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CBSM Effects on Sickness Behavior and Pro-Inflammatory Cytokine Mechanisms in Breast Cancer Survivors

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CBSM EFFECTS ON SICKNESS BEHAVIOR AND PRO-INFLAMMATORY CYTOKINE MECHANISMS IN BREAST CANCER SURVIVORS

By

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The concept of sickness behavior offers a framework to view both the neurovegetative and psychological symptoms that accompany illness as a common entity that results from increased inflammatory activation. Despite the prevalence of sickness behavior in medical populations, to our knowledge this study provides the first attempt to develop a standardized measure to assess sickness behavior using standard self-report questionnaires commonly used with cancer patients. The set of items included in the measure match theoretical conceptualizations of sickness behavior and target symptoms that comprise anhedonia, depressed mood, cognitive dysfunction, social disinterest, fatigue, low libido, poor appetite, somnolence, sensitivity to pain, and malaise. The measure showed high internal consistency, adequate test-retest reliability, and good convergent validity with both psychological and biological correlates. A confirmatory factor analysis also determined that a two-factor, rather than a single-factor measurement model, encompassing a physical and a psychological sickness symptom dimension, accounted for sickness behavior. Future psychometric work is still needed to further validate this new practical assessment tool.

Descriptive analyses revealed relatively low levels of sickness behavior symptoms in the sample as a whole with both physical and psychological sickness

behavior symptoms exhibiting a significant linear decrease over time. As expected, both physical and psychological sickness behavior symptoms showed associations with two pro-inflammatory cytokine markers, IL6 and TNF-alpha and a neuroendocrine marker, cortisol. Longitudinal associations suggest that higher levels of the pro-inflammatory cytokine TNF-alpha may impact the progressive decline of physical sickness symptoms over time with symptoms taking longer to disappear. Because cortisol was associated with more rather than less physical sickness symptoms, results raise the question of whether the anti-inflammatory neuroendocrine activity may be dysregulated in breast cancer survivors. The mechanistic basis for these associations requires further examination.

In this study it was also evaluated whether a cognitive behavioral stress management intervention and relaxation training intervention could reduce sickness symptoms over time. Breast cancer survivors were assessed at baseline and then randomly assigned to a 10-week cognitive behavioral stress management intervention (N = 70) or a 1-day control condition (N = 55). Psychosocial measures, urine, and blood were obtained from participants at 3 months, 6 months, and 12 months post-intervention to assess relevant behavioral, endocrine and immune variables. Relative to the control group, the experimental group showed marginally more prevalence of physical sickness behavior symptoms in the short term (post-intervention, 3-months; p = .08) and a steadier decline of symptoms in the long-term (15-month follow-up period). The adaptive nature of sickness behavior as a motivational strategy that helps restore homeostatic balance in the long run may be one possible interpretation of these results. Whether these intervention effects on sickness behavior were mediated by changes in pro-inflammatory

cytokines or cortisol was examined but not supported by these data and needs to be further examined in future studies.

Dedication:

To Maxim. Te amo.

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CHAPTER I

Introduction

Diagnosis of breast cancer and subsequent treatment are stressful, and severe emotional reactions are commonly reported among breast cancer survivors (Meyerowitz, 1980; Miller, 1980; Derogatis, Morrow, Fetting, Penman, Piasetsky, Schmale, et al., 1983). Breast cancer is a negative event that continues to be a chronic stressor after treatment (Yehuda, 2003). Approximately 30% of women successfully treated for breast cancer continue to suffer persistent fatigue of unknown origin (Bower, Ganz, Aziz, Fahey, and Cole, 2003). Sleep problems are also commonly reported among breast cancer survivors (Lindley, Vasa, Sawyer, and Winer 1998).

Research has shown that inflammatory stimuli can signal the central nervous system to generate behavioral changes including fatigue and changes in sleep (Dantzer, 1999). Specifically, the production of pro-inflammatory cytokines is considered to play an essential role in the development of sickness behavior, the constellation of symptoms that accompany illness in general and inflammation in particular (Miller, 2003). Sickness behavior symptoms include pain, fatigue, anorexia, and alterations in mood and cognition that can severely impact on the quality of life of cancer patients. In the case of cancer, sickness symptoms can be induced by cytokines produced by tumor cells and inflammatory cells infiltrating or surrounding the tumor, as well as by medical interventions such as radiotherapy and surgery (Capuron and Dantzer, 2003).

In medical populations, such as cancer patients, the assessment of sickness behavior, of which depression is a component, may prove to be beneficial. The concept of sickness behavior offers a framework to view both neurovegetative and psychological symptoms as a part of a cluster phenomena with a common pathophysiology, namely activation of the inflammatory cytokine network (Miller, 2003). Despite the usefulness of the sickness behavior construct, to our knowledge there are no standardized self-report instruments to assess sickness behavior. Developing such an instrument by extracting items from questionnaires typically used in cancer research can prove practical and beneficial for research and clinical practice.

Although sickness symptoms are initially adaptive, when they are sustained for extended periods they can be damaging to functional well-being (Charlton, 2000). In breast cancer survivors, maintenance of sickness symptoms after treatment completion can impair reintegration to social or occupational life (Meyerowitz, 1980). Bolstering the physical and psychological well being of cancer patients by alleviating sickness behavior symptoms may be an essential component in cancer care and control. Cognitive behavioral interventions have been shown to be effective in modulating psychological factors as well as neuroendocrine and immune markers of disease progression in cancer (Davis, 1988; Fawzy, Cousins, Fawzy, Kemeny, et al., 1990; Gruber, Hersh, Hall, Waletzky, Kunz, Carpenter et al., 1993; van der Pompe, Duivenvoordern, Antoni, and Visser, 1997; Cruess, Antoni, McGregor, Killbourn, Boyers et al., 2000; van der Pompe, Antoni, Duivenvoorder, de-Graeff, Simonis, van-der-Vegt, and Heijnen, 2001; see Andersen, 2002 for a review). Breast cancer survivors may benefit from a stress management intervention not only immunologically with reduced inflammation levels,

but also psychologically with concomitant changes in behavioral symptoms such as fatigue and pain. At present, little is known about whether or not inflammatory responses and the associated sickness behavior symptoms can be influenced by stress management interventions in breast cancer survivors.

Sickness Behavior: A Motivational Strategy

Sick individuals experience weakness, malaise, listlessness, and inability to concentrate. They become depressed and lethargic, show little interest in their surroundings, and stop eating and drinking. This constellation of non-specific symptoms is collectively referred to as "Sickness Behavior" (Dantzer, 1999). Sickness behavior was first described in 1988 by Hart as a physiological and psychological adaptation to acute infective and inflammatory illness seen in many mammalian species (Charlton, 2000).

The characteristic pattern of sickness behavior comprises anhedonia, impaired cognitive functioning, anxiety and irritability, psychomotor retardation, anergia and fatigue, anorexia, low libido, somnolence, and increased sensitivity to pain (Miller, 2003; Kent, Bluthe, Kelley, and Dantzer, 1992). Thus, sickness behavior includes both a physical and a psychological component. Capuron and Dantzer (2003) refer to two forms of sickness behavior: a depressive syndrome, very much like major depression; and a neurovegetative syndrome, characterized by hyperalgesia (i.e., increased pain sensitivity) and fatigue.

Because of their wide prevalence in cancer patients, physicians frequently ignore sickness symptoms. Typically they consider sickness behavior the simple result of debilitation and weakness that inevitably occurs when all resources are engaged in a defensive process against pathogens (Dantzer, 1999). However, experimental research

with rodents has made increasingly clear that sickness behavior is a highly organized motivational strategy essential for the survival of the organism (Dantzer, 1999). According to this model the sickness syndrome as reflected in anhedonia, depressed mood, cognitive dysfunction, social disinterest, fatigue, low libido, poor appetite, somnolence, sensitivity to pain, and malaise does not simply represent debilitation and suppression of activity, but rather results from an altered motivational state that redirects energy to metabolic processes and the immune system. Sick individuals reorganize their behavior and change their priorities so that most of the available energy is used in recovery and fighting of infection. In this way, sickness behavior can be advantageous for the species, as it reduces the risk of additional exposure to pathogens, saves energy expenditure by skeletal muscles, and facilitates withdrawal from competition from food and reproduction by the unfit individual (Tilders, Schmidt, Hoogedijk, and Swaab, 1999).

Even though illness responses play a crucial and adaptive role, they are expensive in terms of energy requirements and impose physiological demands on the organism. There can be pathophysiological implications if the constellation of sickness behavior persists for long periods of time (Miller, 2003). When too strong or tool long, the sickness response can easily become detrimental to the organism (Tilders et al., 1999). Thus, if sickness behavior is inappropriately activated or excessively sustained it ceases to be adaptive and can be profoundly damaging to personality, social or occupational life.

Despite is prevalence as a response to illness, few human studies in medical populations have targeted sickness behavior as a constellation of symptoms or determined its biological correlates. Furthermore no studies to our knowledge have

assessed whether or not prolonged sickness behavior can be reduced by a cognitive behavioral intervention.

Cytokines induce sickness behavior

In the past decade it has become clear that inflammatory mediators of the immune system (i.e., cytokines) can regulate complex behavioral processes including affective, motivational, and cognitive variables. Cytokines are the communication molecules between immune cells (Vedhara, Wang, Fox, and Irwin, 1999). Cytokines have wide ranging biological effects that include directing white blood cells towards sites of injury or infection, stimulating the production of other molecules involved in the inflammatory response, and enhancing the killing capacity of certain white blood cells (Golsdby, Kindt, and Osbourne, 2000). Many of the cytokines are referred to as interleukin indicating that they are secreted by leukocytes (white blood cells) and exert their action on other leukocytes.

Activation of the immune system by infection or injury leads to the release of a specific group of cytokines known as pro-inflammatory cytokines or fever inducing cytokines. These cytokines play a key role in the regulation of the immune response and the coordination of the acute inflammatory response in response to infection. The main pro-inflammatory cytokines are Interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrois factor (TNF) (Dantzer, 1999).

The first evidence that pro-inflammatory cytokines can have an impact on behavior comes from clinical trials that used cytokines in the treatment of viral diseases and cancer. Patients were observed to develop flu-like symptoms, followed after several weeks of treatment by the appearance of psychiatric disorders especially in the form of

acute psychosis and major depression. These symptoms regressed on the cessation of treatment (Capuron and Dantzer, 2003). Experimental research with rodents has since then substantiated the capacity of pro-inflammatory cytokines, including tumor necrosis factor (TNF-alpha), IL1 and IL6 to induce the syndrome of sickness behavior (see Dantzer, 1999 for a review of animal research). In addition, extensive research has shown that sickness behavior can be reliably reproduced in rodents by administration of each of the pro-inflammatory cytokines in isolation or by administering agents such as lipopolysaccharide (LPS) to induce the pro-inflammatory cytokine cascade (Raison and Miller, 2003).

The immune mechanism underlying the onset and persistence of sickness behaviors such as fatigue in breast cancer survivors have only started to be determined. For example, in a cross-sectional study, Bower, Ganz, Aziz, and Fahey (2002) showed that fatigued breast cancer survivors had significantly higher levels of several markers associated with pro-inflammatory cytokine activity than non-fatigued survivors. Research can benefit from further clarification of the possible mediating role of pro-inflammatory cytokines in the development and improvement of sickness behavior symptoms in breast cancer survivors.

Sickness Behavior in the Context of Cancer

In the context of neoplastic illness, pro-inflammatory cytokines can be produced not only by tumor cells and inflammatory cells infiltrating or surrounding the tumor, but also by medical interventions such as chemotherapy, radiation, and surgery (Capuron and Dantzer, 2003). Cytokines such as IL-2 and interferon (INF-alpha), used in the treatment of several malignancies, are notorious for inducing depression (Capuron and Dantzer,

2003). In addition, psychological stressors have been shown to increase proinflammatory cytokine activity (Maes, Song, Lin., Gabriels, De Jongh, Van Gastel, et al., 1998; Ackerman, Martino, Heyman, Moyna, and Rabin, 1998), suggesting that inflammatory processes could be sensitive to the stress of breast cancer diagnosis and treatment. Thus, elevated inflammation resulting from activation of the inflammatory cytokine network is common in the context of cancer.

Sickness symptoms, particularly fatigue and cognitive dysfunction, can continue to plague cancer survivors long after the cancer has been successfully treated, significantly impairing quality of life (Bower et al., 2002; Miller, 2003). Approximately 30% of women successfully treated for breast cancer suffer persistent fatigue of unknown origin (Bower, et al., 2003). In contrast, a recent study from the Center for Disease Control (CDC) reported than 12% of the US population (18 to 69 years of age) suffers from fatigue lasting for at least 6 months (chronic fatigue) (Bierl, Nisenbaum, Hoaglin, Randall, Jones, Unger, et al., 2004). Research has also shown that fatigued women are significantly more likely to report other sickness behaviors such as increased somnolence, decreased activity level, decreased interest in planning or initiating social activities, forgetfulness, distractibility, and higher levels of depressed mood (Bower et al., 2002). Cancer patients, like other patients with medical disorders, also experience a higher prevalence of sleep difficulty than the general population; estimates are approximately 23% in post-adjuvant breast cancer patients (Lindley, Vasa, Sawyer, and Winer, 1998). In contrast, only between 8% and 10% of the US population has been reported to suffer from chronic sleep disorders (Gautam, 2001). Median point prevalence rates for depression in patients with cancer range from 22% to 29%, which are also significantly

higher that prevalence rates for the general US population estimated between 10% and 12% (Hotopf, Chidgey, Addington-Hall, and LY, 2002).

Research with fatigued breast cancer survivors has concluded that fatigue and depression might co-occur as part of a coordinated response elicited by cytokine actions (Bower et al., 2002). Recent evidence suggests an association between depressed affect and increased levels of inflammatory products, such as proinflammatory cytokines (e.g. interleukin 1 and 6, tumor necrosis factor-α) and other markers of immune activation (Maes, 1999). Thus, in the context of cancer, depressive symptoms can be seen as a component of a sickness syndrome due to increased inflammation, rather than as a simple psychological reaction to cancer diagnosis.

The high prevalence of sickness behavior symptoms in cancer patients likely to arise as a consequence of pathophysiologic processes inherent to neoplasia and its treatment, suggests that cancer patients are likely to benefit from therapeutic interventions that are able to reduce the inflammatory component of these behavioral symptoms. Research is still needed in this area.

Depression and Sickness Behavior

Major depression and cytokine-induced sickness behavior share many common features. A striking overlap exists between symptoms required to meet DSM-IV criteria for major depression and symptoms commonly observed in the context of illness. Shared symptoms include anhedonia, social disinterest, low energy, anorexia, weight loss, sleep disturbance, cognitive disturbance, decreased libido, and psychomotor retardation. These symptoms common to depression and sickness behavior mostly represent the neurovegetative symptoms of depression. Sickness behavior expands the range of

neurovegetative symptoms to include pain and fatigue. In contrast, symptoms such as depressed mood, guilt/worthlessness, and suicidal ideation, are more common in major depression than illness.

According to Raison and Miller (2003), it is possible that in the context of medical illness such as cancer, depressive symptoms arise from physiologic changes resulting from the specific disease and its treatment. According to the authors, depression and symptoms of illness are difficult to distinguish precisely because they represent the broader pathophysiologic syndrome of sickness behavior, which arises within the context of immune activation.

Diagnosing depression in the context of cancer can be complicated by the widespread tendency to excuse depression as a natural reaction to cancer and the overlap of depressive and sickness symptoms. Recent research suggests that many symptoms of both physical and emotional distress in cancer patients may have a significant inflammatory component, arising out of the body's own attempt to fight disease and at the same time maintain a homeostatic balance (Raison and Miller, 2003). Medical patients may benefit from using an inclusive approach such as sickness behavior, which includes both depression and symptoms of illness such as pain. This perspective highlights the importance of accurately assessing sickness behavior in the context of neoplastic illness.

Assessment of Sickness Behavior

For years there has been no standard way of assessing sickness behavior in animals or humans. In animals, sickness was first studied in an indirect manner. By using the conditioned taste aversion paradigm or by looking for alterations of innate and

learned behavior in rodents, researchers tried to obtain a quantitative indicator of sickness. Animal research has also used changes in general activity, feeding behavior, and social interactions as indicators of sickness behavior by using automated recording of behavior or direct observation (Dantzer, 1999).

In humans, assessment of the constellation of symptoms through direct observation by physicians can be subjective and based on the patient's own accounts. Self-report questionnaires or interview-based assessments seem to be more appropriate for objective assessment of sickness behavior in medical patients. In addition to standard depression questionnaires such as the Beck Depression Inventory (BDI), which emphasizes mood and cognitive symptoms, only the Neurotoxicity Rating Scale, has been recommended as a self-report instrument that assesses a wider range of neurovegetative symptoms shared by depression and physical illness (Raison and Miller, 2003). Previous research by Bower's groups has used a self-designed 23-item questionnaire to assess fatigue related symptoms in breast cancer survivors that impact on quality of life (see Appendix A). Several of the symptoms assessed by Bower's measure correspond to the constellation of sickness symptoms. The scale also measures additional symptoms specific to the process of breast cancer treatment such as nausea, vaginal dryness and tenderness, swelling, discomfort or numbness in the chest wall, breast or arm.

To our knowledge, no self-report questionnaires have been suggested for assessing the full constellation of symptoms that defines sickness behavior. Such a measure should assess both psychological as well as physical symptoms of sickness behavior. Item selection should be based on theoretical conceptualizations and previous

research in sickness and include the following set of symptoms: anhedonia, social disinterest, fatigue, anorexia, weight loss, sleep disturbance, cognitive disturbance, decreased libido, and hyperalgesia. Future research in this area can definitely benefit from the development of a measure targeting this constellation of symptoms.

Psychosocial Interventions in Cancer

To date, the effects of psychosocial interventions on psychological and biological factors have mostly been assessed and reported separately for these two areas. On one hand, several studies have shown the beneficial effects of psychosocial interventions on the well being of cancer patients. For example, Antoni and colleagues tested a 10-week group cognitive behavioral stress management intervention among 100 women newly treated for breast cancer patients. Results showed that the intervention not only decreased the prevalence of mild to moderate depression, but also enhanced benefit finding and increased generalized optimism, which remained significantly elevated at a 3-month follow up (Antoni, Lehman, Kilbourn, Boyers, Culver, Alferi, et al., 2001). In a meta-analytic review, Meyer and Mark (1995) concluded that psychosocial interventions in adult cancer patients can have positive effects on emotional adjustment (e.g., anxiety, depression, self-esteem), functional adjustment (e.g., socializing and going back to work), and on treatment and disease-related symptoms such as pain, nausea. In sum, data on this end of the spectrum suggest that psychosocial interventions can alleviate depressive and anxiety symptoms and improve coping skills and positive responses (Ross, Boesen, Dalton, and Johansen, 2002).

On the other hand, psychooncology research shows that psychological interventions can affect neuroendocrine and immune processes related to cancer

progression including cortisol levels and lymphocyte activity (see Anderson, 2002 for a review; Davis, 1988; Fawzy, Cousins, Fawzy, Kemeny, et al., 1990; Gruber, Hersh, Hall, Waletzky, Kunz, Carpenter et al., 1993; van der Pompe, Duivenvoordern, Antoni, and Visser, 1997; Cruess, Antoni, McGregor, Killbourn, Boyers et al., 2000; van der Pompe, Antoni, Duivenvoorder, de-Graeff, Simonis, van-der-Vegt, and Heijnen, 2001). For example, a hallmark study in this area showed that a 6-week structured psychiatric group intervention for patients with malignant melanoma significantly increased lymphocyte percent and natural killer cell numbers and cytotoxic activity, and decreased the percent of helper T cells (Fawzy, Kemeny, Fawzy, Elanshoff, Morton, Cousins, and Fahey, 1990). In this study, affective measures such as anger, and depressed and anxious mood showed significant correlations with immune cell changes. In sum, this and other studies show that psychosocial interventions can have an impact on biological factors, which can be correlated with changes in psychological and emotional factors.

To our knowledge there have been no reported results of psychosocial interventions' effect on variables that capture the interaction between biological and psychological factors such as sickness behavior. Sickness behavior symptoms may be a more appropriate target for intervention in breast cancer survivors, as it encompasses both physical and depressive symptoms that continue to negatively impact quality of life. The question of whether or not it is possible to alter sickness symptoms with a cognitive behavioral stress management intervention still remains unresolved and providing an answer is a main objective of the current study. Although no interventions to date have shown an impact on the inflammatory cytokine network, effects on related immune

variables suggest that it may be through changes of inflammation markers that psychosocial interventions impact psychological factors.

