54	3.87
Breast Cancer-Specific Mortality	HRSD	-0.08	0.09	0.370	0.92	0.77	1.10
	IL-1β	-0.20	0.49	0.692	0.82	0.31	2.16
	IL-6	0.08	0.42	0.859	1.08	0.47	2.47
	TNF-α	0.36	0.56	0.522	1.43	0.48	4.26
Breast Cancer Recurrence	HRSD	0.00	0.05	0.964	1.00	0.91	1.09
	IL-1β	-0.06	0.32	0.841	0.94	0.50	1.76
	IL-6	-0.12	0.27	0.669	0.89	0.52	1.52
	TNF-α	0.19	0.37	0.600	1.21	0.59	2.48

Note. N = 90; All models adjusted for age, stage, procedure, hormone therapy, and smoking status (covariate associations not shown); *B* = Unstandardized Coefficient; *SE* = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit; HRSD = Hamilton Rating Scale for Depression.

Table 6

Adjusted Cox Proportional Hazards Regressions Showing Effects of Baseline Depressive Symptoms and Pro-Inflammatory Cytokines on Time to Clinical Outcomes at 8-15 Year Follow-up in Invasive Sub-Sample (Aim 1a)

Outcome	Predictor	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
All-Cause Mortality	HRSD	0.01	0.07	0.909	1.01	0.88	1.16
	IL-1β	-0.24	0.48	0.619	0.79	0.31	2.00
	IL-6	0.00	0.39	0.999	1.00	0.46	2.17
	TNF-α	0.37	0.50	0.457	1.45	0.54	3.87
Breast Cancer-Specific Mortality	HRSD	-0.08	0.09	0.370	0.92	0.77	1.10
	IL-1β	-0.20	0.49	0.692	0.82	0.31	2.16
	IL-6	0.08	0.42	0.859	1.08	0.47	2.47
	TNF-α	0.36	0.56	0.522	1.43	0.48	4.26
Breast Cancer Recurrence	HRSD	0.00	0.05	0.964	1.00	0.91	1.09
	IL-1β	-0.06	0.32	0.841	0.94	0.50	1.76
	IL-6	-0.12	0.27	0.669	0.89	0.52	1.52
	TNF-α	0.19	0.37	0.600	1.21	0.59	2.48

Note. N = 73; All models adjusted for age, stage, procedure, hormone therapy, and smoking status (covariate associations not shown); *B* = Unstandardized Coefficient; *SE* = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit; HRSD = Hamilton Rating Scale for Depression.

Table 7

Fully Adjusted Cox Proportional Hazards Regressions Showing Effects of Baseline Depressive Symptoms and Pro-Inflammatory Cytokines on Disease Free Interval at 8-15 Year Follow-up in Full Study Sample and Invasive Sub-Sample (Aim 1a)

Predictor	Sample	*N*	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
HRSD	Full	64	0.08	0.07	0.222	1.09	0.95	1.24
IL-1β	Full	64	0.24	0.51	0.634	1.27	0.47	3.43
IL-6	Full	64	-0.36	0.46	0.434	0.70	0.28	1.73
TNF-α	Full	64	-0.23	0.70	0.746	0.80	0.20	3.12
HRSD	Invasive	53	0.08	0.07	0.222	1.09	0.95	1.24
IL-1β	Invasive	53	0.24	0.51	0.634	1.27	0.47	3.43
IL-6	Invasive	53	-0.36	0.46	0.434	0.70	0.28	1.73
TNF-α	Invasive	53	-0.23	0.70	0.746	0.80	0.20	3.12

Note. N = 64 represents total study sample with BMI data; N = 53 represents invasive disease sub-sample with BMI data; All models adjusted for age, stage, procedure, hormone therapy, smoking status, and BMI (covariate associations not shown); *B* = Unstandardized Coefficient; *SE* = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit; HRSD = Hamilton Rating Scale for Depression.

Table 8

Unadjusted Linear Regressions Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 1b Paths A) in Total Sample

Model	IV	Model Mediator	β	*SE*	*t*	*df*	*p*	R^2
1	Baseline HRSD	Baseline IL-1β	0.26	0.02	2.54	88	0.013*	0.07
2	Baseline HRSD	Baseline IL-6	0.20	0.02	1.87	88	0.064∞	0.04
3	Baseline HRSD	Baseline TNF-α	0.23	0.02	2.20	87	0.031*	0.05
4	Baseline IL-1β	Baseline HRSD	0.26	0.58	2.54	88	0.013*	0.07
5	Baseline IL-6	Baseline HRSD	0.20	0.47	1.87	88	0.064∞	0.04
6	Baseline TNF-α	Baseline HRSD	0.23	0.66	2.20	87	0.031*	0.05

Note. ∞$p < 0.100$; *$p < 0.050$; N = 90; HRSD = Hamilton Rating Scale for Depression; β = Standardized Coefficient; *SE* = Standard Error.

