Online Exclusive Article

Dose Effects of Relaxation Practice on Immune Responses in Women Newly Diagnosed With Breast Cancer: An Exploratory Study

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Cancer diagnosis and treatment can cause significant psychological stress (Bleiker, Pouwer, van der Ploeg, Leer, & Adèr, 2000; Epping-Jordan et al., 1999; Yang, Brothers, & Andersen, 2008). Although most patients experience a gradual decline of stress over time, some continue to experience high levels of stress for years, even after the successful completion of cancer treatment (Bleiker et al., 2000). Others experience post-traumatic stress disorder precipitated by a cancer diagnosis (Kangas, Henry, & Bryant, 2002). In addition, in a study by Palmer, Kagee, Coyne, and DeMichele (2004), 41% of women with breast cancer reported significant fear, helplessness, or horror related to their experience with cancer.

Stress can lead to a variety of adverse health outcomes, including greater upper respiratory tract infections and periodontal diseases, accelerated aging, and increased cardiovascular diseases, in diverse populations (Cohen, 1995; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002a, 2002b). The well-controlled studies of animal models of cancer also showed that stress decreased the efficacy of or resistance to chemotherapeutic agents (Kerr, Hundal, Silva, Emerman, & Weinberg, 2001; Su et al., 2005), and high stress was associated with low physical and psychological quality of life in women with breast cancer (Golden-Kreutz et al., 2005; Härtl et al., 2010; Luecken & Compas, 2002; Yang et al., 2008). In addition, women with metastatic or recurrent breast cancer who had experienced one or more highly stressful or traumatic events in their lives showed a significantly shorter disease-free interval (median = 31 months) compared with women who had not experienced such events (median = 62 months)

Purpose/Objectives: To determine the dose effects of relaxation practice on immune responses and describe the types of relaxation techniques preferred and the extent of relaxation practice over 10 months.

Design: Descriptive, prospective, repeated measures.

Setting: An interdisciplinary breast clinic at a university-affiliated comprehensive cancer center in the United States.

Sample: 49 women with newly diagnosed breast cancer and undergoing adjuvant therapy who participated in a stress management intervention.

Methods: Relaxation practice was assessed twice a month for 10 months with immune measurements (e.g., natural killer cell activity; lymphocyte proliferation; interferon [IFN]-γ; interleukin [IL]-2, -4, -6, and -10) at the beginning and end of 10-month practice.

Main Research Variables: Relaxation practice (representing the concepts of stress and adherence), relaxation technique, and immune response.

Findings: After adjusting for covariates, the extent of relaxation practice significantly contributed to the variance of natural killer cell activity, lymphocyte proliferation, IL-4, and IL-10 responses in a positive direction; the higher the relaxation practice, the higher the immune responses. In comparison, IFN-γ, IL-2, and IL-6 responses were not affected. The deep-breathing method was most preferred by participants, followed by progressive relaxation and imagination or visualization. The mean weekly frequency of relaxation practice was 5.29 (SD = 3.35), and the mean duration of relaxation practice was 19.16 (SD = 10.81) minutes per session.

Conclusions: Persistent relaxation practice may have positive effects on multiple immune responses in a dose-dependent manner.

Implications for Nursing: Allowing the choice of preferred techniques and emphasizing the importance of long-term adherence, a relaxation program may need to be routinely offered to women under high stress.

(Palesh et al., 2007). These findings collectively indicate that high stress can have a negative impact on health.

Stress can induce various physiologic alterations, including alterations in neuroendocrine and immune responses in healthy and sick populations (Glaser, 2005; Luecken & Compas, 2002; Reiche, Nunes, & Morimoto, 2004; Segerstrom & Miller, 2004). The typical stress-associated activation of the hypothalamic-pituitary-adrenal axis and the sympathetic arousal lead to the release of glucocorticoids and catecholamines with increased inflammation and shifts in immune functions and immune cell traffic (Glaser, 2005; Luecken & Compas, 2002; Reiche et al., 2004; Segerstrom & Miller, 2004). In women with newly diagnosed breast cancer, high stress was associated with low natural killer cell activity (NKCA) and interferon-gamma (IFN-γ) levels, which are important to general immunocompetence (Von Ah, Kang, & Carpenter, 2007). In addition, women with high subjective stress showed poor lymphocyte proliferation, whereas an early, rapid reduction of subjective stress was related to rapid improvement of NKCA in women with breast cancer (Thornton, Andersen, Crespin, & Carson, 2007). These findings together suggest that physiologic alterations, particularly immune alterations, may underlie the central mechanisms for increased susceptibility to adverse health outcomes under stress.

Breast Cancer and Relevant Immune Markers

The immune system is highly complex, and the significance of given immune markers may differ depending on a particular disorder or health concern. To make the findings of the study meaningful to the breast cancer population, the following set of immune markers was selected for its relevance to breast cancer: NKCA, lymphocyte proliferation, and cytokines consisting of IFN-γ, interleukin (IL)-2, IL-4, IL-6, and IL-10. Principal actions of the selected immune markers are briefly presented in Table 1, although each marker contains multiple other functions (Andoniou, Andrews, & Degli-Esposti, 2006; Corwin, 2000).

Because natural killer cells play an important role in the resistance to and control of malignancies and virus-infected cells, they have received much attention (Andoniou et al., 2006; Brittenden, Heys, Ross, & Eremin, 1996; Pross & Lotzová, 1993; Whiteside & Herberman, 1995). NKCA is lower in women with breast cancer than healthy controls, and women with advanced stages of breast cancer have shown lower NKCA than women with earlier stages of breast cancer (Konjevic & Spuzic, 1993). In addition, low NKCA has been linked to a lack of normal diurnal variation of cortisol, which is a prognostic factor for a shorter survival time in women with metastatic breast cancer (Sephton, Sapolsky, Kraemer, & Spiegel, 2000). Head, Elliot, and McCoy (1993) found that lymphocyte proliferation was impaired in 58% of patients with breast cancer in their study, and decreased lymphocyte proliferation was inversely associated with positive nodal status.