CHAPTER II

Rationale and Objectives

Research now shows that sickness behavior is a well-established physiological response to infection that encompasses both depressive and illness symptoms (Kelley, Bluthe, Dantzer, Zhou, Shen, Johnson, and Broussard, 2003). The assessment of sickness behavior as a constellation of physical and psychological symptoms can have added value to health psychology research, especially in medical populations. Although sickness behavior is an adaptive behavioral strategy to help the organism restore its homeostatic balance after illness, if it is maintained long term, it can be detrimental to the organism and negatively impact quality of life (Charlton, 2000). A psychosocial intervention in breast cancer survivors may be able to reduce this constellation of symptoms and improve quality of life over time. Substantial progress has been made in establishing the role of pro-inflammatory cytokines in inducing sickness symptoms. The current study has three primary goals: 1) to develop a standardized instrument to assess sickness behavior and its biological correlates, 2) to specifically examine the effects of a CBSM intervention and relaxation training on sickness behavior, and 3) to determine the pro-inflammatory cytokine mechanisms mediating the effects of the intervention on sickness behavior.

The first goal of the study stems from recent psychoneuroimmunology findings that highlight the connection between psychological and biological processes. Such research discourages the use of independent measures to characterize emotional and

physical distress in patients with medical illnesses, and points to the clinical utility of a broader sickness behavior measure (Raison and Miller, 2003). Despite the prevalence of sickness behaviors in medical populations, to our knowledge there are no standardized instruments that assess the whole constellation of sickness behavior symptoms. This study aims to develop such a measure of sickness behavior using items from questionnaires typically used in cancer research. Selection of items from these questionnaires will be based on theoretical conceptualizations of sickness behavior symptoms (see Kelley et al., 2003 and Dantzer, 2001). We expect that this measure will add practical value to the research community, as it will reduce the time constrains imposed upon research participants. A sickness behavior measure will also add clinical value, as it will conjointly target symptoms of both physical and emotional distress in cancer patients that may stem from a similar biological basis (i.e., inflammation). We hypothesize that depression will only be a component of sickness behavior, and that our sickness behavior measure will be uniquely correlated to immune and endocrine measures relevant to breast cancer.

A second aim of the current study is to try and determine whether a cognitive behavioral stress management intervention and relaxation training can change the progression of sickness behavior in breast cancer survivors. We hypothesize that the current intervention will be effective in reducing both depressive (i.e., psychological) and neurovegetative (i.e., physical) symptoms in breast cancer survivors, which will translate into less sickness behavior. The current psychosocial intervention may be especially relevant to sickness behavior for several reasons. First, relaxation training is an important component of the intervention, and previous research has shown its benefit in the

management of illness related symptoms such as pain in medical populations. Second, cognitive restructuring, another important component of the intervention, has received extensive validation as an empirically supported treatment for depression which shares many overlapping symptoms with sickness behavior. Finally, it focuses on interactions between physical and psychological processes that occur as a response to stress, and sickness behavior is based on this interaction. Thus, through relaxation training, cognitive restructuring, and by targeting the mind-body connection, the current CBSM intervention may be able to alter both physical and psychological factors in cancer recovery and reduce the tendency to experience sickness behavior in breast cancer survivors in the long term.

The final goal of this study is to determine whether the effects of the intervention on sickness behavior are mediated by changes in pro-inflammatory cytokine activity. In the context of breast cancer increased inflammatory activation can occur as part of the neoplasia itself or as a consequence of cancer treatment. We selected two markers of immune activation for inclusion in this study: TNFα and IL-6. TNFα and IL-6 are cytokines that play an important role in initiating inflammatory processes. We hypothesized that those breast cancer survivors who are less able to reduce inflammation levels after treatment may be more vulnerable to a poor recovery after cancer diagnosis and treatment. We expect that this will be evidenced by more sickness behavior. It will be determined if pre- to post-intervention changes in pro-inflammatory cytokines are predictive of changes in sickness behavior over time.

The effects of a CBSM intervention on sickness behavior have never been examined in the context of breast cancer. Furthermore, no research to our knowledge has

examined the pro-inflammatory cytokine mechanisms of intervention effects in a population of breast cancer survivors.

CHAPTER III

Aims and Hypotheses

Specific Aim 1

Develop a psychometric measure of sickness behavior using questionnaire items typically used in breast cancer research.

Hypothesis 1

It is hypothesized that items will either cluster in a unique factor that will assess the sickness behavior symptom constellation or in a two-factor cluster assessing the two different dimensions of sickness behavior: physical and psychological. Refer to Table 1 for specific symptoms hypothesized to potentially load on each factor.

We expect that this measure of sickness behavior will be highly correlated with depression scales, but will however be distinctly different.

Specific Aim 2

The second aim of this research is to determine whether sickness behavior and each of the sickness symptom clusters (i.e., physical and psychological) uniquely correlates with relevant endocrine and immune measures for breast cancer at baseline and over time.

Hypothesis 2

2.1 It is hypothesized that women who report greater levels of sickness symptoms and greater levels of physical and psychological sickness symptom clusters, will have higher levels of stress hormones (i.e., cortisol) at baseline and over time

2.2 It is hypothesized that women who report greater levels of sickness symptoms and greater levels of physical and psychological sickness symptom clusters, will have higher levels of pro-inflammatory cytokines (i.e., IL-6 and TNF-alpha) at baseline and over time.

2.3 The physical symptom cluster is expected to show stronger correlations with biological (i.e., endocrine and immune) variables than the psychological cluster of symptoms.

Specific Aim 3

Determine the effectiveness of a group-based, CBSM intervention in reducing sickness behavior symptoms in general and each of the two different symptom clusters of sickness behavior symptoms (i.e., physical and psychological) in primary early- to middle-stage breast cancer survivors.

Hypotheses 3

3.1 We expect lower levels of sickness symptoms in the experimental group when compared to the control group post intervention, and no significant differences between the groups at baseline. We also expect greater reductions (i.e., bigger negative slope) from pre to post-intervention, and 6 and 12 month follow up, in the experimental group when compared to the control group.

3.2 We expect lower levels of physical sickness symptoms in the experimental group when compared to the control group post intervention, and no significant differences between the groups at baseline. We also expect greater reductions (i.e., bigger negative slope) from pre to post-intervention, and 6 and 12 month follow up, in the experimental group when compared to the control group.

3.3 We expect lower levels of psychological sickness symptoms in the experimental group when compared to the control group post intervention, and no significant differences between the groups at baseline. We also expect greater reductions (i.e., bigger negative slope) from pre to post-intervention, and 6 and 12 month follow up, in the experimental group when compared to the control group.

Specific Aim 4

Determine whether the effects of the CBSM intervention on sickness behavior and each of the sickness symptom clusters (i.e., physical and psychological) are mediated by changes in levels of pro-inflammatory cytokines (i.e., IL6 and TNF-alpha)

Hypotheses 4

4.1 It is hypothesized that the effects of the CBSM intervention on cluster of sickness behavior symptoms and each of the sickness symptom clusters (i.e., physical and psychological) will be mediated by changes in levels of pro-inflammatory cytokines (i.e., IL6 and TNF-alpha).

Specific Aim 5

Determine whether the effects of the CBSM intervention on sickness behavior and each of the sickness symptom clusters (i.e., physical and psychological) are mediated by changes in levels of urinary cortisol.

Hypotheses 5

It is hypothesized that the effects of the CBSM intervention on cluster of sickness behavior symptoms and each of the sickness symptom clusters (i.e., physical and psychological) will be mediated by changes in levels of urinary cortisol.

CHAPTER IV

Methods and Procedures

Overview

This study was done as part of a parent study Coping After Treatment with Breast Cancer (NIH#, PI: Antoni, Project Leaders: Ironson, Duran). In the parent study, subjects (early stage breast cancer patients post adjuvant treatment) were randomly assigned to a CBSM intervention or a control group. Subjects were randomized by cohort in alternating fashion. We used already collected blood and urine to measure immune and endocrine parameters. Data (psychosocial variables, endocrine variables and immune variables) was collected at baseline, post intervention, and at six and 12 months follow up.

Participants

The participants in this study were a volunteer sample of 99 early to middle stage (Stages I to III) breast cancer survivors recruited through a number of Dade and Broward physicians and cancer organizations. Most women contacted the study after receiving a letter from the American Cancer Society or their physician. Other women responded to flyers in medical offices as well and advertisements in the local newspaper. Women interested in participating were interviewed over the phone to assess for eligibility. Breast cancer survivors were recruited during a period between 3 and 12 months after completing adjuvant therapy for breast cancer. Exclusion criteria included a previous diagnosis of cancer, age over 65, metastatic stage breast cancer, acute or chronic

comorbid medical condition with known effects on the immune system (e.g., HIV infection, autoimmune disease, history of endocrine disorders), patients taking medications that act directly as immunomodulators (e.g. interferons), active treatment for cancer (excluding Tamoxifen), major psychopathology and substance dependence in the past year, history of inpatient psychiatric treatment and previous participation in this study or similar study at the University of Miami. Other information such as diagnosis date, staging at time of diagnosis, nodal involvement, surgery type and date, adjuvant treatment received, and medications (i.e., Tamoxifen) and time taking them was also gathered during the phone eligibility assessment.

Procedures

Once a woman agreed to participate in the study and was considered eligible, she was mailed a questionnaire packet and scheduled to come in for assessment. Women were randomized to conditions after returning the questionnaire in order to prevent any influence of knowing their condition assignment on the questionnaire responses. Women were randomized to either a 10-week CBSM intervention or a control condition of a 1-day seminar containing an abbreviated CBSM intervention.

Participants in both conditions met in groups of 3 to 6 women in a large conference room either at the University of Miami Coral Gables Campus or in Broward's Plantation General Hospital. All conference rooms were furnished with tables and chairs. Cushioned mats for the relaxation exercises were provided. Two female therapists trained in the intervention content and CBSM techniques led intervention and control groups.

Participants were then asked to come back for three additional assessment time points corresponding to 3 months, 6 months, and 12 months follow up. At each

assessment time point psychosocial packets were mailed for participants to bring in at the time of the assessment. Urine containers were also mailed to participants to collect urine starting the night before of the assessment. All participants had venous blood samples collected at the time of the assessment between 4:00 p.m. and 6:00 p.m. by a trained phlebotomist. Specimens were kept at room temperature and transported to the laboratory to be analyzed the following day. Blood samples were collected in five sterile evacuated tubes: two green-topped tubes containing sodium heparin (Vacutainer, Cat. #6489, Beckton-Dickinson, Rutherford, NJ); two lavender tubes containing the anticoagulant ethylene diamine tetra acetate (EDTA); and one red tube with no anticoagulant added. Plasma was removed from samples in the green-topped tubes and stored at –20 C until use. Samples collected in the red-topped tube were allowed to clot at 23 C for 30 minutes, at which time serum was separated and stored at –20 C until use for immune and endocrine parameters.

Intervention group. The CBSM intervention consisted of ten, 2 hour weekly sessions of 3 to 6 women. Each of the ten-week sessions contained a relaxation-training component and a didactic information component. The relaxation component consisted of the instruction and practice of a different relaxation technique each week. These included progressive muscle relaxation (Bernstein & Borkovec, 1973), autogenics (Luthe, 1969), guided imagery (Mason, 1986), meditation (Benson & Klipper, 1976) and abdominal breathing (Davis, Eshelman & McKay, 1988). The didactic component included information on physiological effects of stress, recognizing and evaluating emotional, physical, and behavioral responses to stress, identifying negative automatic thoughts and cognitive distortions, cognitive restructuring, adaptive coping responses, anger

management, utilizing social support, assertiveness techniques and discussion of goals and values.

Participants were asked to complete homework between sessions and to practice relaxation techniques. The homework included short exercises that reviewed the previous week's material, and a sleep and relaxation practice log. All sessions were both audio- or video-taped and then discussed with the therapist and a supervisor.

Control group. The control group consisted of a condensed, one-day seminar format presentation of the CBSM intervention didactic and relaxation components. The one-day seminar was offered to the control participants within 10 weeks of the first assessment and generally lasted approximately 5-6 hours. Women attending received an abbreviated presentation of the didactic components from the 10-week program and 4-5 relaxation techniques.

Measures

Control Measures

A number of variables that can affect immune functioning were examined as control variables. These included demographic variables, health behavior items (e.g., alcohol, cigarette and drug use), and all pharmacologic treatments. Medical data consisted of stage of cancer at diagnosis, extent of surgery, time since treatment, and nature of adjuvant therapy. Data on adjuvant therapy [e.g., chemotherapy type, dosage and duration; radiation), axillary node involvement, TNM staging, estrogen receptor status, surgery (mastectomy, lumpectomy), and the commencement/cessation of any other medical procedure was obtained from the initial screening interview. Medications commonly used that could have

significant immunomodulatory effects (i.e., Tamoxifen, beta-blockers, diuretics, antihistamines and analgesics) were assessed at each time point.

Behavioral Measures

Sickness Behavior. A sickness behavior composite score will be designed to measure the constellations of motivational and behavioral symptoms that have been typically found to accompany illness and inflammation. The composite will be constructed using items obtained from the following depression and cancer well-being questionnaires (See appendix B for the original questionnaires):

1) The Center for Epidemiologic Studies on Depression Scale (CES-D) assesses affective and vegetative symptoms of depression measured by 20-item rated on a scale from 1 (rarely) to 4 (most of the time) (Radloff, 1977). The CES-D is a measure of depressive symptoms over the past week. Coefficient alpha ranges from .85 to .90, test-retest reliability is adequate for a state measure (r = .31 - .54), and concurrent validity with both clinical depression and depression-related self-report measures is good (Radloff, 1977). 2).

2) The Beck Depression Inventory (BDI). This is a 21-item questionnaire that assesses the cognitive, affective, and vegetative symptoms of depression. Specific symptoms are assessed over the past week. Items are rated on a 4-point scale from 0 to 3 (Beck, Rush, Shaw, and Emery, 1979). The BDI is a well validated and widely used measure of depression (Derogatis, 1983).

3) The Functional Assessment of Cancer Therapy -Breast (FACT-B). This is a 44-item self- report instrument designed to measure multidimensional quality of life (QL) in patients with breast cancer. It assesses well-being in five different areas of life including:

Physical, Social/Family, Emotional, Functional, and additional concerns. The Physical well being subscale includes 7 items that assess lack of energy and pain among other symptoms. The Social/Family well being subscale contains 7 items that assess social support from family, partner, and friends in relation to the cancer diagnosis. The Emotional well being subscale contains 6 items that assess sadness, worry, and coping. The Functional well being subscale contains 7 items that target quality of life and occupational life. Finally, the Additional Concerns subscale contains 7 items that assess specific symptoms of cancer treatment such as swollen arms and hair loss. All symptoms are assessed over the past seven days. Items ask participants to rate on a 5-point rating scale from 1 (not at all) to 5 (very much). The internal consistency for the FACT-B total score is high (alpha = .90), with subscale alpha coefficients ranging from .63 to .86. Evidence supported test-retest reliability, as well as convergent, divergent, and known groups validity (Brady, Cella, Mo, Bonomi, Tulsky, Lloyd, et al., 1997).

Instrument Development. The goal was to select items from the above scales that parallel the theoretical conceptualization of sickness behavior as proposed by Kent and colleagues (1992), Dantzer (1999), and Miller (2003). The specific symptoms targeted included anhedonia, fatigue, psychomotor slowing, appetite loss, social disinterest, low libido, sleep disturbances, cognitive dysfunction, and increased sensitivity to pain. Items were also selected to match items from an unpublished scale constructed by Bower and colleagues used in previous studies with breast cancer survivors (See Appendix A). A preliminary view of targeted symptoms for the sickness behavior scale can be found in Table 1.

Physiological measures

Urinary Cortisol. We will measure urinary 15-hr whole body output of cortisol at each time point. Subjects were instructed to collect their urine from 6 p.m. in the evening to 9 a.m. the next morning (i.e., 15 hours) by voiding into a cup and then transferring the urine into marked plastic containers containing 700 mcg. of the preservative sodium metabisulfite, and to keep the container refrigerated. Subjects were asked to refrain from large amounts of substances affecting hormone levels (e.g. caffeine and cold medications) and to note how much of certain substances they consumed during the 15 hour collection (e.g. caffeine, bananas, chocolate). Fifteen-hour urines were obtained rather than 24-hour urines because our lab has found that compliance is better if subjects start collecting urine during non-working hours. Specimens were processed and assayed at the University of Miami, Department of Psychiatry Biochemistry/Neuroscience research laboratory. After each sample was delivered to the laboratory, the volume of urine was noted and aliquots (approximately 10 ml.) were made and frozen at -70 for later assay. Hydrochloric acid (HCl) was added to the aliquot to be used for the measurement of urinary hormones as a further method of preservation. After thawing, specimens were adjusted to a pH of 3.0. Cortisol was measured using the radioimmunoassay kit provided by DSL.

Pro-Inflammatory Cytokines. Cytokine assays were performed in duplicate in a single batch using commercially available ELISA kits and tne BioMek 2000 Robotic ELISA instrument (Beckman/Coulter, Miami, FL. The correlation between IL-6 and TNF-alpha will be calculated to determine whether the average of these two pro-

inflammatory cytokines can be used as an additional marker of pro-inflammatory cytokine activity.

CHAPTER V

Statistical Analyses

Preliminary analyses

First, data was checked for outliers and cleaned substituting a maximum of two outliers for the closest highest or lowest number for the specific variable. Second, assumptions of statistical tests were verified. A frequency distribution was done on all variables to determine skewness and kurtosis and the need for any transformations. Descriptive statistics were computed for the entire sample for specific variables within the following areas: demographic characteristics (i.e., age, ethnicity, income, education, employment, and marital status), disease severity (i.e., stage, number of positive lymph nodes, menopausal status, and surgery type, and adjuvant treatment), health behaviors (i.e., caffeine intake, alcohol use, tobacco use, and drug use), and relevant psychological factors (i.e., depression, and guilt measures).

Missing Data

Reasons for missing data included: participants' missing appointments, not being able to perform blood assays within the specified amount of time, and random lab errors (machines malfunctioning) which precluded accurate results. Any missing data due to difficulties in the lab was considered completely independent of the participants and treated using listwise deletion. As for missed appointments, data checks were performed to determine whether participants who missed appointments differed on any biological or psychological measures from those who did not. Analyses of variance as well as

chi-square tests were used to determine whether there were significant differences between completers and non-completers in order to understand the generalizability of results.

Analyses using longitudinal data were analyzed using latent growth-curve modeling which has the ability to use all available data by using a process called full information maximum likelihood (FIML). FIML uses all available data for each person, estimating missing information from relations among variables in the full sample. Confirmatory factor analysis and structural equation models were performed using FIML as implemented by Mplus. Time was recoded to reflect number of months since study entry. Statistics will be interpreted to explain whether the calculated time slopes are significantly different from zero.

Control Variables

Zero-order Pearson correlations were calculated between potential control variables in the areas above (i.e., demographic characteristics, disease severity, and health behaviors) and the outcome variable (i.e., Sickness Behavior). Variables significantly correlated with the outcome variables at baseline (i.e., endocrine and immune measures, and sickness symptoms) ($p = < .10$), were tested independently as predictors of specific outcomes in simple conditional growth models. Only variables that continued to predict the specific outcome over time were accounted for in growth models containing the predictor (i.e., group condition or biological markers).

Special attention was paid to the use of hormonal medications (e.g., Tamoxifen, Arimidex). Animal research has shown that ovarian hormones such as estradiol can modulate immune system activity and responsiveness to cytokines in female mammals

(Butera, Doerflinger, and Roberto, 2002). Tamoxifen use in cancer patients has also been associated with depression (Raison and Miller, 2003). To account for this potential confounding factor, the number of participants using these types of medications was determined and differences between women using versus not using medications on predictive variables (i.e., cytokines, cortisol, and sickness behavior) were explored.

Analyses of variance as well as chi-square tests were also used to determine whether there were systematic differences between the experimental and control groups at baseline that needed to be accounted for in statistical analysis using experimental condition as predictor (i.e., intervention vs. control).