Table 9

Unadjusted Linear Regressions Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 1b Paths A) in Invasive Subsample

Model	IV	Model Mediator	β	*SE*	*t*	*df*	*p*	R^2
1	Baseline HRSD	Baseline IL-1β	0.25	0.02	2.21	71	0.030*	0.06
2	Baseline HRSD	Baseline IL-6	0.17	0.03	1.43	71	0.156	0.03
3	Baseline HRSD	Baseline TNF-α	0.25	0.02	2.14	70	0.036*	0.06
4	Baseline IL-1β	Baseline HRSD	0.25	0.63	2.21	71	0.030*	0.06
5	Baseline IL-6	Baseline HRSD	0.17	0.52	1.43	71	0.156	0.03
6	Baseline TNF-α	Baseline HRSD	0.25	0.68	2.14	70	0.036*	0.06

Note. *$p < 0.050$; N = 73; HRSD = Hamilton Rating Scale for Depression; β = Standardized Coefficient; *SE* = Standard Error.

Table 10

Unadjusted Cox Proportional Hazards Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines and Time to Clinical Outcomes at 8-15 years (Aim 1b Paths B) in Total Sample

Model	IV (Model Mediator)	Covariate	DV	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
1	Baseline IL-1β	Baseline HRSD	All-Cause Mortality	-0.33	0.47	0.472	0.72	0.29	1.78
2	Baseline IL-6	Baseline HRSD	All-Cause Mortality	0.06	0.32	0.846	1.06	0.57	1.98
3	Baseline TNF-α	Baseline HRSD	All-Cause Mortality	0.15	0.42	0.712	1.17	0.52	2.63
4	Baseline HRSD	Baseline IL-1β	All-Cause Mortality	0.08	0.06	0.224	1.08	0.96	1.22
5	Baseline HRSD	Baseline IL-6	All-Cause Mortality	0.06	0.06	0.358	1.06	0.94	1.20
6	Baseline HRSD	Baseline TNF-α	All-Cause Mortality	0.06	0.06	0.351	1.06	0.94	1.19
1	Baseline IL-1β	Baseline HRSD	Breast Cancer-Specific Mortality	-0.07	0.45	0.872	0.93	0.38	2.26
2	Baseline IL-6	Baseline HRSD	Breast Cancer-Specific Mortality	0.27	0.32	0.406	1.31	0.69	2.47
3	Baseline TNF-α	Baseline HRSD	Breast Cancer-Specific Mortality	0.39	0.42	0.355	1.47	0.65	3.35
4	Baseline HRSD	Baseline IL-1β	Breast Cancer-Specific Mortality	0.01	0.08	0.900	1.01	0.87	1.18

5	Baseline HRSD	Baseline IL-6	Breast Cancer-Specific Mortality	-0.01	0.08	0.915	0.99	0.85	1.15
6	Baseline HRSD	Baseline TNF-α	Breast Cancer-Specific Mortality	-0.01	0.08	0.922	0.99	0.85	1.16
1	Baseline IL-1β	Baseline HRSD	Breast Cancer Recurrence	-0.37	0.30	0.218	0.69	0.38	1.25
2	Baseline IL-6	Baseline HRSD	Breast Cancer Recurrence	-0.16	0.23	0.479	0.85	0.55	1.33
3	Baseline TNF-α	Baseline HRSD	Breast Cancer Recurrence	-0.12	0.33	0.709	0.89	0.47	1.67
4	Baseline HRSD	Baseline IL-1β	Breast Cancer Recurrence	0.05	0.05	0.302	1.05	0.96	1.15
5	Baseline HRSD	Baseline IL-6	Breast Cancer Recurrence	0.04	0.05	0.430	1.04	0.95	1.14
6	Baseline HRSD	Baseline TNF-α	Breast Cancer Recurrence	0.02	0.05	0.657	1.02	0.93	1.13

Note. N = 90; All models adjusted for covariate noted (covariate associations not shown); HRSD = Hamilton Rating Scale for Depression; *B* = Unstandardized Coefficient; *SE* = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit.

Table 11

Unadjusted Cox Proportional Hazards Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines and Time to Clinical Outcomes at 8-15 years (Aim 1b Paths B) in the Invasive Sub-Sample

Model	IV (Model Mediator)	Covariate	DV	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
1	Baseline IL-1β	Baseline HRSD	All-Cause Mortality	-0.33	0.47	0.481	0.72	0.29	1.80
2	Baseline IL-6	Baseline HRSD	All-Cause Mortality	0.03	0.33	0.918	1.03	0.54	1.98
3	Baseline TNF-α	Baseline HRSD	All-Cause Mortality	0.07	0.41	0.875	1.07	0.48	2.40
4	Baseline HRSD	Baseline IL-1β	All-Cause Mortality	0.08	0.06	0.187	1.08	0.96	1.22
5	Baseline HRSD	Baseline IL-6	All-Cause Mortality	0.07	0.06	0.285	1.07	0.95	1.20
6	Baseline HRSD	Baseline TNF-α	All-Cause Mortality	0.07	0.06	0.266	1.07	0.95	1.20
1	Baseline IL-1β	Baseline HRSD	Breast Cancer-Specific Mortality	-0.07	0.44	0.870	0.93	0.39	2.22
2	Baseline IL-6	Baseline HRSD	Breast Cancer-Specific Mortality	0.24	0.33	0.466	1.27	0.67	2.43
3	Baseline TNF-α	Baseline HRSD	Breast Cancer-Specific Mortality	0.30	0.42	0.479	1.34	0.59	3.04
4	Baseline HRSD	Baseline IL-1β	Breast Cancer-Specific Mortality	0.02	0.08	0.816	1.02	0.88	1.18
5	Baseline HRSD	Baseline IL-6	Breast Cancer-Specific Mortality	0.00	0.08	0.957	1.00	0.87	1.16