Table 1. Principal Action of Selected Immune Markers

Immune Marker	Principal Action
IFN-γ	Inhibits viral replication Enhances natural killer cell activity
IL-2	T-cell proliferation and differentiation Activation of cytotoxic lymphocytes and macrophages
IL-4	B-cell growth factor Ig isotype selection–IgE Inhibits breast cancer cell growth
IL-6	B-cell differentiation Induces acute phase proteins Induces "sickness behaviors" Proinflammatory
IL-10	Anti-inflammatory Inhibits IL-1 synthesis
Lymphocyte proliferation	Lymphocyte proliferation to enhance immunity
Natural killer cell activity	Controls the growth and spread of pathogens and tumors

IFN—interferon; Ig—immunoglobulin; IL—interleukin

IFNs and IL-2 are cytokines that typically enhance NKCA (Sinkovics & Horvath, 2005). Low production of IFN-γ was significantly correlated with increased tumor burden (Elsässer-Beile, von Kleist, Sauther, Gallati, & Mönting, 1993), and women with breast cancer showed significantly lower IL-2 levels than their healthy counterparts even before the initiation of cancer treatment (Elsässer-Beile, von Kleist, & Gallati, 1991; Elsässer-Beile et al., 1993). Lower levels of IL-2, on the other hand, predicted a shorter survival time (Lissoni, Barni, Rovelli, & Tancini, 1991) and increased risk for breast cancer relapse (Arduino et al., 1996). Similarly, high levels of serum IL-6 were predictive of shorter disease-free and overall survival in women with metastatic breast cancer (Bachelot et al., 2003; Bozcuk et al., 2004). The roles of IL-4 and IL-10 in breast cancer are less well known, but in vitro studies have shown that IL-4 inhibited the growth of breast cancer cells (Blais, Gingras, Haagensen, Labrie, & Simard, 1996; Toi, Bicknell, & Harris, 1992) and increased apoptosis (programmed cell death) in breast cancer cell lines MCF-7 and MDA-MB-231 (Gooch, Lee, & Yee, 1998), suggesting a potentially beneficial role in breast cancer. IL-10 has shown mixed results on tumor cell growth or inhibition for different types of tumors;

more information can be found in Vicari and Trinchieri (2004). In breast tumors, IL-10 expression was high, whereas expression of lymphocyte activation proteins was low. Although specific tumor microenvironment may be important in the control of tumor progression (Llanes-Fernández et al., 2009), peripheral IL-10 responses in circulation may increase understanding of IL-10 in breast cancer.

Stress Management, Adherence, and Immune Responses

Given the potential adverse effects of stress on immune responses and health outcomes, early management of stress may be beneficial to women with newly diagnosed breast cancer who are undergoing cancer treatment. A number of stress management programs have been implemented in various populations, but their impacts on immune responses have not been uniform. For example, cognitive-behavior stress management (CBSM) is one of the most widely used programs (Antoni, 2003; Antoni et al., 2001; Claesson et al., 2006; Claesson et al., 2005; Cruess et al., 2000; McGregor et al., 2004). A 10-week CBSM intervention improved lymphocyte proliferative responses at the three-month follow-up in women with early-stage breast cancer (McGregor et al., 2004) and favorably changed the distribution of CD4 (helper T cells) and CD8 (suppressor or cytotoxic T cells) lymphocyte subsets in men with HIV (Antoni, 2003). However, other investigators found no significant changes in other physiologic responses (e.g., C-reactive protein) to CBSM in women with ischemic heart disease (Claesson et al., 2006; Claesson et al., 2005).

Mindfulness-based stress reduction (MBSR) is another common stress reduction program. An eight-week MBSR program increased NKCA and IFN-γ production and decreased IL-4, IL-6, and IL-10 in women with breast cancer (Witek-Janusek et al., 2008). However, other investigators have found that a similar eight-week MBSR program increased T cell production of IL-4, but decreased T cell production of IFN-γ and natural killer cell production of IL-10 in breast and prostate cancer survivors (Carlson, Speca, Faris, & Patel, 2007; Carlson, Speca, Patel, & Goodey, 2003), therefore showing similar programs that resulted in different responses.

The precise reasons for inconsistent findings are not fully understood. One reason is the variability in adherence to the stress management practice. Adherence is the extent of following the prescribed treatment and/or behavior recommendations. Variability in adherence has been a major issue in medical management and behavior-modification programs, including exercise, dietary modification, screening behaviors, and medication taking, in a variety of populations (Dew et al., 2009; Erlen & Sereika, 2006; Fappa et al., 2008; Forkan et al., 2006; Webber, Tate, Ward, & Bowling, 2010). In the older adult population, for example, an individualized home exercise program was prescribed, but 37% of participants did not exercise at all, whereas 28% exercised more than four times a week, showing wide variability in adherent behaviors (Forkan et al., 2006). Even in a 12-week telephone-based program specifically designed to improve medication adherence, only 43% of the participants adhered to receiving all 12 sessions of the program. On average, participants received only eight sessions (Erlen & Sereika, 2006). These findings indicate adherence to be a continuous challenge in behavior interventions, despite greater adherence being associated with better outcomes (Alhassan, Kim, Bersamin, King, & Gardner, 2008; Fappa et al., 2008). Poor adherence also may skew the findings from the true possible effects of the intervention. Similarly, the variability in the extent of stress management practice may lead to variable immune responses; however, in-depth investigations in this area have been limited.

Conceptual Framework

The Expanded Biobehavioral Interaction Model provided the conceptual basis of the current study (Kang, Rice, Park, Turner-Henson, & Downs, 2010). The model consists of six large domains (psychosocial, behavioral, individual, environmental, biological [physiological], and health-related outcomes) with various factors within each. The basic tenets of the model are that factors in the first four domains individually and/or interactively influence biologic responses, which, in turn, shape health and health-related outcomes. In particular, the cumulative effects may arise acutely from multiple factors simultaneously occurring during a short period or from the chronicity of fewer factors persisting over a long period to alter biologic responses and then health-related outcomes.

Factors selected for the study were stress (a psychosocial factor), adherence (a behavioral factor), and immune responses (biological factors) as major variables, and age, cancer stage, type of cancer adjuvant therapy, and menopausal status (individual factors) as potential covariates (see Figure 1). The concept of stress was intervened with relaxation practice to reduce stress, and the interaction of relaxation practice and adherence was conceptualized to form the extent of relaxation practice cumulative over a 10-month period. The overall extent of relaxation practice was further operationalized by multiplying the average frequency of relaxation practice per week and the average duration of relaxation practice per session over 10 months to examine its effects on immune responses, controlling for the effects of covariates.

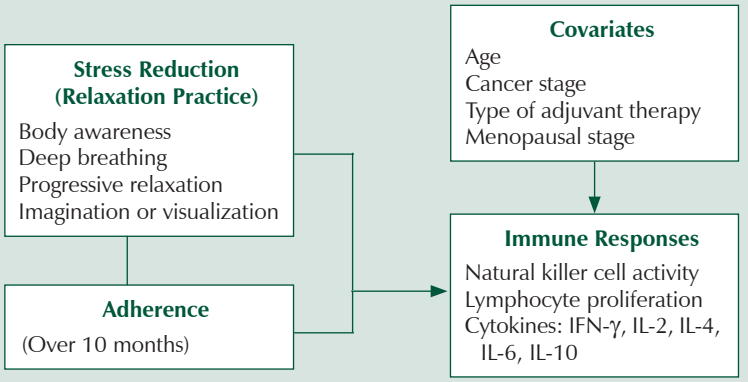


Figure 1. Conceptual Diagram of the Study

Purpose

The specific aims of the current study were to (a) determine the impact of the overall extent of relaxation practice on immune responses, and (b) document the preferred relaxation techniques used and the extent of relaxation practice over 10 months during the first year of cancer diagnosis and treatment in women with breast cancer. The central hypothesis was that the higher overall extent of relaxation practice would influence immune responses in a more favorable manner (i.e., higher immune responses for all markers except for IL-6).