Statistical Analyses for Aim 1: Sickness Behavior Measure

Items from the BDI, FACT-B, and CES-D were selected to match theoretical accounts of sickness symptoms by Miller (2003) and Dantzer (1999). Tests of multivariate normality were performed on the final BDI, CES-D and FACT-B selected items. Logarithmic transformations were used to normalize distributions of specific item sets and used in the final item set for consistency. Responses to the selected item set were analyzed by means of a confirmatory factor analysis using M-plus. A Chi-square difference test was used to determine whether a unitary factor or a two-factor model better describes the sickness behavior item set. Mean scores were calculated for the final item set by recoding items to match in range and in the description of symptoms. Factor scores and mean scores of sickness behavior and each of the symptom clusters were correlated and mean scores used as indicators of sickness behavior.

Reliability analysis using SPSS software was used to test the internal consistency of the measure. Time inter-correlations were used for test-retest reliability. Convergent

validity was assessed using standard depression scales to determine correlations with the sickness behavior measure at baseline. Biological markers were also used to obtain validity coefficients in order to further validate the sickness behavior measure.

Statistical Analyses for Aim 2: Endocrine and Immune Correlates of Sickness Behavior

Logarithmic transformations were used to normalize distributions of pro-inflammatory cytokines (i.e., IL-6 and TNF-alpha) and cortisol. In order to determine whether sickness behavior and biological markers were correlated at baseline, zero-order Pearson correlations were calculated between baseline indicators of sickness behavior (i.e., means scores of physical and psychological symptom clusters) and baseline levels of IL-6, TNF-alpha, and urinary cortisol.

A conditional latent curve growth model (LGM), a form of structural equation modeling, was used to determine the correlation between baseline levels of biological markers (IL6, TNF-alpha, and urinary cortisol) and changes in physical and psychological sickness behavior over the four assessment time points. LGM was also used to test the relationship between changes in the trajectory of pro-inflammatory cytokines and cortisol and changes in the trajectory of sickness behavior. As implemented in Mplus, LGM computes the trajectory of change over repeated measurements for each participant. Differences in the properties of these trajectories are then predicted from relevant variables (i.e., baseline levels and changes in IL6, TNF-alpha and cortisol). The properties of interest are the intercept (the trajectory's starting value) and slope of change over repeated measurements. These properties were modeled from data at Times 1, 2,3, and 4. The main predictors were either baseline levels or

change scores of each of the pro-inflammatory cytokines (i.e., Il6 and TNF-alpha) and cortisol. For the slope, loadings represent the time linked to each assessment point: 0 represents the initial assessment (i.e., T1), 3 represents the 3-months elapsed until de second assessment (i.e., T2) , 9 represents the time elapsed until the third assessment (i.e., T3), and 15 represents the 15-months elapsed until the fourth and last follow up assessment (i.e., T4). The structure of these two models are presented in Figures 5a and 5b.

Several indexes of model fit are reported for each model of sickness behavior as predicted by biological markers including chi-square (in which the ideal is a nonsignificant chi-square); comparative fit index (CFI), for which values above .95 indicate a good fit; the root mean square error of approximation (RMSEA), for which values below .06 indicate a good fit; and the standardized root-mean square residual (SRMR), for which values below .10 indicate good fit (Kline, 2005). Specific effects were tested with the *z* statistic, with a .05 two-tailed significance level.

Statistical Analyses for Aim 3: CBSM effects on Sickness Behavior

The intervention effects on sickness behavior were tested both short-term (i.e., over the initial and post-intervention assessment) and over the long term using data from all four assessment time points. Linear regression analyses with SPSS statistical software was used to test short-term intervention effects. Long-term intervention effects on sickness behavior were tested by LGM as implemented with Mplus. As in analyses done to evaluate the second aim of this study, LGM computed the trajectory of change over repeated measurements for each participant. The differences in the intercept and slope of change over repeated measurements of these trajectories were modeled from data at

Times 1, 2,3, and 4 and then predicted from the experimental condition. Thus, in this model experimental condition was main predictor (i.e., intervention versus control condition) coded as 0 versus 1. For the slope, loadings represent the time linked to each assessment point: 0 represents the initial assessment (i.e., T1), 3 represents the 3-months elapsed until de second assessment (i.e., T2) , 9 represents the time elapsed until the third assessment (i.e., T3), and 15 represents the 15-months elapsed until the fourth and last follow up assessment (i.e., T4). The structure of this model is presented in Figures 6.

The conditional growth model is represented by the following equations where Time 1 to Time 4 Sickness behavior scores derived from the factor analysis represent the outcome variable at Level 1, and group randomization (i.e., experimental or control) represents the Level 2 predictor of initial levels and change trajectory of sickness behavior.

Level 1: y_{ti} (Sickness Behavior) $= \pi_{0i} + \pi_{1i}$ (Time) $+ e_{ti}$

Level 2a: $\pi_{0i} = \beta_{00} + \beta_{01}$*(condition) $+ r_{0i}$

Level 2b: $\pi_{1i} = \beta_{10} + \beta_{11}$*(condition) $+ r_{1i}$

Where:

y_{ti} = Sickness Behavior score for participant i at time point t
π_{0i} = Sickness Behavior score at entry to the study for the ith participant
π_{1i} = Slope representing linear change in Sickness Behavior for participant i
e_{ti} = Residual term for participant i at time t
β_{00} = Group average initial Sickness Behavior score
β_{01} = Effect of group assignment (i.e. Experimental/Control) on initial Sickness Behavior average score (expected to be not significant)
β_{10} = Average linear change in Sickness Behavior per month
β_{11} = Effect of group assignment (i.e. Experimental/Control) on linear change in Sickness Behavior

Similar indexes of model fit are reported for this model of sickness behavior as predicted by condition including chi-square (in which the ideal is a nonsignificant chi-square); comparative fit index (CFI), for which values above .95 indicate a good fit; the root mean square error of approximation (RMSEA), for which values below .06 indicate a good fit; and the standardized root-mean square residual (SRMR), for which values below .10 indicate good fit (Kline, 2005). Specific effects were tested with the *z* statistic, with a .05 two-tailed significance level.

Statistical Analyses for Aims 4 and 5: Mediation of CBSM Effects by Pro-inflammatory Cytokine and Urinary Cortisol

Baron and Kenny (1999)'s mediation model guided assumptions to determine whether the effects of the CBSM intervention on sickness behavior were mediated by pro-inflammatory cytokines (i.e., IL-6, TNF-alpha) and urinary cortisol. According to their model, the following hypothesis were expected to hold true: 1) Experimental assignment would predict sickness behavior; 2) Experimental assignment would predict pro-inflammatory cytokine activity/urinary cortisol; and 3) The effects of experimental assignment on sickness behavior will become non significant when the change in pro-inflammatory cytokine activity/urinary cortisol levels are included in the model. The mediation hypotheses were tested using longitudinal data from the first time point to the final follow up assessment at 15 months by LGM as implemented by Mplus. Similar analyses were done for each cytokine separately (i.e., IL-6 and TNF-alpha) and cortisol using similar latent growth models as the ones described in Aims 2 and 3.

Three different 2 level equations models will be used to test these three mediation hypotheses as follows:

1) Level 1: y_{ti} (Sickness Behavior) $= \pi_{0i} + \pi_{1i}$ (Time) $+ \pi_{2i}$ (Time^2) $+ e_{ti}$

Level 2a: $\pi_{0i} = \beta_{00} + \beta_{01}$*(condition) $+ r_{0i}$

Level 2b: $\pi_{1i} = \beta_{10} + \beta_{11}$*(condition) $+ r_{1i}$

Note: This model is equivalent to the one presented above in analyses for aim 3

2) Level 1: y_{ti} (Cytokine/Cortisol)' $= \pi_{0i}' + \pi_{1i}$ (Time)' $+ e_{ti}$

Level 2a: $\pi_{0i}' = \beta_{00}' + \beta_{01}$*(condition) ' $+ r_{0i}$

Level 2b: $\pi_{1i}' = \beta_{10}' + \beta_{11}$*(condition) ' $+ r_{1i}$

Where:

y_{ti}' = Cytokine/cortisol level for participant i at time point t
π_{0i}' = Cytokine/cortisol level at entry to the study for the ith participant
π_{1i}' = Slope representing linear change in Cytokine levels for participant i
e_{ti} = Residual term for participant i at time t
β_{00}' = Group average initial
β_{01}' = Effect of group assignment (i.e. Experimental/Control) on initial Cytokine/cortisol average level (expected to be not significant)
β_{10}' = Average linear change in Physical Sickness Behavior per month
β_{11}' = Effect of group assignment (i.e. Experimental/Control) on linear change in cytokine/cortisol levels

3) Level 1: y_{ti} (Sickness Behavior) $= \pi_{0i} + \pi_{1i}$ (Time) $+ \pi_{2i}$ (Time^2) $+ e_{ti}$

Level 2a: $\pi_{0i} = \beta_{00} + \beta_{01}$*(condition) $+ \pi_{1i}' + r_{0i}$

Level 2b: $\pi_{1i} = \beta_{10} + \beta_{11}$*(condition) $+ \pi_{1i}' + r_{1i}$

Level 2c: $\pi_{2i} = \beta_{20} + \beta_{21}$*(condition) $+ \pi_{1i}' + r_{2i}$

Where:

y_{ti} = Sickness Behavior score for participant i at time point t
π_{0i} = Sickness Behavior score at entry to the study for the ith participant
π_{1i} = Slope representing linear change in Sickness Behavior for participant i
π_{2i} = Slope representing quadratic change in Sickness Behavior for participant I
e_{ti} = Residual term for participant i at time t

β_{00} = Group average initial Sickness Behavior score

β_{01} = Effect of group assignment (i.e. Experimental/Control) and change in cytokine/cortisol levels over time on initial Sickness Behavior average score (expected to be not significant)

β_{10} = Average linear change in Sickness Behavior per month

β_{11} = Effect of group assignment (i.e. Experimental/Control) and change in cytokine/cortisol levels over time on linear change in Sickness Behavior

CHAPTER VI

Results

Preliminary Analysis

Participants in this study were 125 female cancer patients who had already completed their treatment for breast cancer. Seventy women were assigned to the intervention group, which met once a week for ten weeks. The control group comprised 55 women who attended a one-day seminar. One hundred six participants (n= 48 & n= 58, in the control and experimental groups respectively) had completed psychosocial data post-intervention (i.e., 3 months after baseline for both groups). Of those participants providing psychosocial data post-intervention, 96 (44 control and 52 experimental) returned for their assessment at the 6 months follow up period, and of those 83 (38 control and 45 experimental) returned for their final assessment at 12 months follow up.

Sample Characteristics

The mean age of the entire sample at baseline was 50.1 (SD = 7.74). The race/ethnicity of the sample was as follows: 65% of the sample was Caucasian, 24% Hispanic, 6% African American, 2.5% Asian American, and 2.5% Caribbean Islander. The sample as a whole was highly educated with approximately 73% with college education. Sixty-seven percent of the sample was employed full or part-time. In terms of marital status, 65% of the sample was married, 20.5 % was

separated or divorced, 13% was single, and 1.5% widowed. 71% had children. Table 2 summarizes demographic breakdowns by group.

Women with Stage I and II breast cancer both accounted for approximately 42% of the sample (n= 42 and n= 42 respectively). Stage III breast cancer was diagnosed in approximately 11% (n= 11) of the sample. Three percent of the women were diagnosed with Stage 0 in situ carcinoma (n= 4). The majority of women had no positive lymph nodes (59%), although the range of number of nodes varied from 0 to 33 (M = 2.3 nodes, SD = 5.4). Thirty six percent (n=38) of the sample received a mastectomy, 5% (n=5) a bilateral mastectomy, and 60% (n=64) received a lumpectomy. The majority of the sample had received some type of adjuvant therapy (i.e., chemotherapy, radiation). At the beginning of the study, 66% (n= 83) of the sample had received radiation therapy, and 59% (n=74) had received chemotherapy. Over the course of the study, 60% (n= 75) of the women were using Tamoxifen (an antineoplastic medication). Women using Tamoxifen did not differ from women not using this medication in any of the predictive variables including biological markers and sickness behavior (ps > .10). See Table 3 for a breakdown of disease and treatment variables in the intervention and control groups.

The mean score of general depression measured according to the CES-D scale was in the depressed range (M = 31.9, SD = 10.8). With respect to health habits at baseline, 94% of the sample participants were not-smokers. Half of the sample (50 %) did not consume any alcoholic drinks per week. With regard to caffeine use, the majority of the sample (61%) reported drinking 4 or less

caffeinated beverages (i.e., coffee, tea, cola) per week. With respect to drug use, only 3% of the sample reported smoking marihuana during the week (n =3), and none of the women reported using any other substance (i.e., cocaine, sedatives, amphetamines). In general the sample seemed mindful with regard to the healthy behaviors. Refer to Table 4 for a breakdown of the means and standard deviations of health behaviors in each group.

Group Baseline Differences

One way ANOVA and Chi Square analyses revealed that the experimental and control groups did not differ significantly in demographic characteristics at baseline including age, education in years, marital status, number of children, ethnic background, and employment status (all ps > .10). There were also no significant differences between the groups in baseline CES-D depression scores (p > .10). In terms of disease severity, group comparisons revealed no significant differences between the experimental and control groups in breast cancer stage, number of positive lymph nodes, adjuvant treatment type (i.e., chemotherapy, and radiation), surgery type, Tamoxifen use, and menopausal status (all ps > .10). Finally in terms of health behaviors, group comparisons revealed no significant differences between the groups in alcohol consumption, caffeine use, cigarette smoking, and drug use (all ps > .10).

Differential Dropout

Follow up data was missing for 9 of the 67 original participants who were assigned to the Intervention; these participants did not return for their 10-week follow up. Of the 58 participants who returned for their Time 2 assessment, 52

completed the 6-month follow up assessment and 45 completed the final 12-month follow up assessment after the intervention. For the control group, 7 of the 55 original Controls did not complete the 10-week follow up. Of the 48 control participants who returned for their Time 2 assessment, 44 completed the 6-month follow up assessment and 37 completed the final 12-month follow up assessment.

To determine whether systematic differences were related to whether participants returned for follow-up, those who did and those who did not return, were compared on a number of demographic and health-related variables. Results indicated that completers did not differ from non-completers in age, employment status, ethnicity, and number of children (all ps > .10). A trend was observed for marital status (X^2 = 8.6, p = .071) and education level (F = 3.0, p = .09), such that completers for follow-up were more likely to be married, less likely to be divorced, and slightly more educated (M = 15.3, SD = 3.4) on average than non-completers (M = 13.8, SD = 3.4).

In terms of health behaviors, completers did not differ from non-completers in drug use, and alcohol use (all ps > .10). However non-completers were significantly more likely to smoke (M = 4.6, SD = 9.2) than completers (M = .21, SD = 1.6). There was a trend for caffeine consumption, such that completers (M = 5.1, SD = 2.9) were more likely to drink caffeinated beverages than non-completers (M = 2.3, SD = 6.2). With respect to disease indicators, there were no differences according to the number of positive lymph nodes, chemotherapy, Tamoxifen use, menopausal status, surgery type, or stage

(all ps > .10). However, non-completers were more likely to have received radiation treatment than completers (X^2 = 7.6, p = .02). Completers were also significantly less depressed (M = 31.0, SD = 9.9) than non-completers (M = 37.3, SD = 13.7).

In terms of relevant outcome variables, completers did not differ from non-completers in sickness behavior scores, pro-inflammatory cytokine levels and urinary cortisol levels at baseline (all ps > .10). However, there was a trend for the physical component of sickness behavior, such that non-completers (M = .97, SD = .71) were more likely to report physical symptoms of sickness than completers (M = .72, SD = .52).

Aim 1: Sickness Behavior Measure

1) Selection of Items. Items from the BDI, FACT-B, and CES-D were selected to match theoretical accounts of sickness symptoms by Miller (2003) and Dantzer (1999). A review of theoretical conceptualizations of sickness symptoms by these authors yielded the following 10-symptoms: Anhedonia, depressed mood, cognitive dysfunction, social disinterest, fatigue, low libido, poor appetite, somnolence, sensitivity to pain, and malaise. Although both Dantzer and Miller also include psychomotor retardation as a representative symptom of sickness behavior, it was decided to exclude this specific symptom given the self-report nature of the measure. Between 1 and 4 items from one or more of the standardized questionnaires (i.e., BDI, CES-D, FACT-B) were selected to represent each of the above-mentioned symptoms. Refer to table 5 for the final set

of items selected from the BDI, CES-D, and FACT-B and the sickness behavior symptoms they assess.

2) Normative Data. Prior to conducting confirmatory factor analytic procedures, and considering the sensitivity of this analysis to the distributional characteristics of the data set (N = 122), tests of multivariate normality were performed on the 22 BDI, CES-D and FACT-B selected items. Logarithmic transformations were used to normalize distributions of specific item sets and used in the final item set for consistency. Two of the 22 originally selected items (i.e., FACT-B "I am able to work" and "I am forced to spend time in bed") were excluded from the CFA as they continued to have elevated kurtosis after log-transformations (> 6). One additional item (BDI 18 "How has your appetite been this week?") was also excluded from the analysis, as it showed no variability in the sample (i.e., all values = 0). Both the symmetry (skewness) and the flatness (kurtosis) of the remaining 19 items were within normal limits.

3) Confirmatory Factor Analysis (CFA). A CFA using Mplus for Windows was conducted based on hypothesized accounts of sickness behavior. The specification of the model began by defining two latent factors called Physical and Psychological to account for the hypothesized two-factor structure of sickness behavior. The Physical latent factor was defined by eight observed indicator variables (sickness behavior items) whereas the Psychological latent factor was defined by 11 observed indicator variables as shown in Table 6. In order to test hypothesis 1, a chi square difference test was used to determine

whether observed data are consistent with a single (all items) or a two-factor (Psychological and Physical) measurement model of sickness behavior.

In order to compare the fit of the two-factor versus the one-factor model of sickness behavior, the variances and covariances of the two-factor model were standardized and set to one transforming the two-factor model into a one factor model with a perfect correlation between the Physical and Psychological latent factors. This allowed for a comparison of the two models using a Chi-square difference test. Several indexes of model fit are reported, including chi-square (in which the ideal is a nonsignificant chi-square); comparative fit index (CFI), for which values above .95 indicate a good fit; the root mean square error of approximation (RMSEA), for which values below .06 indicate a good fit; and the standardized root-mean square residual (SRMR), for which values below .10 indicate good fit (Kline, 2005).

The two factor model of sickness behavior was associated with a X^2 (144, N = 122) =214.67, $p < .01$) and fit indices as follows: CFI = .92, RMSEA = .063, and SRMR = .064. Factor loadings ranged from .40 to .84 and are listed in Table 7. The correlation between the Psychological and the Physical latent factors was high ($r = .81$, $p < .01$). The one factor model was associated with a X^2 (145, N = 122) = 241.94, $p < .01$) and fit indices as follows: CFI = .89, RMSEA = .074, and SRMR = .069. Factor loadings for the one-factor model ranged from .32 to .82 (refer to Table 7). Although both models had significant chi-squares, the two factor model had better indices of model fit than the single factor model. Furthermore, a Chi-square difference test 241.94 – 214.67 /(145-144) = 27.27 (p

< .01) showed that the two-factor model had a better fit for the data. Given these results, two different scores for sickness behavior, a physical composite and a psychological composite are used in all follow up analyses.

4) Sickness Behavior Mean Scores. In order to obtain sickness behavior mean scores, items from scales used to assess sickness behavior were recoded to standardize the composite of sickness behaviors based on a 4 point rating Lykert type scale, from 0 (not at all/none of the time) to 3 (quite a bit/very much of the time). Items from the BDI and the CES-D used a 4-point rating scale from 0 (not experiencing the specific symptom) to 3 (experiencing the symptom a lot of the time). Items from the FACT-B use a 5-point rating scale from 1 (not at all) to 5 (very much) and were therefore transformed into a scale of 1 to 4 by grouping the 4 and 5 point- ratings. Since items for all three scales ask participants to rate symptoms over the past week, the time frame of the measure is consistent for time. Positive items such as "I sleep well" were recoded into negative items. Mean scores where obtained by averaging all items belonging to each sickness behavior factor (i.e., physical and psychological).