6	Baseline HRSD	Baseline TNF-α	Breast Cancer-Specific Mortality	0.00	0.08	0.954	1.01	0.86	1.17
1	Baseline IL-1β	Baseline HRSD	Breast Cancer Recurrence	-0.36	0.30	0.227	0.70	0.39	1.25
2	Baseline IL-6	Baseline HRSD	Breast Cancer Recurrence	-0.22	0.24	0.356	0.80	0.50	1.28
3	Baseline TNF-α	Baseline HRSD	Breast Cancer Recurrence	-0.20	0.32	0.537	0.82	0.44	1.53
4	Baseline HRSD	Baseline IL-1β	Breast Cancer Recurrence	0.05	0.05	0.238	1.05	0.97	1.15
5	Baseline HRSD	Baseline IL-6	Breast Cancer Recurrence	0.05	0.05	0.305	1.05	0.96	1.15
6	Baseline HRSD	Baseline TNF-α	Breast Cancer Recurrence	0.04	0.05	0.459	1.04	0.94	1.14

Note. N = 73; All models adjusted for covariate noted (covariate associations not shown); HRSD = Hamilton Rating Scale for Depression; *B* = Unstandardized Coefficient; *SE* = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit.

Table 12

Adjusted Linear Regressions Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 1b Paths A) in Total Sample

Model	IV	Model Mediator	β	*SE*	*t*	*df*	*p*	R^2
1	Baseline HRSD	Baseline IL-1β	0.29	0.02	2.78	81	0.007**	0.23
2	Baseline HRSD	Baseline IL-6	0.19	0.02	1.79	81	0.077∞	0.16
3	Baseline HRSD	Baseline TNF-α	0.30	0.02	2.94	80	0.004**	0.25
4	Baseline IL-1β	Baseline HRSD	0.30	0.62	2.78	81	0.007**	0.19
5	Baseline IL-6	Baseline HRSD	0.20	0.49	1.79	81	0.077∞	0.15
6	Baseline TNF-α	Baseline HRSD	0.32	0.69	2.94	80	0.004**	0.21

Note. ∞$p < 0.100$; *$p < 0.050$; **$p < 0.010$; N = 90; All models adjusted for age, stage, procedure, hormone therapy, and smoking status (covariate associations not shown); HRSD = Hamilton Rating Scale for Depression; β = Standardized Coefficient; *SE* = Standard Error.

Table 13

Adjusted Linear Regressions Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 1b Paths A) in Invasive Subsample

Model	IV	Model Mediator	β	*SE*	*t*	*df*	*p*	R^2
1	Baseline HRSD	Baseline IL-1β	0.28	0.02	2.60	65	0.012*	0.32
2	Baseline HRSD	Baseline IL-6	0.15	0.03	1.27	65	0.208	0.23
3	Baseline HRSD	Baseline TNF-α	0.29	0.02	2.57	64	0.013*	0.27
4	Baseline IL-1β	Baseline HRSD	0.34	0.72	2.60	65	0.012*	0.18
5	Baseline IL-6	Baseline HRSD	0.17	0.58	1.27	65	0.208	0.11
6	Baseline TNF-α	Baseline HRSD	0.32	0.75	2.57	64	0.013*	0.18

Note. *$p < 0.050$; N = 73; All models adjusted for age, stage, procedure, hormone therapy, and smoking status (covariate associations not shown); HRSD = Hamilton Rating Scale for Depression; β = Standardized Coefficient; *SE* = Standard Error.

Table 14

Adjusted Cox Proportional Hazards Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines and Time to Clinical Outcomes at 8-15 years (Aim 1b Paths B) in Total Sample

Model	IV (Model Mediator)	Additional Covariate	DV	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
1	Baseline IL-1β	Baseline HRSD	All-Cause Mortality	-0.31	0.53	0.552	0.73	0.26	2.06
2	Baseline IL-6	Baseline HRSD	All-Cause Mortality	-0.01	0.42	0.973	0.99	0.44	2.23
3	Baseline TNF-α	Baseline HRSD	All-Cause Mortality	0.40	0.54	0.454	1.50	0.52	4.31
4	Baseline HRSD	Baseline IL-1β	All-Cause Mortality	0.03	0.08	0.719	1.03	0.88	1.20
5	Baseline HRSD	Baseline IL-6	All-Cause Mortality	0.01	0.07	0.905	1.01	0.87	1.17
6	Baseline HRSD	Baseline TNF-α	All-Cause Mortality	-0.01	0.08	0.881	0.99	0.85	1.15
1	Baseline IL-1β	Baseline HRSD	Breast Cancer-Specific Mortality	0.01	0.54	0.989	1.01	0.35	2.92
2	Baseline IL-6	Baseline HRSD	Breast Cancer-Specific Mortality	0.20	0.42	0.636	1.22	0.54	2.77
3	Baseline TNF-α	Baseline HRSD	Breast Cancer-Specific Mortality	0.76	0.60	0.209	2.13	0.65	6.95
4	Baseline HRSD	Baseline IL-1β	Breast Cancer-Specific Mortality	-0.08	0.10	0.415	0.92	0.76	1.12