The data for the study were drawn from the parent study, which was a randomized clinical trial conducted to examine biobehavioral outcomes of the integrated CBSM and exercise intervention in women with newly diagnosed, early-stage breast cancer (Kang et al., 2011). Immune responses were the major biologic outcomes of the parent study (Kang et al., 2011). Because relaxation was a central component in the CBSM, after the completion of the focused eight-week CBSM and exercise intervention, participants were prescribed to continue with their relaxation practice (for at least 20 minutes per day for five days per week) over the next 10 months of the study period. Participants were given a choice to use any of the four relaxation techniques introduced during the eight-week CBSM (body awareness, deep breathing, progressive relaxation, and imagination or visualization).

Methods

Design

As a descriptive study based on a subset of the data generated from the parent study, only the data from the intervention group were used to achieve the specific aims of the current study. The major goal of the parent study was to examine the immune responses and psychological and clinical outcomes to an eight-week integrated CBSM and exercise intervention in women with newly diagnosed, early-stage breast cancer who have received treatment (Kang et al., 2011). During a one-year study period, data were collected four times prospectively: before the start of the eight-week intervention (before the beginning of adjuvant therapy), immediately following completion of the intervention, and at four and 10 months postintervention. Following the completion of the eight-week intervention, women in the intervention group were instructed to continue with the learned relaxation practice at home, and the level of relaxation practice was assessed via phone calls twice per month until the end of the study. The relaxation practice data gathered throughout the 10-month period and the participants' immune responses were the focus of the current study.

Sample

Of 213 eligible women, 100 enrolled in the parent study (Kang et al., 2011). Forty-nine women were randomized into the eight-week intervention group. All women were (a) newly diagnosed with breast cancer, (b) receiving chemotherapy and/or radiotherapy, (c) aged 30 years or older, (d) absent of known psychiatric illness, (e) not participating in other structured support or exercise programs, and (f) able to comprehend and respond in English. Exclusion criteria were (a) pregnancy, (b) diffuse bony metastasis with high risk of pathologic fractures, and (c) no access to a telephone. The study protocol was approved by the University of Alabama at Birmingham and the University of Alabama at Birmingham Hospital institutional review board.

Power analysis of the parent study was based on an earlier finding on NKCA difference between the experimental and control groups (Peters, Lötzerich, Niemeier, Schüle, & Uhlenbruck, 1994) because NKCA was regarded as the most important immune response of interest. A total of 90 participants, 45 in each group, was needed, with three follow-up measurements per subject to detect the difference in NKCA between the two groups, with 80% power and 5% alpha based on a two-sided, two-sample t test (Diggle, Liang, & Zeger, 1994). From each group, 10 participants withdrew from the study during the one-year study period, and 39 participants in the intervention group completed the study.

Recruitment and Data Collection Procedure

Participants were recruited through posted flyers in the clinic waiting areas, word of mouth, and invitations from the clinic staff and research teams. When patients showed an interest in the study at the initial contact,

research staff contacted them and provided the details of the study, including the purpose and procedure, expectations, data collection plan, and potential risks and benefits. When the patient was ready, written consent was obtained and the participants were stratified by cancer stage (stages I–IIB versus III and above) and randomized into either the intervention or the wait-list control group using a computer-generated randomization table. Women in the intervention group participated in the eight-week integrated intervention of CBSM and exercise that began when adjuvant therapy was initiated. The first set of baseline data of the parent study was collected before the beginning of adjuvant therapy (Kang et al., 2011).

After completion of the eight-week intervention, participants were instructed to continue what they learned during the intervention in the home setting and were given multiple copies of a simple diary form to record the date, type of relaxation technique used, and the frequency and duration of relaxation practice daily. The study coordinator then called the participants twice per month to obtain the diary data. Blood samples (15–20 ml) to determine immune responses were collected by a phlebotomist in the clinic laboratory or by a trained nurse from 8:30 am–noon during routine clinic visits prior to any treatment.

Intervention of the Parent Study and Relaxation Technique

The intervention of the parent study consisted of eight weekly sessions of CBSM and moderate-intensity aerobic exercise three times per week. CBSM was implemented in small groups of three or four women using a closed-group approach to provide stable membership and sense of community. Each session lasted 90 minutes and was led by the same trained nurse facilitator of the research team, except for the first group (because of staff turnover), in a school of nursing conference room. The date and time of the sessions were determined by each group to facilitate their attendance. The major goal of CBSM was to reduce stress using cognitive-behavior and supportive-expressive strategies. The participants learned the skills and information necessary to manage distressing thoughts and behaviors at each session following the structured workbook instructions (Davis, Eshelman, & McKay, 1998). Various stress management skills (e.g., relaxation techniques), coping strategies and problem-solving skills (e.g., making a stressful events hierarchy by creating a list of stressful events and ranking them, applying relaxation techniques to the hierarchy, learning stress-coping thoughts working for individuals), and cancer and treatment-related information were included. Supportive-expressive strategies provided a forum for the participants to share and freely express their concerns and feelings with others.

The major component of CBSM sessions was training of the relaxation techniques to reduce stress. Because individual preference might vary, participants learned about four common relaxation techniques together over the first four weeks of the intervention and then practiced their own preferred relaxation techniques during the last four weeks. At each session, the nurse facilitator introduced one new relaxation technique: body awareness at week 1, deep breathing at week 2, progressive relaxation at week 3, and imagination or visualization at week 4. All participants then practiced the technique together with the facilitator, following the professionally developed audiotape instructions (Davis et al., 1998). Participants were provided with a copy of a relaxation audiotape each week with a tape recorder and instructed to practice the new technique at home and record the frequency and duration of practice daily. Diaries were brought to the sessions to serve as a source of discussion and motivation. During each consecutive session, the previous relaxation technique and home practice were reviewed, and then another relaxation technique was introduced and practiced. From week 5 to week 8, participants practiced their own choice of relaxation technique using a separate earphone and audiotape. When the eight-week intervention was completed, participants kept all audiotapes and were instructed to continue their relaxation practice using either single or combined techniques based on their preference. Participants also were instructed to keep a practice diary for phone calls they were to receive twice per month for practice data collection, and a convenient time for phone calls was arranged individually.