Sickness behavior factor scores obtained from the CFA were correlated with mean scores to confirm their predictive value. Correlations between factor scores and mean scores were high for both physical ($r = .95$, $p < .01$) and psychological ($r = .96$, $p < .01$) sickness behavior composites suggesting that factor scores and mean scores could be used interchangeably. For a clear interpretation of results mean scores were used in subsequent analyses.

5) Validity and reliability. *Content validity* is the degree to which elements of an assessment instrument are relevant to and representative of the targeted construct for a particular assessment purpose (Haynes, Richard, and Kubany, 1995). Content validity is ordinarily to be established deductively, by defining a universe of items and sampling systematically within this universe to establish the test. For the current measure, selection of test items was based on reflecting all symptoms mentioned in current conceptualization of the sickness behavior construct (see Dantzer 1999; Raison and Miller 2003). In addition, the fact that experts in the field agree on the set of symptoms that define sickness behavior (i.e., anorexia, cognitive dysfunction, lack of energy) adds to the measure's content and construct validity.

Criterion-related validity was established with both psychological and biological measures. Validity coefficients showed a high convergent validity with two well established self-report depression scales, the BDI and the CES-D. Correlations were all significant at every assessment time point for both the physical and the psychological composite of sickness behavior with the BDI and CES_D respectively across time (all $\underline{p}$s $< .01$). Validity coefficients were also calculated for both composite scores of sickness behavior (i.e., physical and psychological) and two measures of pro-inflammatory cytokine activity (i.e., IL-6 and TNF-alpha). Convergent validity of the sickness behavior measure with biological measures was moderate. Multiple cross-lagged correlations showed that IL-6 was marginally associated with physical sickness symptoms at every follow up assessment (i.e., T1 with T2, T2 with T3 and T4, and T3 with T4) (see figure 1). Physical symptoms at baseline were also significantly related to IL-6 levels after 3-months ($\underline{r} = .30$, $\underline{p} = .04$) and after 15-months ($\underline{r} = .42$, $\underline{p} = .04$). TNF-alpha at baseline

was also correlated with physical sickness symptoms after 9-months (r = .27, p = .06) and after 15-months (r = .33, p = .03). The psychological index of sickness behavior did significantly correlate cross-sectionally with TNF-alpha at Time-3 (r = .37, p = .04). Also, TNF-alpha at Time-1 and at Time-3 predicted psychological symptoms at Time-4 (r = .27, p = .08 and r = .43, p = .02 respectively).

Although most correlation coefficients were marginal, sample size needs to be taken into account, as biological data was available only for less than half of the sample. Due to the sample size relationships between sickness behavior and cytokines could not be assessed for the experimental and control groups separately. As expected significant correlations across time points emerged mostly for the physical composite of sickness behavior while correlations between the psychological composite of sickness behavior and pro-inflammatory cytokines and cortisol were mostly non-significant.

Reliability was approached mainly as test-retest reliability as the same set of items was administered to the same sample of subjects over four different time points with time intervals between 3 and 6 months. *Test-retest* reliability of the two-factor model was moderate to high for both the physical and psychological composite scores of sickness behavior. Correlations for both subscales ranged between .62 and .75 across the four different assessment time points (all ps < .01).

Internal consistency was also assessed to evaluate the consistency of subjects' responses within the single-factor and the two-factor (i.e., physical and psychological) models of sickness behavior. Internal consistency for the one-factor sickness behavior model was fairly strong (α = .92). Internal consistency of the eight physical sickness

symptom items was also strong ($\alpha = .81$) and was comparable to that of the 11 items forming the psychological sickness behavior factor ($\alpha = .83$).

6) Descriptive analyses. Descriptive analyses showed that most of the sample (66%) reported feeling psychological sickness symptoms rarely or none of the time (ratings below 1). At baseline, 28% of the sample reported feeling some psychological sickness symptoms a little of the time (ratings between 1 and 2), and 6% of the women reported occasionally feeling symptoms a moderate amount of the time (ratings above 2). Similarly, for physical symptoms of sickness behavior, most of the sample (68%) rarely reported symptoms, 26% reported physical sickness symptoms a little of the time, and 6% of the sample reported feeling physical symptoms a moderate amount of the time.

Pearson and Spearman correlations determined that baseline levels of physical and psychological sickness behavior were both significantly and positively related to depression scores as measured by both the CES-D and the BDI with correlation scores ranging between $\underline{r} = .68$ and .83 (all $\underline{ps} = < .01$). Also both index composite scores were significantly and positively correlated with whether women were taking pain, anxiety, sleep, and depression medications with correlation scores ranging between $\underline{r} = .23$ and .46 (all $\underline{ps} <$ or $= .01$). Sickness behavior was marginally negatively correlated with the number of caffeinated drinks reported ($\underline{r} = -.26$, $\underline{p} = .06$). The physical sickness symptom index was significantly correlated with breast cancer stage and employment status at baseline. Specifically, higher cancer stage correlated with higher physical sickness symptom ratings ($\underline{r} = .23$, $\underline{p} = .03$). Women employed full time had less physical sickness behavior than unemployed women ($\underline{r} = .25$, $\underline{p} = .01$). The psychological sickness

symptom index was marginally correlated with employment status and significantly correlated with insurance and marriage status at baseline. Specifically, women with insurance had less psychological sickness behavior symptoms than uninsured women (r = .21, p = .02). Being separated, divorced or widowed correlated with higher psychological sickness symptom ratings than being married or single (r = .27, p < .01). Sickness behavior index scores were not significantly related to any other demographic variables, disease severity indicators, or health behaviors (all ps > .10). CES-D and BDI depression, medication use, cancer stage and employment status are examined as potential confounding factors in subsequent analyses.

Unconditional growth model analyses also revealed that both physical and psychological sickness behavior symptoms exhibited a significant linear decrease over the 4 assessment time points (z = -2.11 and z = -5.39 respectively). Overall sickness behavior decreased over the first two assessment time points and tends to increase at the 1 year follow up, however, ratings do not reach original baseline levels and continue decreasing over time. Refer to Table 8 and 9 for the means and standard deviations of physical and psychological sickness symptoms over the four time points respectively. Table 10 lists means and standard deviations of overall sickness symptoms (physical and psychological combined) over the four time points. The possibility that changes over time in sickness behavior are related to pro-inflammatory cytokine and cortisol levels was tested in the following analyses.

Aim 2: Immune and Endocrine Correlates of Sickness Behavior

Biological data was available as follows. Immune data on proinflammatory cytokines was available for 58 participants at baseline (32 Experimental (E) and 26

Controls (C)). Of these 58 participants, 48 women returned for their T2 assessment (27 E, 21 C), 33 for the six months follow up (21 E, 12 C), and 26 returned for the final T4 assessment at 15 months (15 E, 11 C). Endocrine data was available for 101 participants at baseline (56 E, 45 C). Seventy-four women returned for their T2 assessment (40 E, 34 C), 65 returned for the six months follow up (38 E, 27 C), and 50 for the final T4 assessment at 15 months (27 E, 23 C).

1) Descriptive Analyses. Descriptive statistics showed that IL-6 increased from the first to the second and third assessment, returning to original baseline levels at the final follow up assessments at 15-months. Refer to Table 11 for the means and standard deviations of IL-6 over the four time points and to Figure 2 for a plot of the means for the full sample. TNF-alpha showed a different pattern decreasing from the first to the second assessment, increasing sharply at the third follow up assessment, with levels decreasing again to end below baseline levels in the final follow up assessment at 15-months. Refer to Table 12 for the means and standard deviations of TNF-alpha over the four time points and to Figure 3 for a plot of the means for the full sample. Urinary cortisol showed a very similar trajectory to TNF-alpha; however, the rate of increase from the second to the third assessment time point was smaller. Refer to Table 13 for the means and standard deviations of TNF-alpha over the four time points and to Figure 4 for a plot of the means for the full sample.

Pearson and non-parametric Spearman correlations determined that baseline levels of Il-6 were significantly negatively related to alcohol use at baseline ($\underline{r}$ = -.37, $\underline{p}$ = .01). Levels of IL-6 were also marginally negatively correlated with tea consumption ($\underline{r}$ =-.25, $\underline{p}$ = .09), the use of pain medication ($\underline{r}$ =-.25, $\underline{p}$ = .07), and insurance status ($\underline{r}$ =-.23,

p = .09). Both IL-6 and urinary cortisol levels were marginally related to having had radiation but in opposite ways. Women who had radiation as part of their cancer treatment lower levels of urinary cortisol (r = -.18, p = .09), but higher levels of IL-6 (r =.25, p = .07). Urinary cortisol was also marginally positively related to years of education (r =.18, p = .07) and negatively related to cigarette smoking (r =-.17, p = .09). Levels of Il-6, TNF-alpha, and cortisol were not significantly related to any other demographic variables (i.e., age, ethnicity, employment, marital status, and having children), disease severity indicators (i.e., cancer stage, number of positive lymph nodes, surgery type, chemotherapy, Tamoxifen use, and menopausal status), or other health behaviors (i.e., caffeine use, drug use). Alcohol use, tea consumption, pain medication, insurance status, and radiation were examined as potential confounds in subsequent IL-6 analyses. Education, cigarette smoking and radiation were examined as potential confounds in subsequent analyses with urinary cortisol.

Although we expected significant correlations between IL6 and TNF-alpha to possibly combine the scores into one single pro-inflammatory cytokine marker, results showed that IL-6 and TNF-alpha were not significantly correlated with each other or with urinary cortisol levels (all ps > .10). Therefore three different indices of biological activity (IL6, TNF-alpha, and cortisol) were used as correlates and predictors of each of the sickness behavior composite scores (Physical and psychological).

2) Biological Correlates of Sickness Behavior at Baseline. Pearson correlations were used in order to test the hypothesis that women with higher levels of pro-inflammatory cytokines (i.e., IL-6 and TNF-alpha) and higher levels of cortisol at baseline will report greater levels of sickness symptoms (physical and psychological) at

baseline. Results showed that baseline indexes of sickness behavior (i.e., Physical, Psychological) were not significantly related to baseline immune or endocrine measures (all ps > .10).

In order to determine whether baseline levels of cytokines and cortisol predicted changes over time in sickness behavior, a latent growth curve model was specified for each sickness behavior composite (i.e., physical and psychological) with the trajectory of change in sickness behavior symptoms over time (i.e., slope) and baseline symptoms (i.e., intercept) as two latent variables required for model identification. Fixed effects were time (0, 3, 9, and 15 months), T1 biology (i.e., baseline levels of IL6, TNF-alpha, and cortisol respectively), and the interaction of T1 x time. Variances at each time point were made all equal to each other. Thus it was possible to examine whether the baseline levels of biological markers affected sickness symptoms over time. The structure of this model is shown in Figure 5a.

Analyses for the physical composite of sickness behavior with baseline levels of IL-6, TNF-alpha, and cortisol suggest an adequate fit for the data with all indices meeting criteria specified above. Specifically, X^2 (9, N = 124) ranged between 7.17 and 8.36, (all ps > .10); (CFI = 1.0, RMSEA = .00, SRMR = .03). Results showed that baseline levels of IL6 did not predict the intercept or the slope of physical sickness symptoms (z = -.84 and z = .86 respectively). Refer to Table 14. In contrast, models with baseline levels of TNF-alpha and cortisol as predictors showed that these markers predicted variation in the slope but not the intercept of physical sickness symptoms (z = 2.12 and z = 2.66, respectively for effects on the slope). Specifically, 1-unit increases in baseline levels of TNF-alpha changed the direction of the slope of physical sickness symptoms from

negative –0.024 to 0.005. Thus, higher baseline levels of TNF-alpha predict increases in physical sickness symptoms over the 15-month period of the study. Similarly, a 1-unit increase in baseline cortisol changed the direction of the slope of physical sickness symptoms from negative –0.037 to 0.007, actually predicting augmented physical symptoms over time. Tables 15 and 16 show the conditional growth model of psychological sickness behavior as predicted by baseline levels of TNF-alpha and cortisol respectively.

Analyses for the psychological composite of sickness behavior with baseline levels of IL-6, TNF-alpha, and cortisol showed that models using baseline levels of TNF-alpha and cortisol as predictors had better model fit than the IL6 model. While the model with baseline IL6 had two indices suggesting reasonable model fit (X^2 (9, N = 124) = 19.29, p = .02 (CFI = .96, RMSEA = 0.1, SRMR = .06), at least three indices suggested adequate model fit in analyses using TNF-alpha and cortisol. Specifically, X^2 (9, N = 124) = 15.08 and 15.01 respectively for TNF-alpha and cortisol (ps = .10); (CFI = .98, RMSEA = .07, SRMR = .05). A significant interaction of Intercept and Slope (z = -2.5) in all three models (i.e., with Il6, TNF-alpha, and cortisol) indicated that psychological sickness behavior symptoms tend to decrease more in women who begin the study with higher levels of symptoms. Results again showed that baseline levels of IL6 did not predict the intercept or the slope of psychological sickness symptoms (z = -.11 and z = .24 respectively). Refer to Table 17. Cortisol also failed to yield an effect on the intercept and the slope of psychological sickness symptoms (z =.31 and z = 1.17 respectively). Refer to Table 18. In contrast baseline levels of TNF-alpha yielded a significant effect predicting variation in the slope but not the intercept of psychological

sickness symptoms ($\underline{z}$ = .02 and $\underline{z}$ = 2.46 respectively). Specifically, 1-unit increases in baseline levels of TNF-alpha predicted a reduced rate of decline in psychological sickness symptoms from –0.034 to -0.001. Tables 19 shows the conditional growth model of psychological sickness behavior as predicted by baseline levels of TNF-alpha.

3) Biological Correlates of Sickness Behavior Over Time. In order to determine whether changes over time in each of the sickness symptom clusters (i.e., physical and psychological) uniquely correlate with changes overtime in endocrine and immune measures, M-plus was used to create an unconditional growth model for each one of the biological variables. The unconditional model for both immune and endocrine variables did not fit the data well as it showed a pattern of correlations over the four assessment time points that was inconsistent with a model of change (i.e., positive and negative correlations with no consistent pattern over time; see Table 20, 21, and 22 for time intercorrelations of IL-6, TNF-alpha, and Cortisol respectively).

Due to these inconsistencies, a change score was calculated for both immune and endocrine variables to correlate changes in biological measures with change in sickness behavior over time. Due to the negative correlation between IL6 levels at Time 1 and Time 2, Time 3 was used instead to calculate the IL6 change score. Time 1 and Time 2 were used to calculate change scores for TNF-alpha and cortisol. Six latent growth curve models were specified using M-plus, three for each sickness behavior composite (i.e., physical and psychological) as predicted by each of the relevant biological measures (i.e., IL-6, TNF-alpha, and cortisol). The trajectory of change in sickness behavior symptoms over time (i.e., slope) and baseline sickness symptoms (i.e., intercept) were modeled as latent variables from data at Time 1, 2, 3 and 4 (i.e., 0, 3, 9, and 15 months). The main

predictor of sickness behavior was the change score calculated for IL-6, TNF-alpha, and cortisol respectively for each model. Variances at the first three time points were made all equal to each other. The structure of this model is shown in Figure 5b.Analyses for the physical composite of sickness behavior with all three biological variables (i.e., IL-6, TNF-alpha, and cortisol) suggest an adequate fit for the data. Specifically, when change from Time 1 to Time 3 in IL6 levels was used as predictor of physical sickness behavior, X^2 (9, N = 123) = 9.47, p = .40 (CFI = .99, RMSEA = .021, SRMR = .039). Results showed that there was a significant decrease in physical sickness symptoms over time. However, the increase in IL6 levels from T1 to T3 was not a significant predictor of changes in physical sickness symptoms over time. Refer to Table 23 for the conditional growth model of physical sickness symptoms and as predicted by changes in IL6 levels from Time 1 to Time 3. The growth model with change in TNF-alpha predicting physical sickness symptoms also had adequate fit. Indices were as follows: X^2 (9, N = 123) = 7.69, p = .57; CFI 1.0, RMSEA = .00, SRMR = .032. Again, although there was a significant decrease in physical symptoms over time, the change in TNF-alpha from Time 1 to Time 2 did not predict the change in sickness symptoms over the 4 assessment time points. Table 24 shows the conditional growth model for TNF alpha and physical sickness symptoms. The third growth model used changes in cortisol from Time 1 to Time 2 to predict changes in physical sickness symptoms over the four assessment time points. Similar results were obtained. The model fit the data well: X^2 (9, N = 123) = 10.13, p = .34 (CFI = .99, RMSEA = .032, SRMR = .034). However changes in cortisol in the first two time points did not predict changes in physical sickness symptoms over time (z = -1.40) (refer to Table 25).

In analyses for the psychological composite of sickness behavior as predicted by changes in biological (i.e., IL-6, TNF-alpha, and cortisol) measures, at least two indices suggest that there was reasonable model fit. For the model using changes in IL-6 as predictor of change in psychological sickness symptoms indices were as follows: X^2 (9, N = 123) = 18.84, p = .03 (CFI = .97, RMSEA = .094, SRMR = .06). Indices for the model using TNF-alpha changes as predictor were as follows, X^2 (9, N = 123) = 15.04, p = .09 (CFI = .98, RMSEA = .074, SRMR = .047). Indices for the model using urinary cortisol as predictor gave the following indices: X^2 (9, N = 123) = 15.82, p = .07 (CFI = .98, RMSEA = .079, SRMR = .052). In general results show that, similarly to physical symptoms, psychological sickness symptoms significantly decrease over the four assessment time points. A significant interaction of Intercept and Slope ($\underline{z}$ = -2.5) also indicated that psychological sickness behavior symptoms tend to decrease more in women who begin the study with higher levels of symptoms. In terms of specific biological markers, changes in IL6 levels emerged as a significant predictor of the intercept and the slope of psychological sickness behavior ($\underline{z}$ = 2.81). Specifically, a 1-unit increase in IL6 from Time 1 to Time 3 predicts a slower the rate of decline in psychological symptoms over the four assessment time points from -0.017 to -0.001. Results of the model also show that a 1-unit increase in IL6 from T1 to T3 reduces baseline psychological symptoms from .78 to .42 ($\underline{z}$ = - 2.6). At Table 26 shows the conditional growth model of psychological sickness behavior as predicted by changes in IL6 levels. Changes in TNF-alpha and cortisol over the first and second assessment times were not significant predictors of the decline in psychological sickness symptoms or of

baseline symptom levels (i.e., slope and intercept). Refer to Tables 27 and 28 for models on TNF-alpha and cortisol respectively.

Aim 3: Intervention Effects on Sickness Behavior

To determine the effectiveness of a group-based CBSM intervention in reducing physical and psychological sickness behavior symptoms respectively, both regression analysis with SPSS statistical software and structural equation modeling using Mplus statistical package were used to test the short term and long term effects of the intervention respectively.

First, a linear regression analysis was conducted to determine whether group assignment predicted post-intervention levels of sickness symptoms composites controlling for baseline levels of sickness symptoms. When group assignment was used to predict post-intervention levels of Physical sickness behavior, a marginal trend was observed. Results indicated that post intervention levels of physical sickness behavior varied according to group assignment (F (1,102) = 3.19, p = .077) (See Table 29). Although physical sickness symptoms from pre to post intervention decreased for women in both the experimental and condition conditions, post-intervention levels of physical sickness symptoms were significantly lower for women in the control condition than for women in the experimental condition. Results from a regression with pre and post-intervention psychological sickness behavior showed that group assignment did not predict post-intervention levels of psychological sickness behavior when baseline levels of symptoms were accounted for ($p > .10$). Refer to Table 30 for specific results.

Follow up analysis were conducted overtime using Mplus to determine whether the effects of the intervention on sickness behavior were maintained over the two follow

up periods. A latent growth curve model was specified for each sickness behavior composite (i.e., physical and psychological) with the trajectory of change in sickness behavior symptoms over time (i.e., slope) and baseline symptoms (i.e., intercept) as two latent variables required for model identification. Fixed effects were time (0, 3, 9, and 15 months), group (i.e., 10-week CBSM intervention vs. 1-day seminar/control), and the interaction of groupXtime. Variances at each time point were made all equal to each other. Thus it was possible to examine whether the intervention was effective in reducing sickness symptoms over time. The structure of this model is shown in Figure 6.