5	Baseline HRSD	Baseline IL-6	Breast Cancer-Specific Mortality	-0.09	0.09	0.326	0.91	0.76	1.10
6	Baseline HRSD	Baseline TNF-α	Breast Cancer-Specific Mortality	-0.14	0.11	0.201	0.87	0.70	1.08
1	Baseline IL-1β	Baseline HRSD	Breast Cancer Recurrence	-0.07	0.36	0.840	0.93	0.46	1.87
2	Baseline IL-6	Baseline HRSD	Breast Cancer Recurrence	-0.12	0.29	0.667	0.88	0.50	1.55
3	Baseline TNF-α	Baseline HRSD	Breast Cancer Recurrence	0.34	0.40	0.400	1.40	0.64	3.05
4	Baseline HRSD	Baseline IL-1β	Breast Cancer Recurrence	0.00	0.05	0.962	1.00	0.91	1.11
5	Baseline HRSD	Baseline IL-6	Breast Cancer Recurrence	0.00	0.05	0.939	1.00	0.91	1.10
6	Baseline HRSD	Baseline TNF-α	Breast Cancer Recurrence	-0.04	0.05	0.432	0.96	0.86	1.07

Note. N = 90; All models adjusted for age, stage, procedure, hormone therapy, smoking status, and additional covariate noted (covariate associations not shown); HRSD = Hamilton Rating Scale for Depression; *B* = Unstandardized Coefficient; *SE* = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit.

Table 15

Adjusted Cox Proportional Hazards Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines and Time to Clinical Outcomes at 8-15 years (Aim 1b Paths B) in the Invasive Sub-Sample

Model	IV (Model Mediator)	Additional Covariate	DV	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
1	Baseline IL-1β	Baseline HRSD	All-Cause Mortality	-0.31	0.53	0.552	0.73	0.26	2.06
2	Baseline IL-6	Baseline HRSD	All-Cause Mortality	-0.01	0.42	0.973	0.99	0.44	2.23
3	Baseline TNF-α	Baseline HRSD	All-Cause Mortality	0.40	0.54	0.454	1.50	0.52	4.31
4	Baseline HRSD	Baseline IL-1β	All-Cause Mortality	0.03	0.08	0.719	1.03	0.88	1.20
5	Baseline HRSD	Baseline IL-6	All-Cause Mortality	0.01	0.07	0.905	1.01	0.87	1.17
6	Baseline HRSD	Baseline TNF-α	All-Cause Mortality	-0.01	0.08	0.881	0.99	0.85	1.15
1	Baseline IL-1β	Baseline HRSD	Breast Cancer-Specific Mortality	0.01	0.54	0.989	1.01	0.35	2.92
2	Baseline IL-6	Baseline HRSD	Breast Cancer-Specific Mortality	0.20	0.42	0.636	1.22	0.54	2.77
3	Baseline TNF-α	Baseline HRSD	Breast Cancer-Specific Mortality	0.76	0.60	0.209	2.13	0.65	6.95
4	Baseline HRSD	Baseline IL-1β	Breast Cancer-Specific Mortality	-0.08	0.10	0.415	0.92	0.76	1.12
5	Baseline HRSD	Baseline IL-6	Breast Cancer-Specific Mortality	-0.09	0.09	0.326	0.91	0.76	1.10

6	Baseline HRSD	Baseline TNF-α	Breast Cancer-Specific Mortality	-0.14	0.11	0.201	0.87	0.70	1.08
1	Baseline IL-1β	Baseline HRSD	Breast Cancer Recurrence	-0.07	0.36	0.840	0.93	0.46	1.87
2	Baseline IL-6	Baseline HRSD	Breast Cancer Recurrence	-0.12	0.29	0.667	0.88	0.50	1.55
3	Baseline TNF-α	Baseline HRSD	Breast Cancer Recurrence	0.34	0.40	0.400	1.40	0.64	3.05
4	Baseline HRSD	Baseline IL-1β	Breast Cancer Recurrence	0.00	0.05	0.962	1.00	0.91	1.11
5	Baseline HRSD	Baseline IL-6	Breast Cancer Recurrence	0.00	0.05	0.939	1.00	0.91	1.10
6	Baseline HRSD	Baseline TNF-α	Breast Cancer Recurrence	-0.04	0.05	0.432	0.96	0.86	1.07

Note. N = 73; All models adjusted for age, stage, procedure, hormone therapy, smoking status, and additional covariate noted (covariate associations not shown); HRSD = Hamilton Rating Scale for Depression; *B* = Unstandardized Coefficient; *SE* = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit.