The other component of the integrated eight-week intervention was moderate-intensity aerobic exercise three times per week for at least 30 minutes per session. Through a graded exercise test, each participant's exercise tolerance was tested, and a heart-rate range corresponding to moderate-intensity exercise was prescribed. Participants learned how to check and maintain heart rates to be within the prescribed range of exercise by wearing a heart-rate monitor. Most participants came to the school of nursing exercise facility to exercise under supervision, except for occasional cases of exercising at home with a monitor on as desired. After the eight-week training, exercising in the home setting without a heart-rate monitor was prescribed and encouraged by research staff. However, staff noted that the frequency of exercise often was irregular even during the eight-week intervention period, and collecting the exercise-related data became increasingly difficult because of considerable irregularity and vagueness about the exercise information.

Measurements

Overall extent of relaxation practice: This was generated by multiplying the average frequency of practice per week and the average duration of practice per

session (minutes) over the 10-month period. The data were generated from the practice data, which were collected twice per month via telephone for a total of 20 sets.

Types of relaxation techniques: The practice diary included a column to record which of the four relaxation techniques (body awareness, deep breathing, progressive relaxation, and imagination or visualization) were used each time, as well as a column to record any other techniques used. That information was obtained along with other relaxation practice data. If more than one technique was used, the authors collected primary and secondary techniques as well as other self-generated techniques used.

Immune assays: For certain immune assays, heparinized blood samples were processed to separate mononuclear cells first, using the Ficoll-Hypaque density-gradient method. Mononuclear cells were washed twice with sterile phosphate-buffered saline ([PBS], without Ca^{2+} and Mg^{2+}, pH 7.4), centrifuged at 450 g for 10 minutes, and resuspended in complete RPMI 1640 (RPMI supplemented with HEPES 25 mM, L-glutamine 2 mM, 50 units penicillin, and 50 µg streptomycin per ml) at 2 x 10^6 cells per ml. The cell viability was greater than 98% (Kang, Coe, & McCarthy, 1996; Kang, Coe, McCarthy, & Ershler, 1997).

Natural killer cell activity: The chromium-51 (Cr-51) release cytotoxicity assay was used with K562 target cells (Kang et al., 1997). Target cells were labeled with 125 µCi Cr-51 for one hour at 37°C, washed and centrifuged twice, and resuspended at 4 x 10^4 cells per ml. Mononuclear cells were incubated in triplicate with labeled K562 target cells and 60% heat-inactivated pooled human serum at the 25:1 and 50:1 effector-to-target cell ratios. Spontaneous and maximal lysis was determined by incubating target cells with medium or 10% sodium dodecyl sulfate solution. Following a four-hour incubation at 37°C, cell activity was counted with a gamma counter. Cytotoxicity was calculated as follows: NKCA (%) = ([sample release – spontaneous release]/[maximum – spontaneous release]) x 100. The assay sensitivity was 0.1% with 2%–6% intra-assay coefficients of variation (Kang et al., 1996; Kang et al., 1997).

Lymphocyte proliferation: Mononuclear cells (10^5) were cultured in triplicate with 60% heat-inactivated pooled human serum and phytohemagglutinin at 10 µg per ml. Following a 54-hour incubation at 37°C, cells were pulsed with 1 mcCi of tritiated thymidine, incubated for an additional 18 hours, and harvested onto filters (MASH harvester, Otto Hiller, Madison, WI). Cells were counted by a liquid scintillation counter (Beckman LS6500). The results indicated net counts per minute.

Cytokines: Whole-blood cell culture assay was used, which was believed to better reflect the in vivo conditions. Blood was diluted 1:10 with the complete RPMI medium and was incubated for four days at 37°C with phytohemagglutinin 10 mcg per ml and lipopolysaccharide 2.5 mcg per ml. Culture supernatant was collected and stored in aliquots at –80°C until assayed. Each cytokine level was determined by a standard two-step sandwich enzyme-linked immunosorbant assay using each cytokine-specific commercial kit. The assay sensitivity was ranged from 0.04–5 pg per ml with intra- and interassay CV 4%–9.6% for all cytokines.

Covariates: Demographic information (e.g., age, education, employment status, weight, height, marital status, menopausal status) was collected using a questionnaire. Body mass index was calculated from weight (kg) divided by height (m^2). Clinical information on cancer diagnosis, cancer stage, and type of adjuvant therapy was collected from medical records. For covariates, age was assessed in years, and cancer stage was categorized as: stage I = 1, IIA = 2, IIB = 2.5, and IIIA = 3. Adjuvant therapy was categorized as: chemotherapy = 1, radiotherapy = 2, chemotherapy plus radiotherapy = 3. Finally, menopausal status was categorized as: premenopause = 1, postmenopause = 2, and perimenopause = 3.

Data Analysis

Using the SPSS® statistical package of PASW statistics, version 18.0, data were examined for distributions and missing values by generating descriptive statistics appropriate to measurement levels (e.g., categorical, continuous). With the attrition of 10 intervention participants over the study period, 39 participants completed the study. The amount of missing data was minimal in that the relaxation practice data collection rate was 94.6% throughout the entire 10-month period. For immune responses, one or two blood samples were missing for immune assays, and five samples were missing for lymphocyte proliferation because of equipment malfunction. To test the hypothesis, sequential multiple regression analyses (Tabachnick & Fidell, 2000) were performed. To control for potential effects of covariates, demographic and clinical factors (e.g., age, cancer stage, type of cancer adjuvant therapy, menopausal status) were entered in the first step, followed by baseline immune response at the beginning of the 10-month relaxation practice period in the second step. Finally, in the third step, the overall extent of relaxation practice was entered as an independent variable to test its unique variance on immune responses (dependent variables). The significance level was set at 0.02.

Results

Characteristics of the Participants

The demographic and clinical characteristics of study participants are presented in Tables 2 and 3. The mean

Table 2. Demographic Characteristics

Characteristic	$\bar{X}$	SD	Range
Age (years)	49.4	8.6	34–69
Body mass index	27.6	5.6	19–41.5
Characteristic		**n**	
Education			
High school or less		14	
Trade school or some college		16	
Bachelor's degree		10	
Some graduate school or graduate degree		9	
Employment status			
Full-time (40 hours per week)		32	
Not employed		12	
Part-time		5	
Body mass index			
19–24.9		20	
25–29.9		13	
30–46.6		13	
Missing		3	
Ethnicity			
Caucasian		34	
African American		13	
Native American		2	
Religion			
Protestant		40	
Catholic		5	
Other		4	
Marital status			
Married or living as married		34	
Separated, divorced, or widowed		12	
Single		2	
Missing		1	
Menopausal status			
Postmenopause		28	
Premenopause		16	
Perimenopause		5	

N = 49

age of the participants was 49.4 years, with a mean body mass index of 27.6. Participants were relatively well educated, mostly Caucasians, and married. About half of the participants were pre- or perimenopausal, and the other half were postmenopausal. Most participants had stage I or II breast cancer, and the most common treatment was a combination of chemotherapy and radiotherapy. Typical regimens of chemotherapy included about 42% of the participants receiving doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 together every two to three weeks for four doses, and about 50% of the participants receiving either doxorubicin 60 mg/m^2, paclitaxel 145 mg/m^2, and cyclophosphamide 600 mg/m^2 sequentially every two to three weeks for three doses each, or doxorubicin 50 mg/m^2 plus cyclophosphamide 500 mg/m^2 together every two to three weeks for four doses followed by docetaxel 75 mg/m^2 every two to three weeks for four doses. For radiotherapy, a total dose of 45–65 Gy was typically given over six weeks, with 15–20 Gy boost dose toward the end of treatment.