In analyses for the physical composite of sickness behavior, it was determined that the model was an adequate fit for the data X^2 (10, N = 125) = 16.00, p = .10 (CFI = .975, RMSEA = .069, SRMR = .044). Although there was a significant decrease in physical sickness symptoms over time, the experimental and the control groups did not differ significantly in their decline in physical sickness behavior symptoms over time. Refer to Table 31 for the conditional growth model of physical sickness symptoms and group assignment and to Table 32 for means and standard deviations by group. Figure 7 shows a plot of the means by group over the four assessment time points.

Similarly, in analyses for the psychological composite of sickness behavior, it was determined that the model was an adequate fit for the data X^2 (9, N = 125) = 16.59, p = .06 (CFI = .972, RMSEA = .082, SRMR = .048). Again although there was a significant decrease in psychological sickness symptoms over time, group assignment did not predict variation in intercept or slope for psychological sickness symptoms overtime ($\underline{z}$ = -.003). Results of this model also showed that levels of psychological sickness symptoms tend to decrease more over time in women who have higher symptom levels at baseline

(z =-2.51) Refer to Table 33 for the conditional growth model of psychological sickness symptoms and group assignment and to Table 34 means and standard deviations by group. Figure 8 shows a plot of the means by group over the four assessment time points.

Aims 4 and 5: Mediation

The last two aims of this study intended to test whether the effects of the CBSM intervention on sickness behavior are mediated by changes in levels of pro-inflammatory cytokines (i.e., IL6 and TNF-alpha) and by changes in levels of urinary cortisol. Mediation is suggested if CBSM intervention effects on sickness behavior cease to be significant when IL6-, TNF-alpha, or cortisol are included in the model. Because no intervention-related effects were observed on the psychological sickness behavior symptom cluster and no relationship was observed between physical sickness behavior and changes in biological markers (i.e., IL6, TNF-alpha, and urinary cortisol), mediation effects could not be established. In addition due to the inconsistent pattern of correlations seen in immune and endocrine variables over time we were unable to examine whether there were intervention related effects on changes in immune and endocrine measures over time using structural equation modeling. When SPSS was used to test whether group assignment predicted short-term changes in biological markers, no significant effects were observed (all ps >.10) Figure 9 shows a plot of IL-6 mean levels over the four time points by group. Figure 10 shows the plot of TNF-alpha mean levels over the four time points by group, and Figure 11 shows the plot of cortisol mean levels over the four time points by group.

CHAPTER VII

Discussion

The purpose of this study was three-fold: 1) to develop a new measure that targets the constellation of behavioral changes that develop in sick individuals during the course of an infection, referred to as sickness behavior; 2) to determine the immune and endocrine correlates of sickness behavior; and 3) to assess whether sickness symptoms assessed with this measure are affected by a cognitive behavioral intervention and relaxation training and whether the effects are mediated by biological markers.

A Sickness Behavior Measure

In this investigation we were able to characterize a pattern of symptom responses among cancer survivors that map onto the constellation of sickness behavior symptoms. According to our expectations, this scale conceptually corresponded with a specific response pattern that included items measuring anhedonia, depressed mood, cognitive dysfunction, social disinterest, fatigue, low libido, poor appetite, somnolence, sensitivity to pain, and malaise. The set of items included in the measure match theoretical conceptualizations of sickness behavior by pioneers in the field (Dantzer, 2001; Miller, 2003) and therefore attests to the construct validity of the measure. The sickness behavior measure also showed high internal consistency and strong test-retest reliability, which add substantial support to the measurement model.

Convergent validity was established with both biological and psychological criteria. Specifically, as predicted, depressed mood as measured by standard depression

scales (i.e., BDI and CES-D) showed strong correlations with both physical and psychological sickness behavior symptoms. This supports previous research postulating a considerable degree of overlap between sickness behavior and major depression (De-La Garza, 2005). At the molecular level, the set of behavioral changes that develop in sick individuals has been predicted to arise due to the brain effects of proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα), and the activation of the HPA axis (De-La Garza, 2005, Dantzer, 2001). Results from this study showed multiple cross-lagged correlations between IL-6 and physical sickness symptoms at every assessment time point. Also physical sickness symptoms at baseline correlated with IL-6 levels at 3- and 15-months. TNF-alpha at baseline was also correlated with physical sickness symptoms at 9- and15-months. These correlations between sickness behavior and pro-inflammatory cytokine markers further support the validity of the sickness behavior measure at another level.

At baseline approximately 30% of the sample reported feeling some sickness symptoms (28% and 26% of the sample for physical and psychological symptoms respectively). This coincides with previous findings indicating that approximately one third of breast cancer survivors will continue to experience fatigue after successful treatment completion (Bower, 2002). Women who reported sickness behavior symptoms also reported taking pain, anxiety, sleep, and depression medications. This finding coincides with the debilitating nature of sickness symptoms. As expected, higher cancer stage at diagnosis was related to higher sickness behavior ratings. This finding supports Raison and Miller's (2003) argument stating that more aggressive cancers are more likely to be associated with behavioral disturbances due to stronger inflammatory reactions.

Correlations of composite scores with other demographic measures also revealed that women employed full time and covered by some type of insurance reported less sickness symptoms than unemployed and uninsured women.

Descriptive analyses revealed that both physical and psychological sickness behavior symptoms exhibited a significant linear decrease over time. Overall sickness behavior decreased over the first two assessment time points and tends to increase at the 1-year follow up, however, ratings do not reach original baseline levels and continue decreasing over time. In the case of cancer, cytokines and sickness behavior are not only produced by tumor cells and inflammatory cells infiltrating or surrounding the tumor, but also by medical interventions (Capuron and Dantzer, 2003). The fact that both physical and psychological sickness symptoms showed a significant decrease over time is consistent with the impact of cancer treatments such as surgery, radiation and chemotherapy on patients' bodies also fading over time.

Because the set of items included in the Sickness Behavior Measure encompass both physical and psychological symptoms of sickness behavior, an important aspect in the development of a sickness behavior measure was to determine the relative utility of a single- versus a two-factor model of sickness behavior. A confirmatory factor analysis using Mplus software was used to determine the better fit between the two hypothesized models (i.e., single factor vs. two-factor) and the observed data. Two latent factors called Physical and Psychological were specified to account for the hypothesized two-factor structure of sickness behavior. The Physical latent factor was defined by eight observed indicator variables (sickness behavior items) whereas the Psychological latent factor was defined by 11 observed indicator variables. This two-factor model was then transformed

into a single-factor model to compare the two different solutions by means of a chi-square difference test. Results showed that although there was a fairly strong correlation between physical and psychological symptoms of sickness behavior, the two-factor solution provided a better fit for the data than the single-factor solution. Although Raison and Miller (2003) discourage the use of independent measures to assess emotional and physical distress in patients with medical illness and point to a broader sickness behavior measure, results of this study encourage the use of two indicators of sickness behavior targeting physical and psychological symptoms respectively. As predicted the physical symptom cluster showed stronger and more frequent correlations with biological (i.e., endocrine and immune) variables than the psychological cluster of symptoms. This finding adds supports the idea that it is important to assess emotional and physical aspects of sickness behavior separately.

Capuron and Dantzer (2003) in their research with cancer patients who are treated with pharmacological doses of cytokines refer to two main dimensions of symptoms: a neurovegetative dimension and a psychological dimension. The neurovegetative dimension includes fatigue, loss of appetite, and sleep disorders. Patients who are at risk are identified by a higher pituitary-adrenal response to cytokine treatment. The psychological dimension included depressed mood, anxiety, and cognitive dysfunction. Patients who are at risk are identified by higher scores of depressed mood. The parallel between the two dimensions of symptoms proposed by Capuron and Dantzer and the physical and psychological dimensions of the sickness behavior measure is evident. Future investigations aiming at assessing these two dimensions of symptoms may benefit

from using this sickness measure as a non-invasive assessments tool for identifying these different set of medical patients.

Immune and Endocrine Correlates of Sickness Behavior

Considerable clinical and experimental data support the existence of a relationship between the immune system and sickness behavior. Specifically, pro-inflammatory cytokines including TNF-alpha, IL1 and IL-6 released in the context of immune activation and inflammation have been shown to impact neurotransmitter and neuroendocrine function and induce the syndrome of sickness behavior (Yirmiya, Weidenfeld, Pollak, Morag, Morag, and Avitsur, 1999). In this study we evaluated whether baseline levels and changes over time in two inflammatory immune markers and an endocrine marker were related to physical and psychological sickness behavior both at baseline and over time.

Specifically, with regards to the immune system, we hypothesized that higher levels of two pro-inflammatory cytokines IL-6 and TNF-alpha, would predict higher levels of sickness behavior symptoms at baseline and over time. As predicted, baseline levels of the pro-inflammatory cytokine TNF-alpha emerged as significant predictor of the sickness behavior over time. Specifically, higher baseline levels of TNF-alpha predicted changes in both physical and psychological sickness symptoms, such that women with higher cytokine levels at baseline showed a slower rate of decline in their sickness symptoms over time, with physical symptoms actually starting to increase rather than decrease as TNF-alpha levels increased. This finding not only supports our hypothesis that higher levels of pro-inflammatory cytokines are correlated with more sickness behavior, but also shows that sickness behavior symptoms in women with higher

levels of this cytokine take longer to return to pre-functioning levels. Previous studies have shown that pro-inflammatory cytokines can cause sickness behavior. However, to our knowledge this is the first study to show that levels of pro-inflammatory cytokines are predictive of the duration of sickness symptoms over time. Cancer patients who are treated with pharmacological doses of cytokines as well as healthy individuals treated with low doses of pro-inflammatory cytokines frequently report sickness behaviors (Capuron, Ravaud, and Dantzer, 2000, Spath –Schwalbe, Hansen, Schmidt, Schrezenmeier, Marshall, Burger, et al., 1998). Although future studies are needed to understand the mechanisms involved, this finding has clinical implications in cancer care and control pointing out the relevance of taking into account the level of pro-inflammatory cytokines during cancer treatment. In particular, the use of cytokine antagonists may be a promising direction for future interventions.

While baseline levels of IL6 did not predict changes in sickness symptoms, lagged correlations showed that IL6 was marginally associated with physical sickness symptoms at every follow up assessment (i.e., T1 with T2, T2 with T3 and T4, and T3 with T4). While changes in IL6 levels were not related to changes in physical symptoms over time, when short-term change scores were used as predictors of long-term changes in sickness behavior, IL6 emerged as a significant predictor of psychological sickness behavior. Specifically, changes in IL6 from baseline to the 9-month follow up assessment predicted changes in the psychological sickness behavior over the 15-months of the study. Specifically, Il6 level increases from baseline to the third follow-up assessment predicted a slower rate of decline of psychological sickness symptoms over the course of the study.

With respect of the endocrine system, baseline levels of cortisol predicted the slope of physical sickness behavior but were unrelated to psychological symptoms over the 15-month period of the study. Specifically, results showed that higher baseline levels of cortisol predicted increases in physical sickness symptoms over time. This results contrast with previous research showing that the hypothalamic-pituitary-adrenal (HPA) axis is a potent modulator of the immune system with suppressive effects on proinflammatory cytokine production and activity (McEwen, Biron, Brunson, Bulloch, Chambers, Dhabbar, et al., 1997). The anti-inflammatory effects of cortisol would therefore warrant less sickness symptoms. It is possible that alterations in glucocorticoid signaling may be responsible for the opposite direction of this finding indicating impaired control of pro-inflammatory cytokines by the HPA axis. In support of this hypothesis a recent study by Bower, Ganz, Aziz, Olmstead, Irwin, and Cole (2007) provided evidence of enhanced inflammatory processes in fatigued breast cancer survivors stemming in part from decrease glucocorticoid response to stress. Whether higher levels of cortisol predicted increased physical sickness symptoms by way of impaired action of cortisol on pro-inflammatory cytokines cannot be determined from this study. It is recommended that subgroups be created for future analysis depending on the direction of the association between cortisol and pro-inflammatory cytokines, such that a positive correlation between immune markers and cortisol may indicate a glucocorticoid resistant subgroup whereas a negative correlation between cortisol and cytokines indicates a subgroup with normal neuroendocrine anti-inflammatory activity. Future studies assessing glucocorticoid resistance in breast cancer survivors can help clarify the physiologic basis

for a potentially altered neuroendocrine response and its impact on cancer-related sickness behavior.

Results from cross-sectional correlation analyses did not show any significant associations between immune and endocrine markers and physical or psychological sickness behavior at the baseline assessment. It is possible that the time interval was not enough to capture the relationships between pro-inflammatory cytokines and sickness symptoms at baseline. As precursors of behavioral changes, pro-inflammatory cytokines and cortisol may need to be assessed at least 3 months before sickness symptoms to allow for relevant changes to emerge and be noticed by patients. It is also possible that non-inflammatory processes control sickness symptoms closer to cancer treatment. This possibility remains to be explored in future studies.

The negligible relationships observed on baseline analyses correlating biological measures with sickness behavior contrast with the effects observed when changes in sickness behavior symptoms were evaluated over time, and point to the relevance of including several assessment points in this type of research. It seems that the length of the follow up period used in the current study allowed for pro-inflammatory activity to have an effect on behavior and be captured in the data. It is important that similar or longer follow up periods be used in future studies to continue to advance the field.

Intervention Effects on Sickness Behavior

In this study we tested the impact of a CBSM group intervention on the physical and psychological sickness symptoms of women who had completed adjuvant therapy for early-stag breast cancer. First, linear regression analysis was used to account for the short term effects of the intervention and determine whether group assignment influenced post-

intervention levels of sickness symptoms accounting for symptoms at baseline. Results from this first line of analysis showed a marginal trend for physical symptoms. Specifically, regression analysis indicated that, when baseline levels of physical sickness behavior were accounted for, post-intervention levels of physical sickness behavior were significantly different in the experimental and control conditions, with lower physical symptoms for women in the control condition. Although this finding was not in the expected direction, it is possible that it is still beneficial to have sickness symptoms at this point in time. Sickness behavior has been conceptualized as an adaptive motivational strategy in response to infectious agents and no longer adaptive either if it is out of proportion with the set of causal factors that triggered it, or if the sickness response is prolonged and taxes the organism's resources (Dantzer and Kelley, 2007). Cancer treatment, especially chemotherapy and radiation, are very aggressive treatments that not only get rid of tumor cell but can also take a toll on the mind and the body (Castellon, Ganz, Bower, Peterson, Abraham, and Greendale, 2004). It may be that the effects of adjuvant treatment are so strong that continued sickness behavior symptoms are required in order to be able to withdraw from the environment, seek rest and care for the body to finally resume social and occupational activities. It is difficult to establish the adequate interval of time where sickness symptoms cease to be adaptive and become debilitating which remains to be explored in future studies.

Another plausible explanation of this finding showing relatively more elevated physical sickness symptoms in the experimental group than in the control group stems from the nature of the intervention itself. Previous studies by this group in a different sample of women undergoing treatment for breast cancer obtained evidence that the

active ingredient in the intervention effects on well-being was women's confidence in their ability to use learned relaxation skills (Antoni, Lechner, Kazi, Wimberly, Sifre, Urcuyo, et al., 2006). Different relaxation techniques are taught to women in this intervention, many of them focusing on bodily responses such as breathing and muscle tension. In addition to relaxation skills, women also learn cognitive techniques that enhance their awareness of the physical symptoms that typically indicate high stress levels (i.e., stress awareness). Therefore it is possible that the relaxation and cognitive skills taught during the intervention enhance the awareness that women have of their physical symptoms and this is reflected in the self-report measure of sickness behavior. The specific relation of relaxation training and sickness behavior remains to be explored in future studies.

Differences between the intervention and control groups were no longer observed when structural equation modeling was used to test the effects of the intervention on physical sickness behavior in the long term. Although there was a significant decrease in symptoms over time, the experimental and the control groups did not differ significantly in their rate of decline in physical sickness behavior over the 15-month follow up period of the study. Still, exploratory analysis revealed that the experimental and condition conditions had very different patterns of change over time in their physical sickness symptoms. While the experimental group showed a steady decline of symptoms over the 15-month period, the control group showed intense fluctuations from one assessment time to the other. Disrupted circadian rhythms, such as random fluctuations in cortisol levels, have been associated with early mortality in patients with advanced breast cancer (Septhon, Sapolsky, Kraemer, and Spiegel, 2000). The fluctuations in physical sickness

symptoms seen in the control group may be detrimental to the body and reflect fluctuations in the immune and endocrine systems. This remains to be explored in future investigations. Future studies may benefit from exploring whether sickness behavior would continue to fluctuate in a similar pattern over a longer follow-up period and whether these fluctuations represent harm or benefit to the body.

Although previous studies using a similar intervention in women undergoing treatment for nonmetastatic breast cancer have provided clear evidence that a CBSM intervention can produce substantial and durable effects on psychosocial factors such as social functioning, reductions of negative affect, and increases in positive experiences (Antoni et al., 2006), results from this study showed that the intervention did not play an important role in changing psychological symptoms of sickness behavior. Both the experimental and the control group showed similar levels of psychological symptoms over time. The difference between these results and previous studies may be attributable in part to the low levels of sickness behavior symptoms reported in this sample as a whole leaving little room for the intervention to have a differential effect. The small elevation in sickness symptoms can also explain the relatively small effect observed in physical sickness symptoms.

Also this sample of women had already completed their adjuvant therapy for breast cancer and was not in active treatment such as in previous studies. Psychiatric disorders, especially major depression, have been reported in a significant proportion of cancer patients several weeks after cancer treatment has been completed (Capuron and Dantzer, 2003). The medical team may have switched from treating physical symptoms to alleviating psychological ones (i.e., prescribing antidepressants). It is possible that

pharmacological treatment overshadows the impact of the intervention on psychological sickness symptoms but not on physical symptoms where marginal effects were observed. Capuron and Dantzer, (2003) have shown that while neurovegetative symptoms (i.e., physical symptoms) are typically resistant to current widely used antidepressants, psychological symptoms are usually responsive to these medications. This tendency would leave less room for a CBSM intervention to produce effect on psychological symptoms than on physical sickness behavior. Also neurovegetative symptoms frequently develop before mood symptoms, which could have allowed for the intervention to have an impact during the length of the study. More research in this respect is needed to determine whether there is a better period of time to intervene with breast cancer survivors.

Limitations of the current study

This study provides a novel measurement tool to assess the sickness behavior syndrome that commonly affects breast cancer survivors and provides insights into the immune and endocrine correlates of sickness symptoms, but several limitations qualify the interpretations of results. First, this study focuses on a small carefully selected group of women who had already completed cancer treatment and were affluent, educated and motivated to participate. Also participants all had nonmetastatic cancers and were free of physical and mental health comorbidities at recruitment. In addition, there were some systematic differences that differentially predicted whether or not participants returned for follow-up. In general it appears that participants who returned for follow-up tended to be less depressed, relatively educated, and health-behavior minded. Also participants who did not complete the study were more likely to have had radiation treatment than

completers. Analysis of this highly selected sample rules out several potential counter-explanations for the presence of sickness behavior but limit the generalizability of study results. Future psychometric work on the sickness behavior measure should include clinical and non-clinical samples, as well as samples of patients presenting with alternative medical conditions. Thus results should be considered preliminary and require replication in a larger and more representative sample.

Second, although behaviorally sickness behavior is very similar to depression seen in medical patients, conceptually it cannot be explained entirely by depression and it is said to be a broader construct (Raison and Miller,2003). While strong correlations with two different depression scales support the concurrent validity of the sickness behavior measure, this study offers little psychometric insights into the discriminant validity of the sickness behavior measure from standard depression scales. Because, many of the sickness symptoms used in the sickness behavior measure were obtained from depression scales, the index of sickness behavior overlaps with depression and future work on discriminant validity is needed. It is important to further ascertain whether this instrument actually is different from standard depression scales and what additional sickness symptoms are needed to discriminate between depression and sickness behavior.

An index of sickness behavior also needs to be distinguished from fatigue which is another common and distressing side effect of cancer and persists long after treatment completion (Bower, Ganz, Desmond, Rowland, Meyerowitz, and Belin, 2000). Recent research with breast cancer survivors has focused specifically on recurrent and persistent fatigue. Bower and colleagues have provided repeated support for the hypothesis that pro-inflammatory cytokines contribute to cancer-related fatigue. Although fatigued

women also report a number of other sickness behaviors, including depressed mood, decreased activity level, decreased social interest, and cognitive problems, fatigue appears to be a distinct symptom in cancer patients and survivors and its association with inflammatory markers remains significant after controlling for these factors (Bower, 2007). The fact that both physical and psychological sickness symptoms showed correlations with pro-inflammatory cytokine markers, particularly TNF-alpha, supports the validity of the sickness behavior measure. However, bearing that sickness behavior and depression symptoms overlap, and that fatigue is a built-in symptom of sickness behavior, it is possible that this association merely reflects immune alterations that typically occur in depressed or fatigued patients. Therefore, interpretation of results showing associations between biological markers and sickness symptom indexes should be done with caution. Future studies may benefit from focusing on whether TNF-alpha differently predicts changes in sickness behavior symptoms, fatigue, and depression symptoms as measured by standard scales.