Table 16

Fully Adjusted Linear Regressions Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 1b Paths A) in Total Sample

Model	IV	Model Mediator	*β*	*SE*	*t*	*df*	*p*	R^2
1	Baseline HRSD	Baseline IL-1β	0.30	0.02	2.52	54	0.015*	0.41
2	Baseline HRSD	Baseline IL-6	0.19	0.03	1.49	54	0.143	0.33
3	Baseline HRSD	Baseline TNF-α	0.30	0.02	2.47	53	0.017*	0.39
4	Baseline IL-1β	Baseline HRSD	0.36	0.73	2.52	54	0.015*	0.29
5	Baseline IL-6	Baseline HRSD	0.21	0.62	1.49	54	0.143	0.24
6	Baseline TNF-α	Baseline HRSD	0.34	0.78	2.47	53	0.017*	0.32

Note. *$p < 0.050$; N = 64 represents total study sample with BMI data; All models adjusted for age, stage, procedure, hormone therapy, smoking status, and BMI; HRSD = Hamilton Rating Scale for Depression; β = Standardized Coefficient; SE = Standard Error.

Table 17

Fully Adjusted Linear Regressions Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 1b Paths A) in Invasive Subsample

Model	IV	Mediator	β	*SE*	*t*	*df*	*p*	R^2
1	Baseline HRSD	Baseline IL-1β	0.33	0.02	2.82	44	0.007*	0.51
2	Baseline HRSD	Baseline IL-6	0.25	0.03	1.92	44	0.062∞	0.41
3	Baseline HRSD	Baseline TNF-α	0.25	0.02	2.67	43	0.011*	0.43
4	Baseline IL-1β	Baseline HRSD	0.46	0.84	2.82	44	0.007*	0.31
5	Baseline IL-6	Baseline HRSD	0.32	0.73	1.92	44	0.062∞	0.24
6	Baseline TNF-α	Baseline HRSD	0.41	0.84	2.67	43	0.011*	0.32

Note. Notes: ∞$p < 0.100$; *$p < 0.050$; N = 53 represents invasive disease subsample with BMI data; All models adjusted for age, stage, procedure, hormone therapy, smoking status, and BMI; HRSD = Hamilton Rating Scale for Depression; β = Standardized Coefficient; SE = Standard Error.

Table 18

Fully Adjusted Cox Proportional Hazards Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines and Disease Free Interval at 8-15 years (Aim 1b Paths B) in Total Sample

Model	IV (Model Mediator)	Additional Covariate	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
1	Baseline IL-1β	Baseline HRSD	-0.21	0.67	0.755	0.81	0.22	3.04
2	Baseline IL-6	Baseline HRSD	-0.85	0.62	0.166	0.43	0.13	1.43
3	Baseline TNF-α	Baseline HRSD	-0.77	0.99	0.433	0.46	0.07	3.19
4	Baseline HRSD	Baseline IL-1β	0.10	0.09	0.273	1.11	0.92	1.33
5	Baseline HRSD	Baseline IL-6	0.15	0.09	0.103	1.17	0.97	1.40
6	Baseline HRSD	Baseline TNF-α	0.10	0.10	0.332	1.10	0.91	1.34

Note. N = 64 represents total study sample with BMI data; All models adjusted for age, stage, procedure, hormone therapy, smoking status, BMI, and additional covariate noted (covariate associations not shown); HRSD = Hamilton Rating Scale for Depression; B = Unstandardized Coefficient; SE = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit.

Table 19

Fully Adjusted Cox Proportional Hazards Showing Relationships among Baseline Depressive Symptoms and Pro-Inflammatory Cytokines and Disease Free Interval at 8-15 years (Aim 1b Paths B) in Invasive Sub-Sample

Model	IV (Model Mediator)	Additional Covariate	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
1	Baseline IL-1β	Baseline HRSD	-0.21	0.67	0.755	0.81	0.22	3.04
2	Baseline IL-6	Baseline HRSD	-0.85	0.62	0.166	0.43	0.13	1.43
3	Baseline TNF-α	Baseline HRSD	-0.77	0.99	0.433	0.46	0.07	3.19
4	Baseline HRSD	Baseline IL-1β	0.10	0.09	0.273	1.11	0.92	1.33
5	Baseline HRSD	Baseline IL-6	0.15	0.09	0.103	1.17	0.97	1.40
6	Baseline HRSD	Baseline TNF-α	0.10	0.10	0.332	1.10	0.91	1.34

Note. N = 53 represents invasive sub-sample with BMI data; All models adjusted for age, stage, procedure, hormone therapy, smoking status, BMI, and additional covariate noted (covariate associations not shown); HRSD = Hamilton Rating Scale for Depression; *B* = Unstandardized Coefficient; *SE* = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit.

Table 20

Unadjusted Cox Proportional Hazards Regressions Showing Effects of Study Condition on Time to Clinical Outcomes at 8-15 Year Follow-up (Aim 2a)

Outcome	Sample	N	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
All-Cause Mortality	Total	90	-0.03	0.71	0.963	0.97	0.24	3.89
Breast Cancer Specific Mortality	Total	90	0.72	0.87	0.404	2.06	0.38	11.26
Breast Cancer Recurrence	Total	90	0.11	0.51	0.826	1.12	0.42	3.01
All-Cause Mortality	Invasive	73	-0.18	0.71	0.802	0.84	0.21	3.37
Breast Cancer Specific Mortality	Invasive	73	0.59	0.87	0.498	1.80	0.33	9.82
Breast Cancer Recurrence	Invasive	73	-0.03	0.51	0.956	0.97	0.36	2.61

Note. B = Unstandardized Coefficient; *SE* = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit.