Impact of Relaxation Practice on Immune Responses

The major aim of the current study was to examine the impact of the overall extent of relaxation practice on immune responses. The central hypothesis was that the higher extent of overall relaxation practice would influence immune responses in a more favorable manner (higher immune responses for all markers except for IL-6).

The hypothesis was partially supported (see Table 4). The overall extent of relaxation practice over 10 months had significant contributions to variances of multiple immune markers. After controlling for the effects of covariates and the beginning immune response, the extent of relaxation practice significantly contributed to the variance of NKCA 25:1, NKCA 50:1, lymphocyte proliferation, IL-4, and IL-10. The unique variance accounted for by relaxation practice ranged from an R^2 change of 0.12–0.3 ($p = 0.018–0.001$). On the other hand, the impact of the extent of relaxation practice was not significant on IFN-γ, IL-2, and IL-6 responses with an R^2 change of 0.02–0.05 ($p = 0.106–0.333$).

For those immune markers significantly impacted by the relaxation practice, the nature of the impact was that the greater extent of relaxation practice was associated with greater immune responses for all markers. The beginning immune responses had significant contributions to final immune responses 10 months later for lymphocyte proliferation, IFN-γ, and IL-2 only, which all were decreased, showing poor immune recovery following adjuvant therapy (see Table 5). In addition, cancer stage had a significant impact on IL-2 (higher stage, higher IL-2) and the type of adjuvant therapy on IL-6 (combination therapy led to higher IL-6).

Extent of Relaxation Practice and Preferred Techniques

The mean frequency of relaxation practice per week over 10 months was 5.29 (SD = 3.35) times per week (range = 0–14), and the mean duration of relaxation practice per session was 19.16 (SD = 10.81) minutes (range = 0–60). As a result, the overall mean extent of relaxation practice was 106.5 (SD = 86.33) minutes per week (range = 0–313.71) (see Figure 2).

Out of the four relaxation techniques introduced (body awareness, deep breathing, progressive relaxation, and imagination or visualization), deep breathing was most preferred by the participants as the primary relaxation technique (65%), followed by progressive relaxation (12%) and imagination or visualization (4%). Three participants used their own techniques of journaling (2%), bathing (2%), and yoga (2%). Seventeen participants (35%) used a secondary technique in addition to a primary technique, and the secondary techniques used were imagination (16%), progressive

Table 3. Clinical Characteristics

Characteristic	n
Stage (tumor-node-metastasis)	
I	13
IIA	19
IIB	7
IIIA	9
Unknown	1
Cancer treatment	
Chemotherapy plus radiotherapy	25
Radiotherapy	13
Chemotherapy	11
Chemotherapy regimen (N = 36)	
DCD or DPC	18
DC	15
Other (e.g., CMF)	3
Estrogen receptor	
Positive	37
Negative	10
Missing	2
Hormonal therapy	
Yes	38
No	11

N = 49, unless otherwise noted

CMF—cyclophosphamide, methotrexate, and 5-fluorouracil; DC—doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 together every two to three weeks for four doses; DCD—doxorubicin 50 mg/m^2 plus cyclophosphamide 500 mg/m^2 together every two to three weeks for four doses followed by docetaxel 75 mg/m^2 every two to three weeks for four doses; DPC—doxorubicin 60 mg/m^2, paclitaxel 145 mg/m^2, and cyclophosphamide 600 mg/m^2 sequentially every two to three weeks for three doses each

relaxation (6%), deep breathing (4%), reading (4%), journaling (2%), and singing (2%). The most frequent combination of relaxation techniques was deep breathing as the primary and imagination or visualization as the secondary technique.

Discussion

The specific aims of the current study were to determine the impact of the overall extent of relaxation practice on immune responses and document the extent of relaxation practice and the common types of relaxation techniques preferred by women during and after the diagnosis and treatment of breast cancer. The central hypothesis was that the higher extent of overall relaxation practice would influence immune responses in a more favorable manner (higher immune responses for all markers except for IL-6).

The authors' findings partially supported the hypothesis by showing a significant impact of the overall extent of relaxation practice on NKCA 25:1, NKCA 50:1, lymphocyte proliferation, and IL-4 and IL-10 responses. After adjusting for the effects of potential covariates (e.g., age, cancer stage, type of cancer adjuvant therapy, menopausal status, baseline immune response at the beginning of the 10-month period), the extent of relaxation practice explained an additional 12%–30% of variance for these immune responses. These findings are similar to those of other stress management programs that showed increased NKCA and natural killer cell counts (Robinson, Mathews, & Witek-Janusek, 2003; Witek-Janusek et al., 2008) and improved lymphocyte proliferation (McGregor et al., 2004). However, the aim of the current study differed from others in that the authors focused on the dose effects of relaxation practice on immune responses within the intervention group, not on the group difference between the intervention and control groups. Although both types of investigations are necessary, the current study highlights the importance of understanding the within-group individual variability in longer-term adherent behaviors on immune responses. In comparison, the extent of relaxation practice did not significantly influence the IFN-γ, IL-2, and IL-6 responses. The responsivity of immune markers to the same stress management program often differs among markers. Other studies also have indicated that certain immune markers, such as NKCA and lymphocyte proliferation, showed improvement with the stress management program but others, such as cytokines, did not when immune responses between the intervention and nonintervention control groups were compared (Carlson et al., 2003, 2007; Witek-Janusek et al., 2008).

The clinical significance of the immune responses is not immediately clear, requiring additional follow-up on meaningful clinical outcomes in a defined setting and in a defined population over time. Previous studies haven shown that NKCA, for example, was significantly lower in women diagnosed with breast cancer or with advanced stage breast cancer than in healthy controls (Konjevic & Spuzic, 1993), suggesting beneficial clinical significance of having higher NKCA. The knowledge of natural killer cells has been expanding rapidly. Natural killer cells command other diverse critical functions in the regulation of immune responses, tumor biology, stress responses, and viral and microbial infections, as well as in the regulation of transplantation outcomes and autoimmune diseases (Becknell & Caligiuri, 2008; Caligiuri, 2008; Di Santo, 2008; Vivier, Tomasello, Baratin, Walzer, & Ugolini, 2008). In addition, natural killer cells are believed to bridge the innate and adaptive immune responses, and natural killer therapy is anticipated to be used for the prevention and treatment of cancer (Becknell & Caligiuri, 2008). That new knowledge suggests a greater role of natural killer cells in the immune system. Similarly, decreased lymphocyte proliferation was inversely associated with positive nodal status (Head et al., 1993), further supporting the potential clinical significance of having more favorable immune responses on these markers. The clinical significance of higher IL-4 and IL-10 is not well explored in cancer.