Future studies are also needed to determine whether this sickness behavior measure has predictive validity. One possibility is that the instrument be given to cancer patients scheduled to undergo cytokine treatment such as interferon alpha (INF-alpha). The questionnaire should be administered before and after to determine whether it discriminates between the presence and absence of sickness symptoms before and after INF-alpha treatment respectively. Concurrent validity can also be established with the same population of cancer patients by asking a physicians or nurses to interview patients during cytokine treatment. Physician assessment can be then used as a criterion of sickness behavior by comparing their assessment to the patient's self-report.

Third, evaluating whether changes over time in biological markers were associated with changes over time in sickness behavior symptoms was complicated by the fact that no consistent model of change could be established for any of the biological markers. Changes over time in biological markers could only be assessed over the short-term instead of using the data obtained over the four assessment-time-points. It is possible that inflammatory activity may need to be assessed as cumulative exposure rather than in single points in time to show significant associations with sickness behavior symptoms. Previous studies have used a cumulative index of cytokine activity reflecting cumulative exposure to cytokine activity (Bower, 2007). It is recommended that such an index be created for future analyses.

It is also possible that the use of medications may have affected the immune and endocrine markers measured in this study making time intercorrelations of cytokines and cortisol change over time with no discernible pattern. Breast cancer surgery and radiation therapy can be associated with long-lasting side effects that usually develop within several months after chemotherapy. The vast majority of complications are mild such as hot flashes and lymphedema, but others can be serious including cardiac impairment (Burnstein and Winer, 2000). Non-steroidal anti-inflammatory drugs and steroid hormones are usually prescribed to manage these symptoms. Beginning a specific medication regimen, dosage changes, as well as interruption of drug treatment can impact pro-inflammatory cytokine markers and cortisol differently at different assessment times explaining the inconsistent changes observed in the data. A careful revision of the type, dosage, and interval of time of medications used by these patients, as well as other

potential confounds such as estradiol levels is warranted to further elucidate this data and in future research in this area.

Finally, the availability of biological data was limited in this sample of women and was greatly reduced from one assessment time point to the next. Thus, the sample size of women with biological data may undermine this study's statistical power to detect influences of inflammatory and endocrine on sickness behavior. While participants were motivated to participate in the psychosocial assessment, many were not willing to provide blood or urine needed for analysis of biological markers. Understandably, many patients refused to undergo additional blood draws and collect urine after having completed cancer treatment. In addition, some participants were excluded from biological assessments due to confounding medical conditions such as a pituitary abnormality. Although many of the observed relationships between physical and psychological sickness and biological markers were marginal and effect sizes were relatively small, statistical power needs to be taken into account when interpreting these results. Indeed, some of the negligible relationships observed in this study (e.g., changes in IL6 as predictor of changes in sickness symptoms) might have emerged as statistically significant in a more strongly powered study.

CHAPTER VIII

Conclusion

Despite the prevalence of sickness behavior in medical populations, to our knowledge this study provides the first attempt to develop a standardized measure to assess sickness behavior using self-report questionnaires. The measurement model showed that sickness behavior was better accounted for by two-factor rather than a single-factor model. These factors accounted for a physical and a psychological sickness symptom dimension, which parallel the neurovegetative and psychological symptom dimensions proposed by Capuron and Dantzer (2003). At the molecular level, these two dimensions of symptoms arise due to the brain effects of pro-inflammatory cytokines (Dantzer and Kelley, 2007). The observed association between physical and psychological sickness symptoms and two of the pro-inflammatory cytokines, IL-6 and TNF-alpha, adds value to the measure as the data suggests that these are in fact symptoms of sickness behavior induced by increased inflammatory activation. The study also provides evidence that levels of pro-inflammatory cytokines are not only important in the induction, but also in the maintenance of sickness symptoms over the long term. Particularly, the present data suggest that greater levels of pro-inflammatory cytokine levels predict more sickness symptoms over longer periods. Because cortisol was associated with more rather than less physical sickness symptoms, results further suggest that anti-inflammatory neuroendocrine activity may be dysregulated in

breast cancer survivors. Although the mechanistic basis for these associations requires further examination, these results identify potential targets for medical interventions to ameliorate aberrant inflammatory biology during cancer and its treatment.

This study also provides some evidence that a group-based stress management intervention and relaxation training can have a short-term impact on sickness behavior symptoms. Although the intervention was not effective in reducing sickness behavior symptoms as expected, and in fact increased the short-term report of physical symptoms, the present data suggests that women may benefit from having physical sickness behavior symptoms shortly after cancer treatment. In support of the view of sickness behavior as an adaptive motivational strategy of the organism, women in the experimental condition showed a more steady decline of sickness symptoms over time than women in the control condition who had less prevalence of symptoms in the short-term but showed more intense fluctuations of symptoms over time.

As the possibility that behavioral alterations in cancer patients represent a sickness syndrome resulting from activation of the inflammatory cytokine network continues to be explored, the current measure can provide a more practical screening tool particularly in primary care settings where studying independently the physical symptoms and the psychological alterations that occur in cancer patients can have implications for treatment. The fact that items included in the sickness behavior measure were selected from scales commonly used with cancer patients also adds practical value to this instrument as it reduces respondent burden in conditions that often necessitate a time-efficient assessment.

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Tables

Table 1

Targeted Symptoms for Sickness Behavior Scale.

Factor	Items
I. Psychological Symptoms	1. Depressed Mood
	2. Anhedonia
	3. Social Disinterest
	4. Cognitive Dysfunction
	5. Low Libido
II. Physical Symptoms	1. Fatigue
	2. Sleep
	3. Pain
	4. Malaise
	5. Poor Appetite
	6. Motor Retardation

Table 2

Demographic Variables for the Intervention and Control Participants

(Intervention (N = 67), Control (N = 55) at Baseline.

Variable	Control	Intervention
Age (years)	50.0 (7.1)	50.0 (8.3)
Education (years)	15.5 (3.9)	14.8 (3.3)
Marital Status:		
Married	69%	61%
Separated	5.5%	4.5%
Divorced	16%	15%
Widowed	2%	1.5%
Single	7%	18%
Ethnic Background:		
Caucasian	74.5%	57%
African American	1.8%	7.5%
Caribbean Islander	1.8%	4.5%
Cuban-American	12.7%	9%
Nicaraguan-American	1.8%	0%
Hispanic	7.3%	15%
Asian-American	0 %	4.5%
Other	0%	1.5%
Menopausal Status		
Pre-Menopausal	22%	32%
Peri-Menopausal	20%	21%
Post-Menopausal	58%	47%

Table 3

Disease and Treatment Variables for Breast Cancer Participants (Intervention (N = 67), Control (N= 55) at Baseline.

Variable	Control	Intervention
Stage		
0	2%	4%
I	44%	41%
II	47%	39%
III	7%	14%
Positive Nodes		
O	70%	50%
More than 1	30%	50%
Procedure		
Lumpectomy	70%	52%
Mastectomy	30%	40%
Bilateral Mastectomy	0%	8%
Chemotherapy		
No	27%	27.5%
Yes	59%	59%
Radiation		
No	14%	25%
Yes	71%	62%
Tamoxifen		
No	23%	26%
Yes	61%	59%

Table 4

Means and Standard Deviations of Control Variables for Each Group (Intervention (N= 67), Control (N=55) At Baseline.

Variable	Control M (SD)	Intervention M (SD)
Cigarettes (# per week)	1.5 (5.3)	.64 (3.7)
Alcohol (# per week)	2.9 (3.9)	2.3 (3.9)
Coffee (# per week)	5.7 (6.8)	3.8 (4.9)
Cola (# per week)	1.9 (3.3)	1.8 (3.3)
Tea (# per week)	1.8 (4.4)	1.9 (3.8)
Marijuana (# per week)	0.0 (0.0)	0.08(0.3)
Cocaine/Other Drugs (# per week)	0.0 (0.0)	0.07 (0.5)

Table 5

Sickness Behavior Items Verbatim as Obtained from the CES-D, BDI, and FACT-B.

Symptom	Scale Item
Depressed Mood	CES-D 6: *I felt depressed*
	FACT-B-E1: *I feel sad*
Anhedonia	BDI 4: *Have you been getting much satisfaction or enjoyment out of anything?*
	CES-D 16: *I enjoyed life (reversed coded)*
	FACT-B-F3: *I am able to enjoy life (reverse coded)*
	FACT-B- F6: *I am enjoying the things I usually do for fun (reversed coded)*
Cognitive Dysfunction	BDI 13: *Have you been having difficulty making decisions?*
	CES-D 5: *I had trouble keeping my mind on what I was doing*
Social disinterest	BDI 12: *Have you lost interest in other people?*
	CES-D 13: *I talked less than usual*
Low Libido	BDI 21: *Has your interest in sex changed lately?*
	FACT-B-S7: *I am satisfied with my sex life (reverse coded)*
Fatigue	BDI 17: *Have you been feeling tired?*
	FACT-B-P1: *I have lack of energy*
Poor Appetite	CES-D 2: *I did not feel like eating; my appetite was poor*
Somnolence	FACT-B-F5: *I am sleeping well (reverse coded)*
Pain	FACT-B-P4: *I have pain*
Malaise	FACT-B-P6: *I feel ill*
Motor Retardation	CES-D 20: *I could not get "going"*

Table 6

Sickness Behavior Items defining the Physical and Psychological latent factors.

Latent Factor	Defining Items
Psychological	CES-D 6: *I felt depressed* FACT-B-E1: *I feel sad* BDI 4: *Have you been getting much satisfaction or enjoyment out of anything?* CES-D 16: *I enjoyed life (reverse coded)* FACT-B-F3: *I am able to enjoy life (reverse coded)* FACT-B- F6: *I am enjoying the things I usually do for fun (reverse coded)* BDI 12: *Have you lost interest in other people?* BDI 13: *Have you been having difficulty making decisions?* CES-D 5: *I had trouble keeping my mind on what I was doing* BDI 21: *Has your interest in sex changed lately?* FACT-B-S7: *I am satisfied with my sex life (reverse coded)*
Physical	BDI 17: *Have you been feeling tired?* CES-D 20: *I could not get "going"* FACT-B-P1: *I have lack of energy* FACT-B-F5: *I am sleeping well (reverse coded)* FACT-B-P4: *I have pain* FACT-B-P6: *I feel ill* CES-D 2: *I did not feel like eating; my appetite was poor* CES-D 13: *I talked less than usual*

Table 7

Factor Loadings for Sickness Behavior Measure Items.

	Item	One-factor Model	Two-factor Model	
			Factor 1	Factor 2
1.	I felt depressed	.73		.72
2.	I feel sad	.61		.60
3.	Have you been getting much satisfaction or enjoyment out of anything?	.75		.76
4.	I enjoyed life*	.56		.56
5.	I am able to enjoy life*	.82		.84
6.	I am enjoying the things I usually do for fun*	.67		.69
7.	Have you been having difficulty making decisions?	.60		.61
8.	I had trouble keeping my mind on what I was doing	.58		.56
9.	Have you lost interest in other people?	.70		.72
10.	I talked less than usual	.47	.53	
11.	Has your interest in sex changed lately?	.46		.48
12.	I am satisfied with my sex life*	.49		.51
13.	Have you been feeling tired?	.52	.55	
14.	I have lack of energy	.56	.65	
15.	I did not feel like eating; my appetite was poor	.32	.40	
16.	I am sleeping well*	.46	.52	
17.	I have pain	.47	.55	
18.	I feel ill	.67	.72	
19.	I could not get “going”	.44	.54	

* Reverse coded
Factor 1 = Physical
Factor 2 = Psychological

Table 8

Mean and Standard Deviation of Physical Index of Sickness Behavior at Pre- and Post-Intervention and at 6- and 12-months follow up.

Physical Sickness Behavior Index	Mean	SD	Minimum	Maximum	N
Time 1 (Pre)	.76	.56	0.00	2.4	122
Time 2 (Post)	.63	.53	0.00	2.4	106
Time 3 (6 months)	.66	.53	0.00	2.3	96
Time 4 (12 months)	.61	.55	0.00	2.0	83

Table 9

Mean and Standard Deviation of Psychological Index of Sickness Behavior at Pre- and Post-Intervention and at 6- and 12-months follow up.

Psychological Sickness Behavior Index	Mean	SD	Minimum	Maximum	N
Time 1 (Pre)	.76	.62	0.00	2.6	122
Time 2 (Post)	.58	.52	0.00	2.3	106
Time 3 (6 months)	.63	.56	0.00	2.6	96
Time 4 (12 months)	.50	.48	0.00	2.2	83

Table 10

Mean and Standard Deviation of Sickness Behavior at Pre- and Post-Intervention and at 6- and 12-months follow up.

Sickness Behavior	Mean	SD	Minimum	Maximum	N
Time 1 (Pre)	.84	.60	0.00	2.9	59
Time 2 (Post)	.69	.50	0.00	2.6	43
Time 3 (6 months)	.64	.49	0.00	2.4	35
Time 4 (12 months)	.69	.50	0.00	2.2	33

Table 11

Mean and Standard Deviation of Pro-Inflammatory Cytokine IL-6 at Pre- and Post-Intervention and at 6- and 12-months follow up.

IL-6	Mean(ug)	SD	Min.(ug)	Max.(ug)	N
Time 1 (Pre)	31.56	44.32	.00	239	58
Time 2 (Post)	50.88	78.03	.00	353	48
Time 3 (6 months)	54.03	87.55	.00	364	33
Time 4 (12 months)	31.95	54.76	.00	205	26

Table 12

Mean and Standard Deviation of Pro-Inflammatory Cytokine TNF-alpha at Pre- and Post-Intervention and at 6- and 12-months follow up.

TNF-alpha	Mean(ug)	SD	Min.(ug)	Max.(ug)	N
Time 1 (Pre)	3.60	3.39	.00	16.00	58
Time 2 (Post)	2.68	2.88	.00	18.10	48
Time 3 (6 months)	3.48	3.80	.20	17.00	33
Time 4 (12 months)	2.45	2.43	.00	9.40	26

Table 13

Mean and Standard Deviation of Cortisol at Pre- and Post-Intervention and at 6- and 12-months follow up.

Cortisol	Mean (ug)	SD	Min. (ug)	Max. (ug)	N
Time 1 (Pre)	3.64	2.86	.52	14.00	101
Time 2 (Post)	3.10	2.36	.16	10.91	74
Time 3 (6 months)	3.43	2.35	.28	8.94	65
Time 4 (12 months)	2.94	2.78	.34	9.88	50

Table 14

Conditional Growth Model of Physical Sickness Behavior Symptom Composite as Predicted by Baseline Levels of IL6.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.876	0.176	4.98 *
T1 IL6	-0.115	0.137	-0.84
TIME	-0.013	0.008	-1.61
TIME * T1 IL6	0.005	0.006	0.86

* = Z value significant at .05 two-tailed significance level

Table 15

Conditional Growth Model of Physical Sickness Behavior Symptom Composite as Predicted by Baseline Levels of TNF-alpha.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.634	0.178	3.57 *
T1 TNF-alpha	0.174	0.295	0.59
TIME	-0.024	0.009	-2.74*
TIME * T1 TNF-alpha	0.029	0.014	2.11*

* = Z value significant at .05 two-tailed significance level

Table 16

Conditional Growth Model of Physical Sickness Behavior Symptom Composite as Predicted by Baseline Cortisol Levels.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.865	0.199	4.33 *
T1 Cortisol	-0.189	0.284	-0.67
TIME	-0.037	0.012	-3.13*
TIME * T1 Cortisol	0.044	0.017	2.66*

* = Z value significant at .05 two-tailed significance level

Table 17

Conditional Growth Model of Psychological Sickness Behavior Symptom Composite as Predicted by Baseline Levels of IL6.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.742	0.196	3.78 *
T1 IL6	-0.017	0.154	-0.11
TIME	-0.012	0.009	-1.43
TIME * T1 IL6	-0.002	0.007	-0.24

* = Z value significant at .05 two-tailed significance level

Table 18

Conditional Growth Model of Psychological Sickness Behavior Symptom Composite as Predicted by Baseline Levels of TNF-alpha.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.717	0.193	3.72 *
T1 TNF-alpha	0.005	0.317	0.02
TIME	-0.034	0.008	-4.05*
TIME * T1 TNF-alpha	0.033	0.013	2.46*

* = Z value significant at .05 two-tailed significance level

Table 19

Conditional Growth Model of Psychological Sickness Behavior Symptom Composite as Predicted by Baseline Cortisol Levels.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.658	0.211	3.12 *
T1 Cortisol	0.093	0.298	0.31
TIME	-0.026	0.011	-2.49*
TIME * T1 Cortisol	0.017	0.015	1.17

* = Z value significant at .05 two-tailed significance level

Table 20

Intercorrelations Between IL6 at Four Time-point Assessments.

Assessment Time	1	2	3	4
1. Baseline	--	-.14	.46*	.17
2. 3 Months		--	.16	.19
3. 9 Months			--	.30
4. 15 Months				--

* Correlation is significant at the 0.05 level

Table 21

Intercorrelations Between TNF-alpha at Four Time-point Assessments.

Assessment Time	1	2	3	4
5. Baseline	--	.04	.08	-.06
6. 3 Months		--	.07	.25
7. 9 Months			--	.37
8. 15 Months				--

* Correlation is significant at the 0.05 level

Table 22

Intercorrelations Between Cortisol at Four Time-point Assessments.

Assessment Time	1	2	3	4
9. Baseline	--	.45**	-.10	.49**
10. 3 Months		--	.24	.02
11. 9 Months			--	-.31*
12. 15 Months				--

** Correlation is significant at the 0.01 level

* Correlation is significant at the 0.05 level

Table 23

Conditional Growth Model of Physical Sickness Behavior Symptom Composite as Predicted by Changes in IL6 Levels from T1 to T3.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.703	0.054	13.12 *
IL6 Delta (T3-T1)	0.227	0.167	1.36
TIME	-0.007	0.003	-2.17*
TIME * IL6 Delta	0.002	0.007	0.26

* = Z value significant at .05 two-tailed significance level

Table 24

Conditional Growth Model of Physical Sickness Behavior Symptom Composite as Predicted by Changes in TNF-alpha Levels from T1 to T2.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.721	0.057	12.68 *
TNF-alpha (T2-T1)	-0.103	0.223	-0.44
TIME	-0.008	0.003	-2.56*
TIME * TNF-alpha	-0.013	0.01	-1.37

* = Z value significant at .05 two-tailed significance level

Table 25

Conditional Growth Model of Physical Sickness Behavior Symptom Composite as Predicted by Changes in Urinary Cortisol Levels from T1 to T2.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.727	0.05	14.59 *
Cortisol (T2-T1)	-0.176	0.32	-0.55
TIME	-0.007	0.003	-2.41*
TIME * Cortisol	-0.024	0.017	-1.40

* = Z value significant at .05 two-tailed significance level

Table 26

Conditional Growth Model of Psychological Sickness Behavior Symptom Composite as Predicted by Changes in IL6 Levels from T1 to T3.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.778	0.055	14.03 *
IL6 Delta (T3-T1)	-0.359	0.140	-2.57*
TIME	-0.017	0.003	-6.17*
TIME * IL6 Delta	0.016	0.006	2.81*

* = Z value significant at .05 two-tailed significance level

Table 27

Conditional Growth Model of Psychological Sickness Behavior Symptom Composite as Predicted by Changes in TNF-alpha Levels from T1 to T2.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.724	0.063	11.53 *
TNF-alpha (T2-T1)	0.022	0.274	0.08
TIME	-0.015	0.003	-5.07*
TIME * TNF-alpha	-0.008	0.012	-0.69

* = Z value significant at .05 two-tailed significance level

Table 28

Conditional Growth Model of Psychological Sickness Behavior Symptom Composite as Predicted by Changes in Urinary Cortisol Levels from T1 to T2.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.713	0.053	13.38 *
Cortisol (T2-T1)	-0.196	0.332	-0.59
TIME	-0.015	0.003	-5.46*
TIME * Cortisol	-0.013	0.015	-0.85

* = Z value significant at .05 two-tailed significance level

Table 29

Linear Regression of Group Assignment as Predictor of Post-intervention Levels of Physical Sickness Behavior Controlling for Baseline Levels.