Table 21

Adjusted Cox Proportional Hazards Regressions Showing Effects of Study Condition on Time to Clinical Outcomes at 8-15 Year Follow-up (Aim 2a)

Outcome	Sample	N	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
All-Cause Mortality	Total	90	-0.33	0.87	0.701	0.72	0.13	3.91
Breast Cancer Specific Mortality	Total	90	0.62	1.04	0.551	1.86	0.24	14.39
Breast Cancer Recurrence	Total	90	0.06	0.58	0.925	1.06	0.34	3.31
All-Cause Mortality	Invasive	73	-0.33	0.87	0.701	0.72	0.13	3.09
Breast Cancer Specific Mortality	Invasive	73	0.62	1.04	0.551	1.86	0.24	14.39
Breast Cancer Recurrence	Invasive	73	0.06	0.58	0.925	1.06	0.34	3.31

Note. All models adjusted for age, stage, procedure, hormone therapy, and smoking status (covariate associations not shown); *B* = Unstandardized Coefficient; *SE* = Standard Error; HR = Hazard Ratio; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit.

Table 22

Fully Adjusted Cox Proportional Hazards Regressions Showing Effects of Study Condition on Disease Free Interval at 8-15 Year Follow-up (Aim 2a)

Sample	N	*B*	*SE*	*p*	HR	95% CI LL	95% CI UL
Total	64	0.52	0.87	0.553	1.67	0.31	9.16
Invasive	53	0.15	0.87	0.553	1.67	0.31	9.16

Note. N = 64 represents total study sample with BMI data; N = 53 represents invasive disease subsample with BMI data; All models adjusted for age, stage, procedure, hormone therapy, smoking status, and BMI; *B* = Unstandardized Coefficient; *SE* = Standard Error; CI = Confidence Interval; LL = Lower Limit; UL = Upper Limit.

Table 23

Unadjusted Linear Regressions Showing Effect of Study Condition on 12 Month Changes in Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 2b Paths A)

Model	Sample	N	DV (Model Mediator)	β	*SE*	*t*	*df*	*p*	R^2
1	Total	90	Δ HRSD	0.14	1.14	1.29	86	0.200	0.02
2	Total	90	Δ IL-1β	0.04	0.21	0.33	88	0.746	0.00
3	Total	90	Δ IL-6	0.02	0.27	0.19	88	0.848	0.00
4	Total	90	Δ TNF-α	-0.05	0.18	-0.44	87	0.659	0.00
1	Invasive	73	Δ HRSD	0.14	1.25	1.21	69	0.230	0.02
2	Invasive	73	Δ IL-1β	0.07	0.23	0.56	71	0.578	0.00
3	Invasive	73	Δ IL-6	0.00	0.30	-0.02	71	0.981	0.00
4	Invasive	73	Δ TNF-α	-0.06	0.21	-0.53	70	0.599	0.00

Note. Δ = 12 month change; HRSD = Hamilton Rating Scale for Depression; *β* = Standardized Coefficient; *SE* = Standard Error.

Table 24

Unadjusted Linear Regressions Showing Effect of Study Condition on 12 Month Changes in Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 2b Paths A) Controlling only for Baseline Value of the Mediator Variable

Model	Sample	N	DV (Model Mediator)	β	*SE*	*t*	*df*	*p*	R^2
1	Total	90	Δ HRSD	0.13	0.94	1.53	85	0.131	0.35
2	Total	90	Δ IL-1β	-0.01	0.16	-0.06	87	0.956	0.41
3	Total	90	Δ IL-6	0.02	0.21	0.18	87	0.856	0.37
4	Total	90	Δ TNF-α	-0.05	0.15	-0.55	86	0.585	0.30
1	Invasive	73	Δ HRSD	0.14	1.06	1.34	68	0.184	0.30
2	Invasive	73	Δ IL-1β	-0.01	0.18	-0.10	70	0.924	0.41
3	Invasive	73	Δ IL-6	-0.02	0.24	-0.19	70	0.853	0.39
4	Invasive	73	Δ TNF-α	-0.07	0.17	-0.68	69	0.497	0.33

Note. All analyses run controlling for baseline value of model mediator; Δ = 12 month change; HRSD = Hamilton Rating Scale for Depression; β = *S*tandardized Coefficient; SE = Standard Error.

Table 25

Adjusted Linear Regressions Showing Effect of Study Condition on 12 Month Changes in Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 2b Paths A)

Model	Sample	N	DV (Model Mediator)	β	*SE*	*t*	*df*	*p*	R^2
1	Total	90	Δ HRSD	0.17	1.25	1.49	79	0.139	0.07
2	Total	90	Δ IL-1β	0.01	0.22	0.06	81	0.949	0.12
3	Total	90	Δ IL-6	0.00	0.28	0.03	81	0.981	0.08
4	Total	90	Δ TNF-α	-0.10	0.19	-0.86	80	0.395	0.08
1	Invasive	73	Δ HRSD	0.18	1.39	1.33	63	0.188	0.05
2	Invasive	73	Δ IL-1β	0.05	0.24	0.36	65	0.719	0.14
3	Invasive	73	Δ IL-6	-0.01	0.33	-0.05	65	0.957	0.09
4	Invasive	73	Δ TNF-α	-0.10	0.23	-0.80	64	0.428	0.10

Note. All models adjusted for age, stage, procedure, hormone therapy, and smoking status (covariate associations not shown); Δ = 12 month change; HRSD = Hamilton Rating Scale for Depression; β = Standardized Coefficient; *SE* = Standard Error.