However, IL-4 has shown the inhibitory effects on the growth of breast cancer cells in vitro (Blais et al., 1996; Gooch et al., 1998; Toi et al., 1992), and IL-10 is a typical anti-inflammatory cytokine, both suggesting potential clinical benefits in this population.

IFNs and IL-2 are typical cytokines that enhance NKCA (Sinkovics & Horvath, 2005), and a subset of natural killer cells produces cytokines to support the host's immune responses. Despite higher NKCA with greater relaxation practice, IFN-γ, IL-2, and IL-6 responses were not significantly affected by the extent of relaxation practice, which suggests that NKCA responses were not dependent on IFN-γ and IL-2 cytokine responses in this setting. In addition, these women were recovering from adjuvant

Table 4. Effects of the Overall Extent of Relaxation Practice for 10 Months on Immune Responses

	Model				Change			Coefficient			
Immune Marker	**R^2**	**AdjR^2**	**F**	**p**	**R^2**	**F**	**p**	**B**	**β**	**t**	**p**
NKCA 25:1											
Covariates	0.07	–0.06	0.53	0.715	–	–	–	–	–	–	–
Baseline IR	0.12	–0.03	0.78	0.57	0.06	1.75	0.197	–	–	–	–
Relaxation practice	0.43	0.3	3.34	0.014	0.3	14.28	0.001	0.07	0.62	3.78	0.001
NKCA 50:1											
Covariates	0.02	–0.12	0.11	0.977	–	–	–	–	–	–	–
Baseline IR	0.07	–0.09	0.45	0.812	0.06	1.77	0.194	–	–	–	–
Relaxation practice	0.35	0.21	2.42	0.053	0.28	11.48	0.002	0.1	0.6	3.39	0.002
LP											
Covariates	0.6	–0.08	0.42	0.794	–	–	–	–	–	–	–
Baseline IR	0.3	0.16	2.13	0.095	0.24	8.48	0.007	–	–	–	–
Relaxation practice	0.45	0.31	3.26	0.017	0.15	6.57	0.017	492.63	0.44	2.56	0.017
(Baseline IR)	–	–	–	–	–	–	–	0.36	0.46	2.63	0.015
IFN-γ											
Covariates	0.24	0.13	2.26	0.087	–	–	–	–	–	–	–
Baseline IR	0.46	0.37	4.81	0.003	0.23	11.71	0.002	–	–	–	–
Relaxation practice	0.51	0.41	4.74	0.002	0.05	2.8	0.106	2.53	0.28	1.68	0.106
(Baseline IR)	–	–	–	–	–	–	–	0.6	0.39	2.52	0.018
IL-2											
Covariates	0.33	0.24	3.6	0.017	–	–	–	–	–	–	–
Baseline IR	0.52	0.43	6.02	0.001	0.19	10.82	0.003	–	–	–	–
Relaxation practice	0.54	0.43	5.18	0.001	0.02	0.97	0.333	0.24	0.16	0.99	0.333
(Cancer stage)	–	–	–	–	–	–	–	59.81	0.42	2.77	0.01
(Baseline IR)	–	–	–	–	–	–	–	0.72	0.42	2.47	0.02
IL-4											
Covariates	0.18	0.06	1.57	0.21	–	–	–	–	–	–	–
Baseline IR	0.21	0.67	1.47	0.231	0.03	1.08	0.308	–	–	–	–
Relaxation practice	0.37	0.23	2.65	0.037	0.16	6.99	0.013	0.43	0.46	2.64	0.013
IL-6											
Covariates	0.3	0.21	3.28	0.024	–	–	–	–	–	–	–
Baseline IR	0.31	0.19	2.55	0.05	0.001	0.05	0.823	–	–	–	–
Relaxation practice	0.34	0.21	2.43	0.051	0.04	1.6	0.217	–1.42	–0.22	–1.26	0.217
(Type of adjuvant therapy)	–	–	–	–	–	–	–	–292.5	–0.51	–3.16	0.004
IL-10											
Covariates	0.26	0.16	2.61	0.055	–	–	–	–	–	–	–
Baseline IR	0.33	0.22	2.91	0.03	0.08	3.33	0.078	–	–	–	–
Relaxation practice	0.46	0.34	3.93	0.006	0.12	6.33	0.018	0.42	0.39	2.52	0.018

AdjR^2—adjusted R^2; Baseline IR—baseline immune response for a given immune marker at the beginning of 10-month relaxation practice; Covariates—age, cancer stage, type of cancer adjuvant therapy, and menopausal stage; IFN-γ (pg/ml)—interferon-gamma; IL (pg/ml)—interleukin; LP (x 1,000 count per minute)—lymphocyte proliferation to stimulation with phytohemagglutinin 10 mcg/ml; NKCA (%)—natural killer cell activity at 25:1 and 50:1 effector-to-target cell ratios

Note. Unstandardized and standardized coefficients are indicated for relaxation practice and only for other individual factors found to be significant in the final model.

Table 5. Level of Immune Responses

Immune Marker	N	Time 1 $\bar{X}$	Time 1 SD	Time 2 $\bar{X}$	Time 2 SD	p
NKCA 25:1	37	11.3	8.1	10.3	7.8	0.71
NKCA 50:1	37	15.3	10.5	15.7	11.9	0.92
LP 10	34	139.6	81.8	99.8	63.5	0.007
IFN-γ	37	1304.7	404.5	1129.3	610.2	0.035
IL-2	37	95.3	55.7	78.9	98.2	0.001
IL-4	37	60.4	64.1	59.5	64.3	0.66
IL-6	37	1043.5	695.1	1168.8	481.8	0.23
IL-10	38	133.9	56.8	106.3	72.1	0.076

IFN-γ (pg/ml)—interferon-gamma; IL (pg/ml)—interleukin; LP (x 1,000 count per minutes)—lymphocyte proliferation to stimulation with phytohemagglutinin 10 mcg/ml; NKCA (%)—natural killer cell activity at 25:1 and 50:1 effector-to-target cell ratios

Note. Time 1 is the beginning of 10-month relaxation practice, and Time 2 is the end of 10-month relaxation practice.