Predictor	β	t	df	P
Initial Physical Sickness Behavior	.712	10.22	1	.000
Randomization	.129	1.79	1	.077

Table 30

Linear Regression of Group Assignment as Predictor of Post-intervention Levels of Psychological Sickness Behavior Controlling for Baseline Levels.

Predictor	β	t	df	P
Initial Psychological Sickness Behavior	.680	11.58	1	.000
Randomization	-.069	-1.02	1	.312

Table 31

Conditional Growth Model of Physical Sickness Behavior Symptom Composite with Group Assignment (Experimental versus Control) as Predictor.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.69	0.07	9.62 *
GROUP	0.09	0.10	0.88
TIME	-0.01	0.004	-2.08*
TIME * GROUP	0.01	0.006	0.88

* = Z value significant at .05 two-tailed significance level

Table 32

Estimated Means and Standard Deviations of Physical Sickness Symptoms at Four Time Points, by Experimental and Control Condition.

Physical Sickness Behavior	Time 1		Time 2		Time 3		Time 4	
	M	SE	M	SE	M	SE	M	SE
Control	.73	.56	.52	.43	.65	.47	.50	.46
Experimental	.78	.55	.72	.58	.66	.57	.71	.61

Table 33

Conditional Growth Model of Psychological Sickness Behavior Symptom Composite with Group Assignment (Experimental versus Control) as Predictor.

Fixed Effect	Coefficient	Standard Error	Z-value
INTERCEPT	0.71	0.08	9.16 *
GROUP	0.02	0.10	0.23
TIME	-0.014	0.004	-3.63*
TIME * GROUP	0.00	0.005	-0.003

* = Z value significant at .05 two-tailed significance level

Table 34

Estimated Means and Standard Deviations of Psychological Sickness Symptoms at Four Time Points, by Experimental and Control Condition.

Psychological Sickness Behavior	Time 1		Time 2		Time 3		Time 4	
	M	SE	M	SE	M	SE	M	SE
Control	.72	.59	.57	.54	.64	.59	.46	.46
Experimental	.79	.65	.59	.51	.63	.53	.53	.49

Figures

Figure 1

Lagged Correlations Between Physical Sickness Behavior and IL6 Over Four Assessment Time-Points.

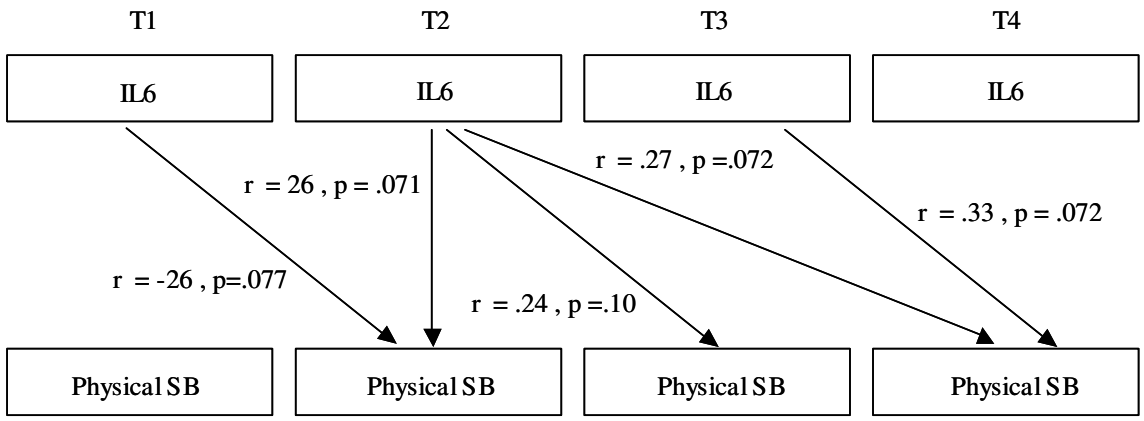


Figure 2

Mean of IL-6 Levels at baseline and at 3, 9 and 15-month follow up.

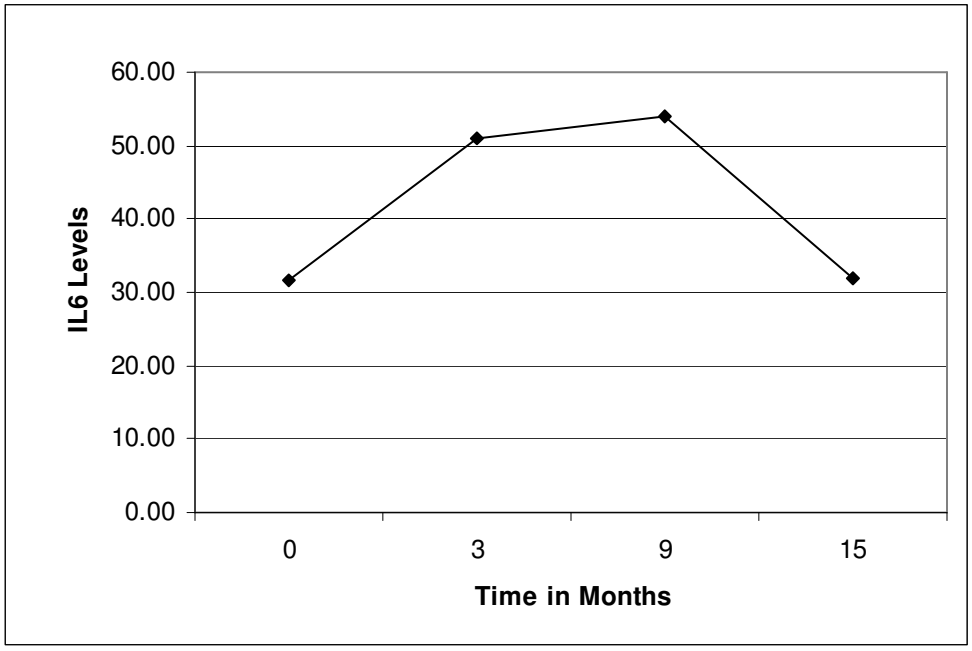


Figure 3

Mean of TNF-alpha Levels at baseline and at 3, 9 and 15-month follow up.

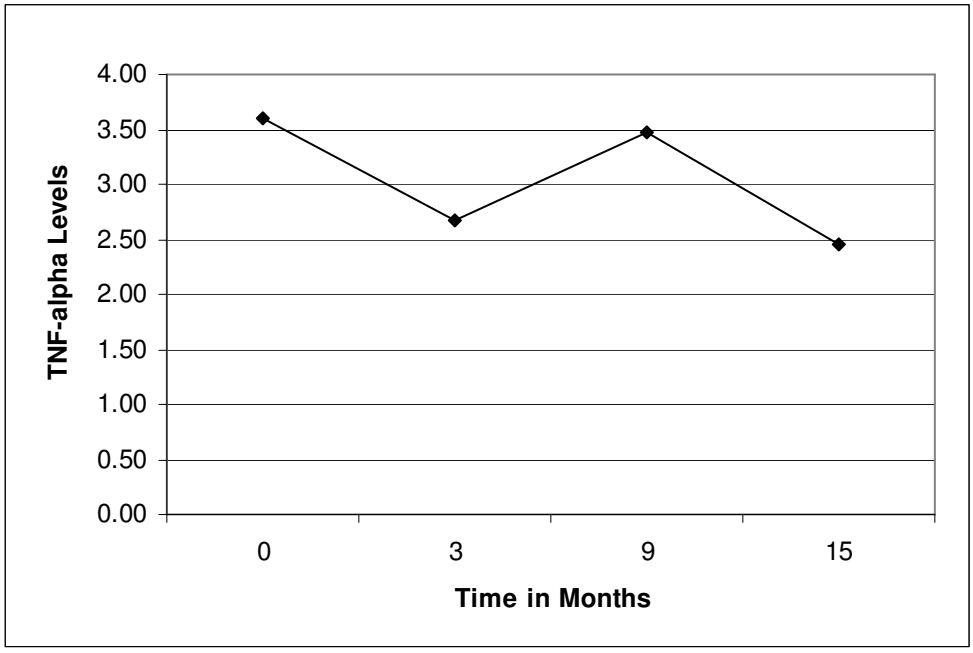


Figure 4

Mean of Cortisol Levels at baseline and at 3, 9 and 15-month follow up.

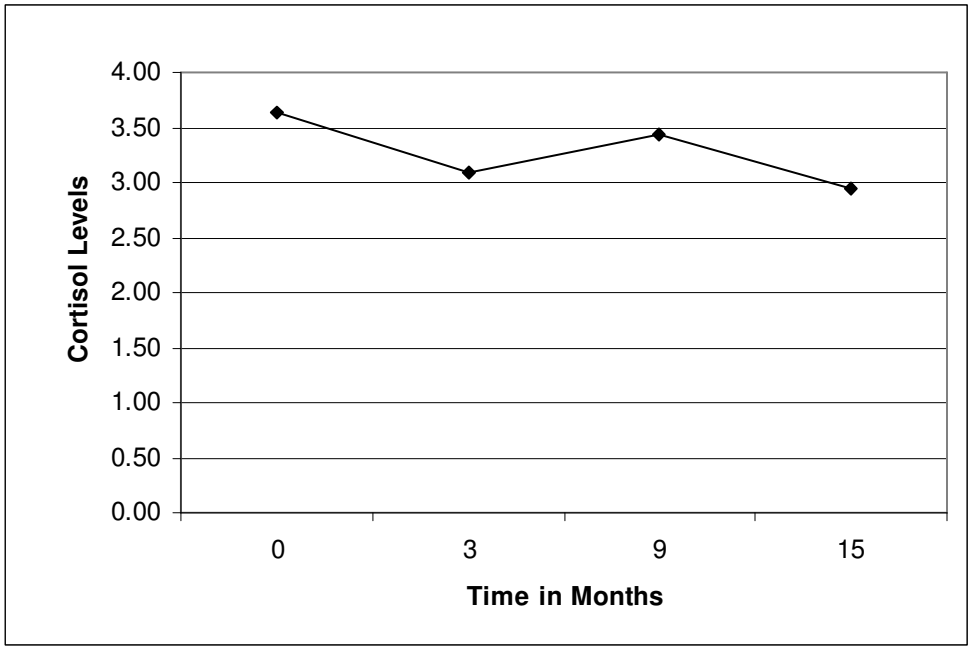


Figure 5a

Structural Model of Latent Growth Using Baseline Levels of Biological Markers to Predict the Intercept and Slope of Sickness Behavior Over Four Time Assessments.

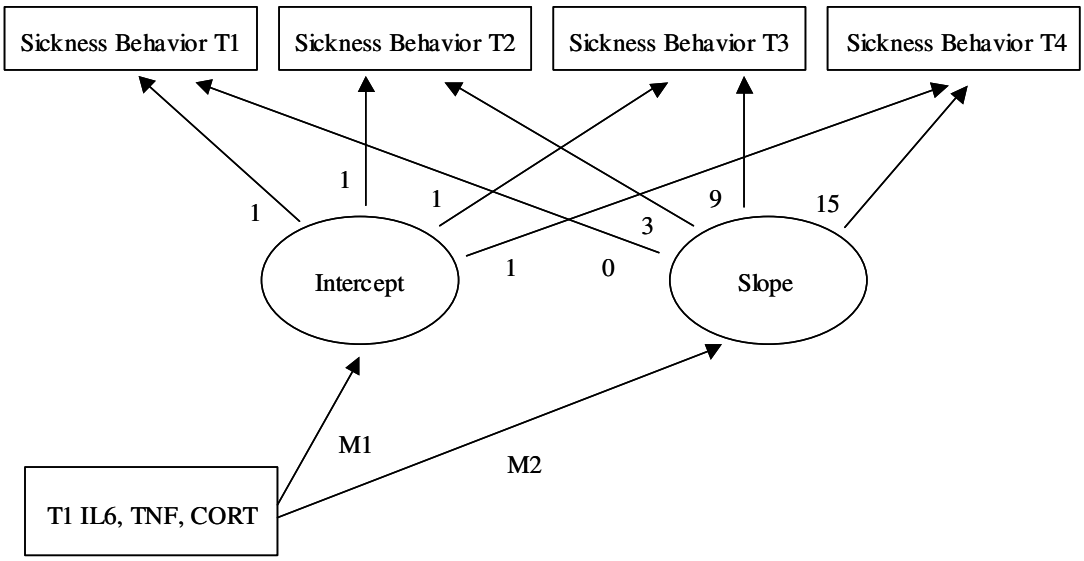


Figure 5b

Structural Model of Latent Growth Using Change Scores in Biological Markers to Predict the Intercept and Slope of Sickness Behavior Over Four Time Assessments.

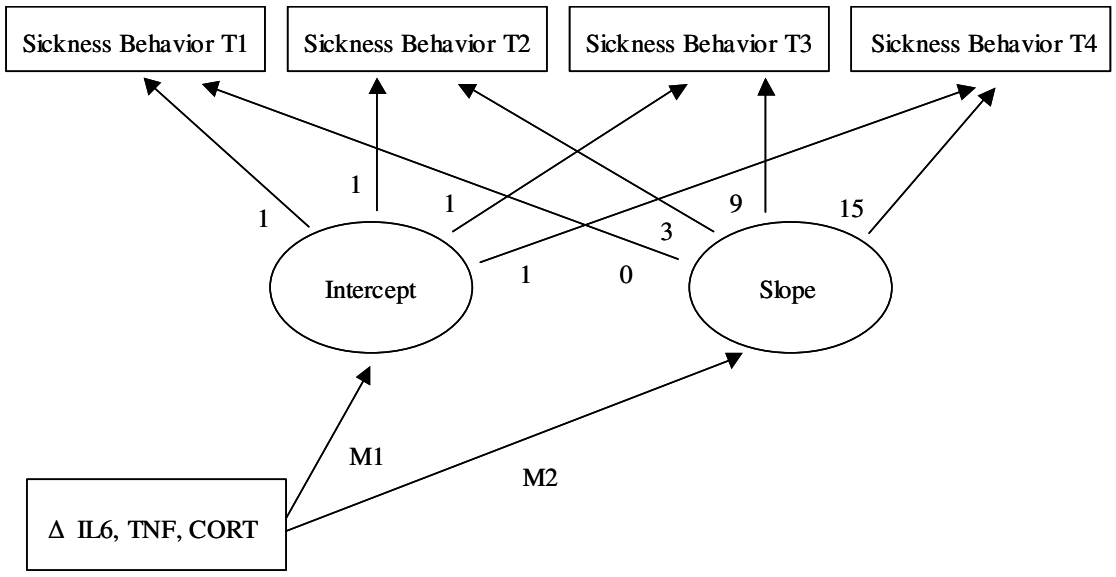


Figure 6

Structural Model of Latent Growth Using Experimental Condition to Predict the Intercept and Slope of Sickness Behavior Over Four Time Assessments.

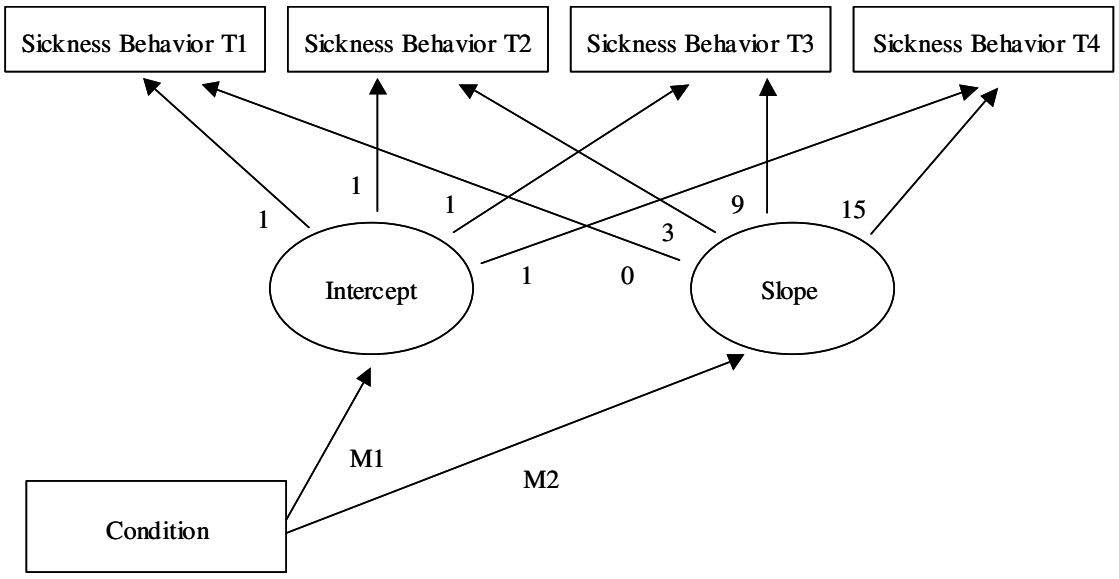


Figure 7

Mean Levels of Physical Sickness Behavior Over Time for Intervention and Control Participants.

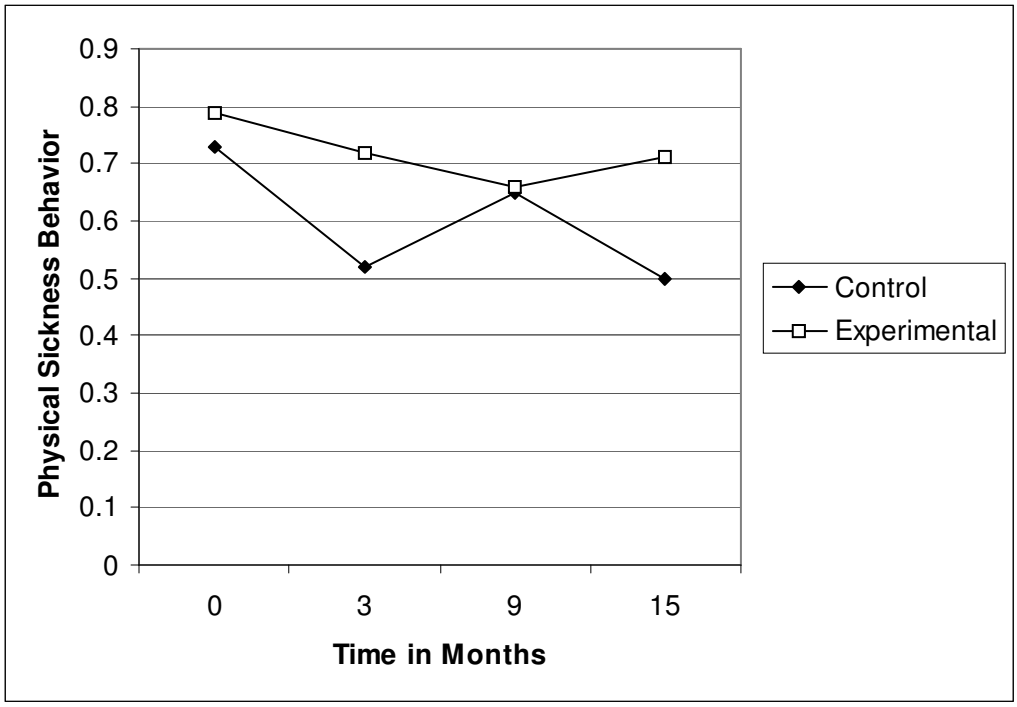


Figure 8

Mean Levels of Psychological Sickness Behavior Over Time for Intervention and Control Participants.