Table 26

Adjusted Linear Regressions Showing Effect of Study Condition on 12 Month Changes in Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 2b Paths A) Additionally Controlling for Baseline Value of Mediator

Model	Sample	N	DV (Model Mediator)	*β*	*SE*	*t*	*df*	*p*	R^2
1	Total	90	Δ HRSD	0.13	1.02	1.39	78	0.170	0.39
2	Total	90	Δ IL-1β	-0.02	0.17	-0.17	80	0.864	0.44
3	Total	90	Δ IL-6	0.01	0.23	0.11	80	0.913	0.39
4	Total	90	Δ TNF-α	-0.07	0.17	-0.73	79	0.466	0.31
1	Invasive	73	Δ HRSD	0.14	1.15	1.27	62	0.208	0.37
2	Invasive	73	Δ IL-1β	-0.03	0.20	-0.26	64	0.794	0.42
3	Invasive	73	Δ IL-6	-0.03	0.27	-0.25	64	0.802	0.41
4	Invasive	73	Δ TNF-α	-0.10	0.19	-0.92	63	0.359	0.34

Note. All analyses run controlling for baseline value of model mediator, age, stage, procedure, hormone therapy, and smoking status (covariate associations not shown); Δ = 12 month change; HRSD = Hamilton Rating Scale for Depression; *β* = Standardized Coefficient; *SE* = Standard Error.

Table 27

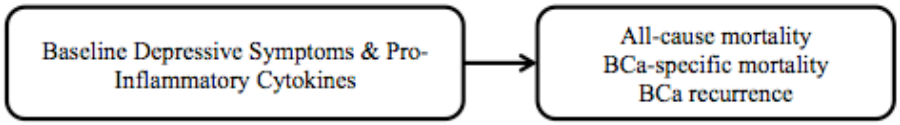
Fully Adjusted Linear Regressions Showing Effect of Study Condition on 12 Month Changes in Depressive Symptoms and Pro-Inflammatory Cytokines (Aim 2b Paths A)

Model	Sample	N	DV (Model Mediator)	β	*SE*	*t*	*df*	*p*	R^2
1	Total	64	Δ HRSD	0.15	1.39	1.04	53	0.305	0.09
2	Total	64	Δ IL-1β	-0.02	0.26	-0.14	54	0.887	0.20
3	Total	64	Δ IL-6	0.01	0.33	0.04	54	0.970	0.14
4	Total	64	Δ TNF-α	-0.02	0.22	-0.14	53	0.889	0.20
1	Invasive	53	Δ HRSD	0.15	1.61	0.98	43	0.335	0.09
2	Invasive	53	Δ IL-1β	0.03	0.31	0.20	44	0.839	0.19
3	Invasive	53	Δ IL-6	0.03	0.39	0.19	44	0.850	0.11
4	Invasive	53	Δ TNF-α	-0.01	0.27	-0.09	43	0.926	0.17

Note. All models adjusted for age, stage, procedure, hormone therapy, smoking status, and BMI; Δ = 12 month change; HRSD = Hamilton Rating Scale for Depression; β = Standardized Coefficient; *SE* = Standard Error.

Figures

A)



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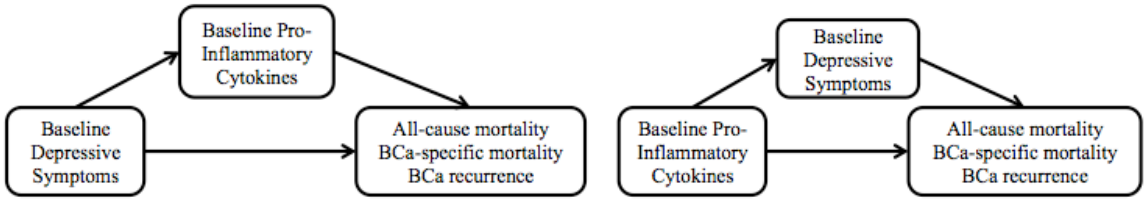
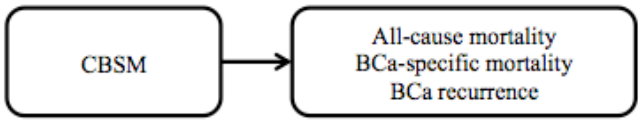


Figure 1. Graphical representation of Aim 1. A) Direct effects of baseline depressive symptoms and serum concentrations of proinflammatory cytokines on time to health outcomes. B) Indirect effects between baseline depressive symptoms and serum concentrations of pro-inflammatory cytokines with time to health outcomes in mediation models.