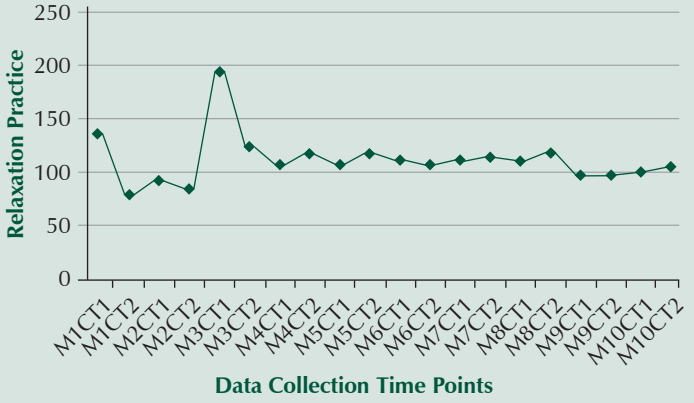
Note. P values represent Wilcoxon signed-ranks test results.

therapy, and their immune responsivity to relaxation practice might have been dampened by slow recovery of immune responses. Immune data presented in Table 5 indicate how overall immune responses are depressed and show poor recovery over time. IL-2 recovery, for example, was most profoundly delayed following adjuvant therapy, particularly following chemotherapy. One year after starting breast cancer adjuvant therapy, only a small fraction of women (6%–18%) had recovered their IL-2 responses to pretreatment levels (Kang et al., 2009). Other studies, however, indicated that high levels of serum IL-6 were predictive of shorter disease-free and overall survival in women with metastatic breast cancer (Bachelot et al., 2003; Bozcuk et al., 2004). Therefore, a lack of change in IL-6 response to relaxation practice might have been a more desirable outcome. Taken together, the overall immune responses to the greater extent of relaxation practice seemed to show favorable immune changes.

The average frequency of relaxation practice was 5.3 times a week for about 19 minutes each time over the 10-month period, during which the women started recovery after completing adjuvant therapy. Although the average frequency and duration of relaxation practice seem to be reasonable, the range and standard deviation indicate considerable variability in the extent of relaxation practice among individuals as found in other studies of adherent behaviors (Dew et al., 2009; Erlen & Sereika, 2006; Fappa et al., 2008; Forkan et al., 2006; Webber et al., 2010). The frequency of practice ranged from 0–14 times per week, whereas the duration of practice per session ranged from 0–60 minutes. The overall trend suggests that their practice pattern may stabilize around month 3 or 4 and become more consistent in subsequent months. How often and how long relaxation practice should be performed to obtain maximum psychosocial and physiologic benefits is unclear, but it will be an important area of future research to find a threshold in a larger sample. In doing so, other factors, such as individual differences in perceived level of stress from cancer diagnosis and treatment and responsivity to relaxation practice in reducing stress, should be considered. Equally important is considering how to promote increased adherence to relaxation practice to gain the most benefits (Alhassan et al., 2008; Fappa et al., 2008). Having the choice to select from different common relaxation techniques may be one way. Out of four relaxation techniques introduced in the current study, deep breathing was the most preferred primary technique. However, some women preferred the use of a combination of more than one technique to achieve relaxation. Exploring different methodologies for promoting adherence may be another important area of continuing research.

Limitations

The findings of the study should be interpreted with caution because of several limitations. First, the extent of relaxation practice is based on self-reported data. Therefore, participants may have overstated or understated the extent of relaxation practice. Even so, researchers often have difficulty verifying the participants' reports and finding alternative ways to better assess the practice behaviors over a long period. To minimize a recall bias and loss of data, however, the practice data were collected twice a month via phone calls for 10 months until the end of the study. The



CT1—first half of the month; CT2—second half of the month; M1–M10—month 1–month 10; relaxation practice—mean frequency of practice per week x mean duration of practice per session in minutes

Figure 2. Extent of Weekly Relaxation Practice Over 10 Months

reported practice data indicated a wide range for the frequency and duration of relaxation practice, partly suggesting that participants were willing to report the poor or absence of practice. Another limitation is the lack of follow-up on the levels of exercise or physical activity over the study period. The moderate-intensity exercise was an integral component of the focused eight-week intervention of the parent study. Although a significant amount of research team effort was allocated to encourage adherence to an exercise regimen, participants showed a considerably higher level of difficulty for adhering to exercise program than to stress management, even during the eight-week focused intervention period. Data collection on exercise became increasingly difficult, with irregular and vague responses to the point that data became too sporadic to collate for a meaningful data set. No clear evidence exists suggesting any potential systematic bias to any one direction on exercise component. Another limitation is a relatively small sample size. Because of the specific purpose of the analysis, the sample size was limited to only the intervention group. In addition, the intense nature of the parent intervention study with multiple biologic assessments limited the size of the sample. Despite the limitations, the study's findings would serve as a basis for many forthcoming inquiries on stress, immune responses, relaxation practice, dose effects, adherence, and more.

Conclusion and Clinical Implications

The study's findings suggest that persistent relaxation practice has positive effects on multiple immune responses in a dose-dependent manner in women treated for new breast cancer and recovering from cancer. Providing a choice for relaxation technique or any other similar interventions may enhance adherence to the prescribed practice. However, additional intervention studies with rigorous designs and larger sample sizes should be conducted to validate the findings of the current study. Once similar findings are validated, stress and other psychosocial factors should be assessed routinely in the clinical areas to provide comprehensive care encompassing the mind and the body, particularly with patients confronting significant healthcare issues. Healthcare providers must be sensitive to patients' psychosocial and emotional needs, be knowledgeable about available resources, and be able to guide the patients to proper resources, including relaxation techniques and other stress reduction programs. At the same time, the importance of long-term adherence to the program to receive the intended benefits should be communicated clearly to promote greater adherence to recommended practice.

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References

Alhassan, S., Kim, S., Bersamin, A., King, A.C., & Gardner, C.D. (2008). Dietary adherence and weight loss success among overweight women: Results from the A to Z weight loss study. *International Journal of Obesity, 32,* 985–991. doi: 10.1038/ijo.2008.8

Andoniou, C.E., Andrews, D.M., & Degli-Esposti, M.A. (2006). Natural killer cells in viral infection: More than just killers. *Immunological Reviews, 214,* 239–250. doi: 10.1111/j.1600-065X.2006.00465.x

Antoni, M.H. (2003). Stress management effects on psychological, endocrinological, and immune functioning in men with HIV infection: Empirical support for a psychoneuroimmunological model. *Stress, 6,* 173–188. doi: 10.1080/1025389031000156727

Antoni, M.H., Lehman, J.M., Kilbourn, K.M., Boyers, A.E., Culver, J.L., Alferi, S.M., . . . Carver, C.S. (2001). Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early-stage breast cancer. *Health Psychology, 20*(1), 20–32.

Arduino, S., Tessarolo, M., Bellino, R., Colombatto, S., Leo, L., Wierdis, T., & Lanza, A. (1996). Reduced IL-2 level concentration in patients with breast cancer as a possible risk factor for relapse. *European Journal of Gynaecological Oncology, 17,* 535–537.