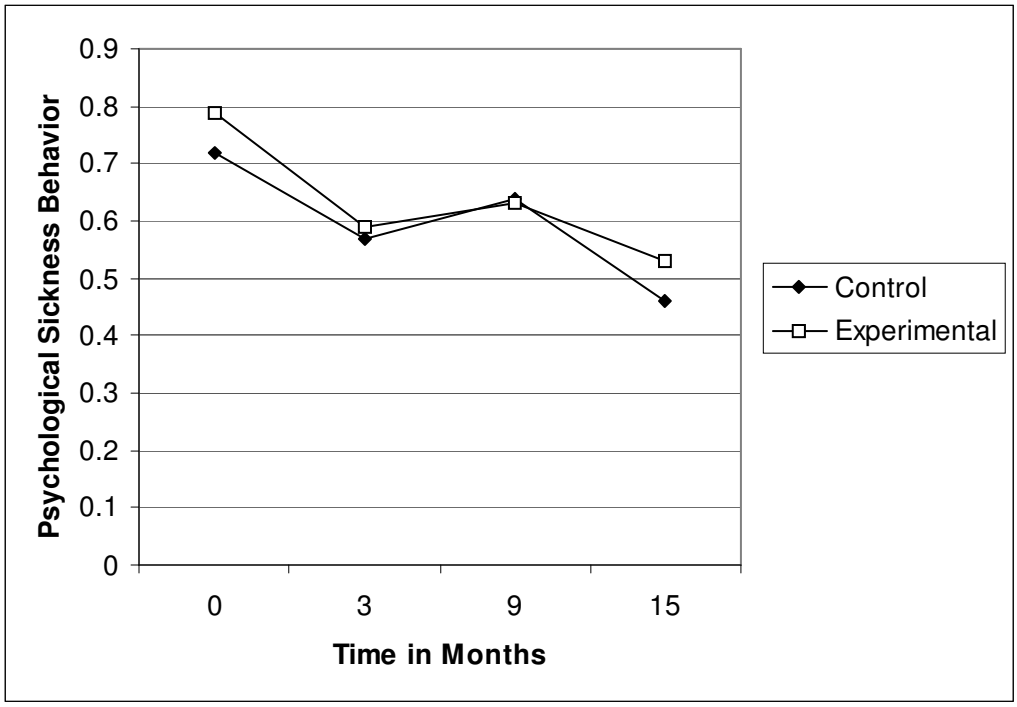


Figure 9

Mean Levels of Pro-inflammatory Cytokine IL-6 Over Time for Intervention and Control Participants.

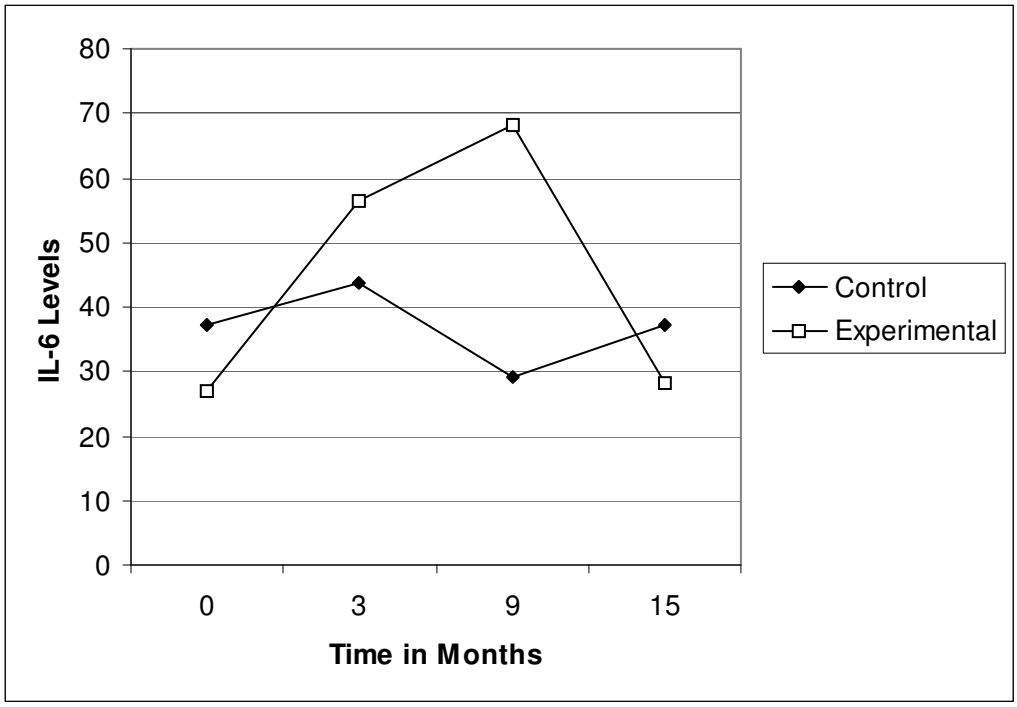


Figure 10

Mean Levels of Pro-inflammatory Cytokine TNF-alpha Over Time for Intervention and Control Participants.

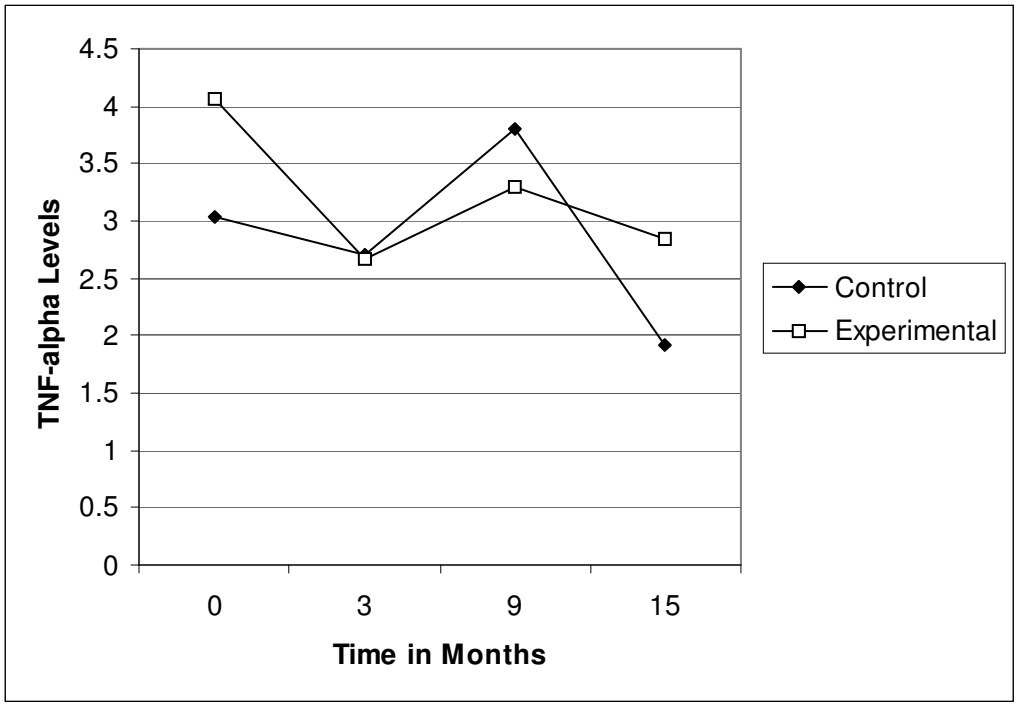
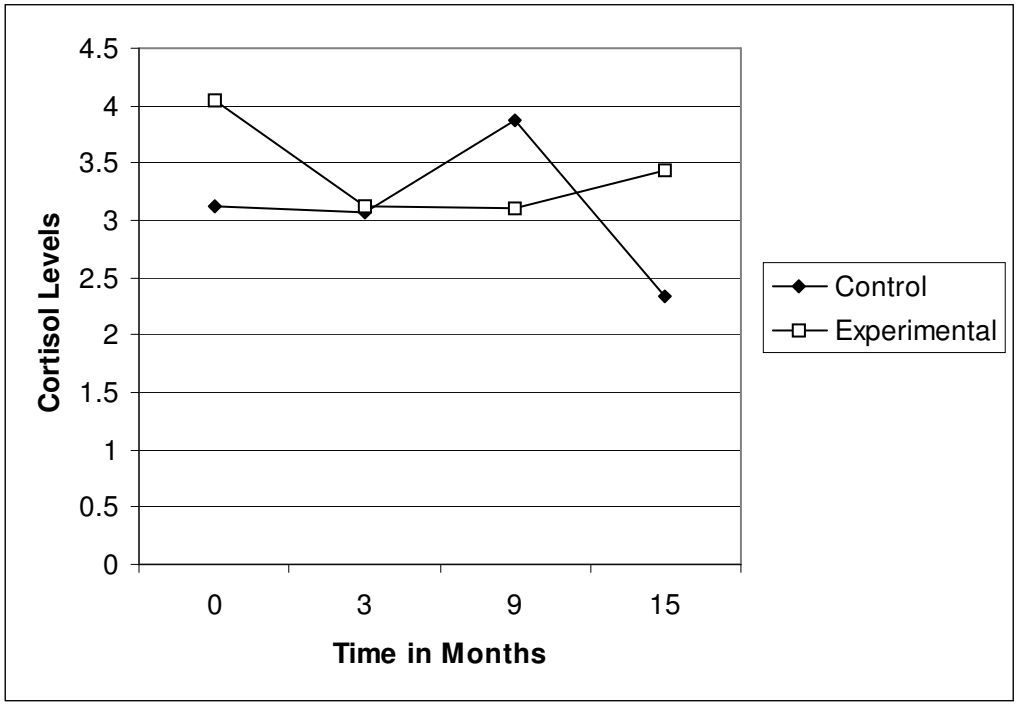


Figure 11

Mean Levels of Cortisol Over Time for Intervention and Control Participants.



Appendix A

Unpublished questionnaire utilized by Bower et al. to assess sickness symptoms:

EVERYDAY PROBLEMS IN LAST WEEK

We are interested in knowing whether you have had any of the following problems **DURING THE PAST WEEK**. Please use the scale below and circle the number that best describes how much each problem bothered you.

	Not at all	A little bit	Moder-ately	Quite a bit	Extremely
1. Hot flashes	0	1	2	3	4
2. Headaches	0	1	2	3	4
3. General aches and pains	0	1	2	3	4
4. Joint pains	0	1	2	3	4
5. Dizziness, faintness	0	1	2	3	4
6. Tenderness, swelling, discomfort or numbness in your chest wall, breast or arm	0	1	2	3	4
7. Reddening or irritation of skin in treated area	0	1	2	3	4
8. Vaginal dryness	0	1	2	3	4
9. Night sweats	0	1	2	3	4
10. Nausea	0	1	2	3	4
11. Difficulty concentrating	0	1	2	3	4
12. Decreased activity level	0	1	2	3	4
13. Tendency to take naps; stay in bed	0	1	2	3	4
14. Less interest in usual activities	0	1	2	3	4
15. Forgetfulness	0	1	2	3	4
16. Feeling lethargic; not wanting to move around or be active	0	1	2	3	4
17. Decreased sexual interest	0	1	2	3	4
18. Not taking your usual care with your personal appearance	0	1	2	3	4
19. Decreased appetite	0	1	2	3	4
20. Less interest in social interaction	0	1	2	3	4
21. Easily distracted	0	1	2	3	4
22. Less interest in initiating or planning social activities	0	1	2	3	4
23. Feeling like you need more rest than usual	0	1	2	3	4

Appendix B

Questionnaires utilized to obtain the index of Sickness Behavior:

1) Beck Depression Inventory (BDI)

BDI

The next sets of questions are going to ask you about how you've been feeling in the **PAST WEEK, INCLUDING TODAY**. Please circle the number of the response that applies to you.

1).	**Have you been feeling sad this week? (If yes, read responses 1 – 3 to rate severity)**
0.	I do not feel sad.
1.	I feel sad.
2.	I am sad all the time and I can't snap out of it.
3.	I am so sad or unhappy that I can't stand it.

2).	**Have you been feeling discouraged or hopeless? (If yes, read responses 1 – 3 to rate severity)**
0.	I am not particularly discouraged about the future.
1.	I feel discouraged about the future.
2.	I feel I have nothing to look forward to.
3.	I feel that the future is hopeless and that things cannot improve.

3).	**Have you been feeling like a failure? (If yes, read responses 1 – 3 to rate severity)**
0.	I do not feel like a failure.
1.	I feel I have failed more than the average person.
2.	As I look back on life, all I can see is a lot of failures.
3.	I feel that I am a complete failure as a person.

4).	**Have you been getting much satisfaction or enjoyment out of anything? (If yes, read responses 1 – 3 to rate severity)**
0.	I get as much satisfaction out of things as I used to.
1.	I don't enjoy things the way I used to.
2.	I don't get real satisfaction out of anything anymore.
3.	I am dissatisfied or bored with everything.

5.)	**Have you been feeling guilty during the past week? (If yes, read responses 1 – 3 to rate severity)**
0.	I don't feel particularly guilty.
1.	I feel guilty a good part of the time.
2.	I feel quite guilty most of the time.
3.	I feel guilty all of the time.

6).	Have you been feeling that you are going to be – or are being – punished? (If yes, read responses 1 – 3 to rate severity)
0.	I don't feel I am being punished.
1.	I feel I may be punished.
2.	I expect to be punished.
3.	I feel I am being punished.

7).	Have you been disappointed in yourself during the past week? (If yes, read responses 1 – 3 to rate severity)
0.	I don't feel disappointed in myself.
1.	I am disappointed in myself.
2.	I am disgusted with myself.
3.	I hate myself.

8).	Have you been critical of yourself? (If yes, read responses 1 – 3 to rate severity)
0.	I don't feel I am any worse than anybody else.
1.	I am critical of myself for my weaknesses or mistakes.
2.	I blame myself all the time for my faults.
3.	I blame myself for everything bad that happens.

9).	Have you had any thoughts about killing yourself? (If yes, read responses 1 – 3 to rate severity)
0.	I don't have any thoughts of killing myself.
1.	I have thoughts of killing myself, but I would not carry them out.
2.	I would like to kill myself.
3.	I would kill myself if I had the chance.

10).	Have you been crying? (If yes, read responses 1 – 3 to rate severity)
0.	I don't cry anymore than usual.
1.	I cry more now than I used to.
2.	I cry all the time now.
3.	I used to be able to cry, but now I can't cry even though I want to.

11).	Have you been feeling irritated during the past week? (If yes, read responses 1 – 3 to rate severity)
0.	I am no more irritated now than I ever am.
1.	I get annoyed or irritated more easily than I used to.
2.	I feel irritated all the time now.
3.	I don't get irritated at all by the things that used to irritate me.

12).	Have you lost interest in other people? (If yes, read responses 1 – 3 to rate severity)
0.	I have not lost interest in other people.
1.	I am less interested in other people than I used to be.
2.	I have lost most of my interest in other people.
3.	I have lost all of my interest in other people.

13).	**Have you been having difficulty making decisions? (If yes, read responses 1 – 3 to rate severity)**
0.	I make decisions about as well as I ever could.
1.	I put off making decisions more than I used to.
2.	I have greater difficulty in making decisions than before.
3.	I can't make decisions at all anymore.

14).	**How have you been feeling about your appearance? (If feeling bad about appearance, read responses 1 – 3 to rate severity)**
0.	I don't feel I look any worse than I used to.
1.	I am worried that I am looking old or unattractive.
2.	I feel that there are permanent changes in my appearance that make me look unattractive.
3.	I believe that I look ugly.

15).	**Has it been taking extra effort to do your work? (If yes, read responses 1 – 3 to rate severity)**
0.	I can work about as well as before.
1.	It takes an extra effort to get started at doing something.
2.	I have to push myself very hard to do anything.
3.	I can't do any work at all.

16).	**How have you been sleeping during the past week? (If sleeping more poorly than usual, read responses 1 – 3 to rate severity)**
0.	I can sleep as well as usual.
1.	I don't sleep as well as I used to.
2.	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3.	I wake up several hours earlier than usual and cannot get back to sleep.

17).	**Have you been feeling tired? (If yes, read responses 1 – 3 to rate severity)**
0.	I don't get more tired than usual.
1.	I get tired more easily than I used to.
2.	I get tired from doing almost anything.
3.	I am too tired to do anything.

18).	How has your appetite been this week? (If appetite poor, read responses 1 – 3 to rate severity)
0.	My appetite is no worse than usual.
1.	My appetite is not as good as it used to be.
2.	My appetite is much worse now.
3.	I have no appetite at all.

19).	Have you lost any weight lately? (If yes, read responses 1 – 3 to rate severity)
0.	I haven't lost much weight, if any.
1.	I have lost more than 5 pounds.
2.	I have lost more than 10 pounds.
3.	I have lost more than 15 pounds.

	Have you been purposely trying to lose weight?
Y or N	I am purposefully trying to lose weight by eating less.

20).	Have you been worried about your health? (If yes, read responses 1 – 3 to rate severity)
0.	I am no more worried about my health than usual.
1.	I am worried about physical problems such as aches and pains, or upset stomach, or constipation.
2.	I am very worried about physical problems and it's hard to think about much else.
3.	I am so worried about my physical problems that it's hard to think about anything else.

21).	Has your interest in sex changed lately? (If yes, read responses 1 – 3 to rate severity)
0.	I have not noticed any recent change in my interest in sex.
1.	I am less interested in sex than I used to be.
2.	I am much less interested in sex than I used to be.
3.	I have lost interest in sex completely.

2) Center for Epidemiologic Studies – Depression Scale (CES-D)

CES-D

Next is a list of the ways you may have felt or behaved over the past week. Please indicate how often you have felt this way **during the past week.** Use these response choices:

1 = Rarely or none of the time (less than 1 day)
2 = Some or a little of the time (1-2 days)
3 = Occasionally or moderate amount of time (3-4 days)
4 = Most or all of the time (5-7 days)

During the past week . . .

_____ 1. I was bothered by things that *usually* don't bother me.
_____ 2. I did not feel like eating; my appetite was poor.
_____ 3. I felt that I could not shake off sad feelings even with help from my family/friends.
_____ 4. I felt that I was just as good as other people.
_____ 5. I had trouble keeping my mind on what I was doing.
_____ 6. I felt depressed.
_____ 7. I felt that everything I did was an effort.
_____ 8. I felt hopeful about the future.
_____ 9. I thought my life had been a failure.
_____ 10. I felt fearful.
_____ 11. My sleep was restless.
_____ 12. I was happy.
_____ 13. I talked less than usual.
_____ 14. I felt lonely.
_____ 15. People were unfriendly.
_____ 16. I enjoyed life.
_____ 17. I had crying spells.
_____ 18. I felt sad.
_____ 19. I felt that people disliked me.
_____ 20. I could not get "going."

3) Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B)

FACT-B

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

Physical Well-being

	Not at all	A little bit	Some-what	Quite a bit	Very much
1. I have a lack of energy.	1	2	3	4	5
2. I have nausea.	1	2	3	4	5
3. Because of my physical condition, I have trouble meeting the needs of my family.	1	2	3	4	5
4. I have pain.	1	2	3	4	5
5. I am bothered by the side effects of treatment.	1	2	3	4	5
6. I feel ill.	1	2	3	4	5
7. I am forced to spend time in bed.	1	2	3	4	5

Social/Family Well-being

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

Emotional Well-being

	Not at all	A little bit	Some-what	Quite a bit	Very much
1. I feel sad.	1	2	3	4	5
2. I am satisfied with how I am coping with my illness.	1	2	3	4	5
3. I am losing hope in the fight against my illness.	1	2	3	4	5
4. I feel nervous.	1	2	3	4	5
5. I worry about dying.	1	2	3	4	5
6. I worry that my condition will get worse.	1	2	3	4	5

Functional Well-being

	Not at all	A little bit	Some-what	Quite a bit	Very much
1. I am able to work (including working at home).	1	2	3	4	5
2. My work (including work at home) is fulfilling.	1	2	3	4	5
3. I am able to enjoy life.	1	2	3	4	5
4. I have accepted my illness.	1	2	3	4	5
5. I am sleeping well.	1	2	3	4	5
6. I am enjoying the things I usually do for fun.	1	2	3	4	5
7. I am content with the quality of my life right now.	1	2	3	4	5

Additional Concerns

	Not at all	A little bit	Some-what	Quite a bit	Very much
1. I have been short of breath.	1	2	3	4	5
2. I am self-conscious about the way I dress.	1	2	3	4	5
3. One or both of my arms are swollen or tender.	1	2	3	4	5
4. I feel sexually attractive.	1	2	3	4	5
5. I am bothered by hair loss.	1	2	3	4	5

6. I worry that other members of my family might someday get the same illness I have.	1	2	3	4	5
7. I worry about the effect of stress on my illness.	1	2	3	4	5
8. I am bothered by a change in weight.	1	2	3	4	5
9. I am able to feel like a woman.	1	2	3	4	5