A)



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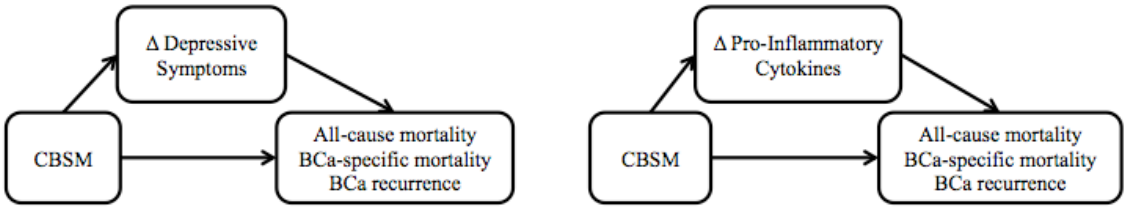

Figure 2. Graphical representation of Aim 2. A) Direct effects of the intervention on time to health outcomes. B) Indirect effects of the intervention on time to health outcomes through 12 month changes in depressive symptoms and serum concentrations of pro-inflammatory cytokines in mediation models.

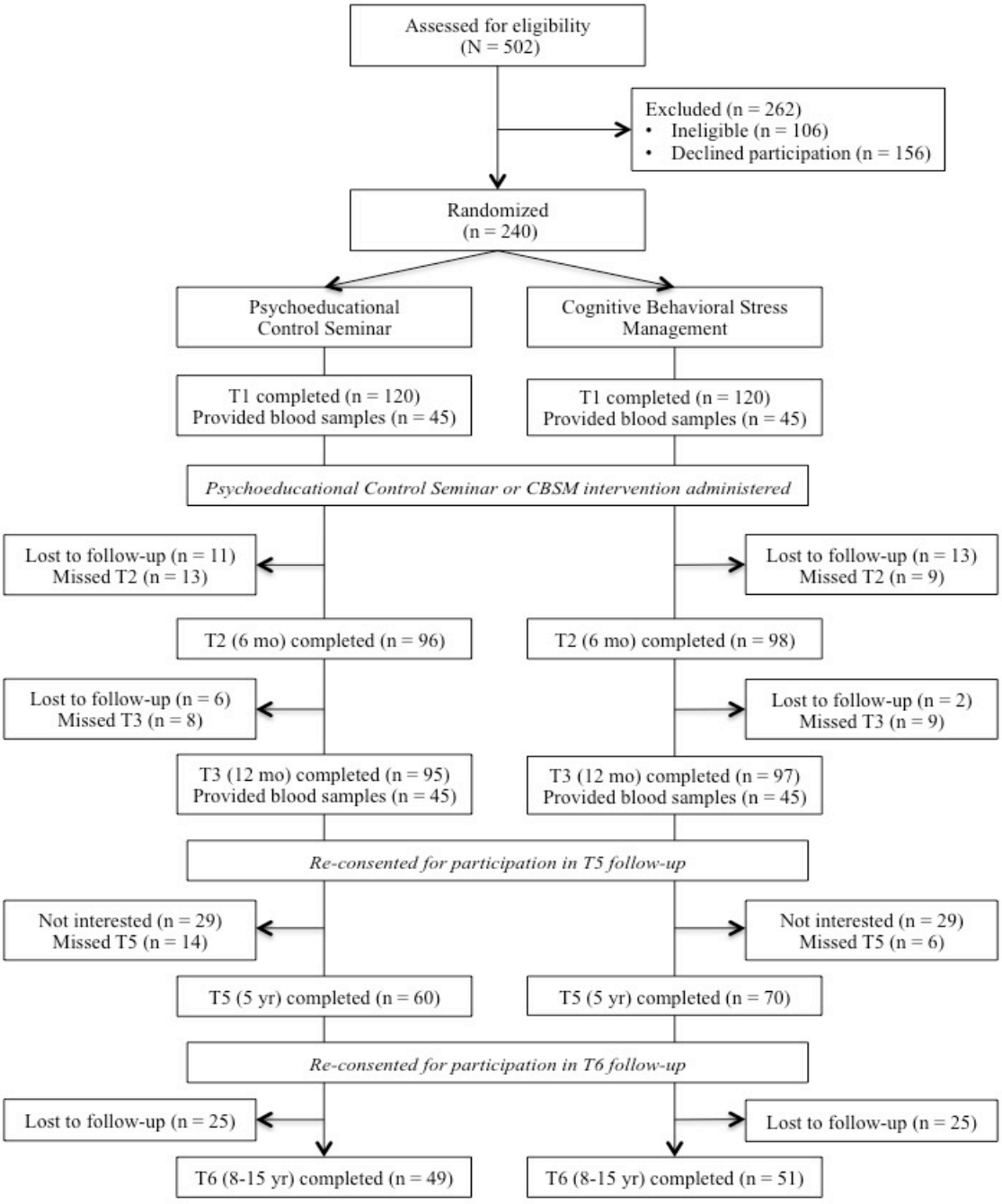

Figure 3. CONSORT Flow Diagram. Ns at T2-T6 indicate the number of participants who completed each assessment out of the n = 120 women who completed the T1 assessment in each study arm.