Bachelot, T., Ray-Coquard, I., Menetrier-Caux, C., Rastkha, M., Duc, A., & Blay, J.Y. (2003). Prognostic value of serum levels of interleukin 6 and of serum and plasma levels of vascular endothelial growth factor in hormone-refractory metastatic breast cancer patients. *British Journal of Cancer, 88,* 1721–1726.

Becknell, B., & Caligiuri, M.A. (2008). Natural killer cells in innate immunity and cancer. *Journal of Immunotherapy, 31,* 685–692. doi: 10.1097/CJI.0b013e318182de23

Blais, Y., Gingras, S., Haagensen, D.E., Labrie, F., & Simard, J. (1996). Interleukin-4 and interleukin-13 inhibit estrogen-induced breast cancer cell proliferation and stimulate GCDFP-15 expression in human breast cancer cells. *Molecular and Cellular Endocrinology, 121*(1), 11–18. doi: 10.1016/0303-7207(96)03843-9

Bleiker, E.M., Pouwer, F., van der Ploeg, H.M., Leer, J.W., & Adèr, H.J. (2000). Psychological distress two years after diagnosis of breast cancer: Frequency and prediction. *Patient Education and Counseling, 40,* 209–217. doi: 10.1016/S0738-3991(99)00085-3

Bozcuk, H., Uslu, G., Samur, M., Yildiz, M., Özben, T., Özdogan, M., . . . Savas, B. (2004). Tumour necrosis factor-alpha, interleukin-6, and fasting serum insulin correlate with clinical outcome in metastatic

breast cancer patients treated with chemotherapy. *Cytokine, 27*(2–3), 58–65. doi: 10.1016/j.cyto.2004.04.002

Brittenden, J., Heys, S.D., Ross, J., & Eremin, O. (1996). Natural killer cells and cancer. *Cancer, 77,* 1226–1243. doi:10.1002/(SICI)1097-0142(19960401)77:7<1226::AID-CNCR2>3.0.CO;2-G

Caligiuri, M.A. (2008). Human natural killer cells. *Blood, 112,* 461–469. doi: 10.1182/blood-2007-09-077438

Carlson, L.E., Speca, M., Faris, P., & Patel, K.D. (2007). One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. *Brain, Behavior, and Immunity, 21,* 1038–1049. doi: 10.1016/j.bbi.2007.04.002

Carlson, L.E., Speca, M., Patel, K.D., & Goodey, E. (2003). Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients. *Psychosomatic Medicine, 65,* 571–581. doi: 10.1097/01.PSY.0000074003.35911.41

Claesson, M., Birgander, L.S., Jansson, J.H., Lindahl, B., Burell, G., Asplund, K., & Mattsson, C. (2006). Cognitive-behavioural stress management does not improve biological cardiovascular risk indicators in women with ischaemic heart disease: A randomized-controlled trial. *Journal of Internal Medicine, 260,* 320–331. doi: 10.1111/j.1365-2796.2006.01691.x

Claesson, M., Birgander, L.S., Lindahl, B., Nasic, S., Aström, M., Asplund, K., & Burell, G. (2005). Women's hearts—Stress management for women with ischemic heart disease: Explanatory analyses of a randomized controlled trial. *Journal of Cardiopulmonary Rehabilitation, 25*(2), 93–102. doi: 10.1097/00008483-200503000-00009

Cohen, S. (1995). Psychological stress and susceptibility to upper respiratory infections. *American Journal of Respiratory and Critical Care Medicine, 152*(4, Pt. 2), S53–S58.

Corwin, E.J. (2000). Understanding cytokines. Part I: Physiology and mechanism of action. *Biological Research for Nursing, 2*(1), 30–40. doi: 10.1177/109980040000200104

Cruess, D.G., Antoni, M.H., McGregor, B.A., Kilbourn, K.M., Boyers, A.E., Alferi, S.M., . . . Kumar, M. (2000). Cognitive-behavioral stress management reduces serum cortisol by enhancing benefit finding among women being treated for early stage breast cancer. *Psychosomatic Medicine, 62,* 304–308.

Davis, M., Eshelman, E.R., & McKay, M. (1998). *The relaxation and stress reduction workbook* (4th ed.). Oakland, CA: New Harbinger

Dew, M.A., Dabbs, A.D., Myaskovsky, L., Shyu, S., Shellmer, D.A., DiMartini, A.F., . . . Greenhouse, J.B. (2009). Meta-analysis of medical regimen adherence outcomes in pediatric solid organ transplantation. *Transplantation, 88,* 736–746. doi: 10.1097/TP.0b013e3181b2a0e0

Diggle, P.J., Liang, K.Y., & Zeger, S.L. (1994). *Analysis of longitudinal data*. New York, NY: Oxford University Press.

Di Santo, J.P. (2008). Natural killer cells: Diversity in search of a niche. *Nature Immunology, 9,* 473–475.

Elsässer-Beile, U., von Kleist, S., & Gallati, H. (1991). Evaluation of a test system for measuring cytokine production in human whole blood cell cultures. *Journal of Immunological Methods, 139,* 191–195. doi: 10.1016/0022-1759(91)90188-L

Elsässer-Beile, U., von Kleist, S., Sauther, W., Gallati, H., & Mönting, J.S. (1993). Impaired cytokine production in whole blood cell cultures of patients with gynaecological carcinomas in different clinical stages. *British Journal of Cancer, 68*(1), 32–36. doi: 10.1038/bjc.1993.282

Epping-Jordan, J.E., Compas, B.E., Osowiecki, D.M., Oppedisano, G., Gerhardt, C., Primo, K., & Krag, D.N. (1999). Psychological adjustment in breast cancer: Processes of emotional distress. *Health Psychology, 18,* 315–326. doi: 10.1037/0278-6133.18.4.315

Erlen, J.A., & Sereika, S.M. (2006). Fidelity to a 12-week structured medication adherence intervention in patients with HIV. *Nursing Research, 55*(2, Suppl.), S17–S22. doi: 10.1097/00006199-200603001-00004

Fappa, E., Yannakoulia, M., Pitsavos, C., Skoumas, I., Valourdou, S., & Stefanadis, C. (2008). Lifestyle intervention in the management of metabolic syndrome: Could we improve adherence issues? *Nutrition, 24,* 286–291. doi: 10.1016/j.nut.2007.11.008

Forkan, R., Pumper, B., Smyth, N., Wirkkala, H., Ciol, M.A., & Shumway-Cook, A. (2006). Exercise adherence following physical therapy intervention in older adults with impaired balance. *Physical Therapy, 86,* 401–410.

Glaser, R. (2005). Stress-associated immune dysregulation and its importance for human health: A personal history of psychoneuroimmunology. *Brain, Behavior, and Immunity, 19,* 3–11. doi: 10.1016/j.bbi.2004.06.003

Golden-Kreutz, D.M., Thornton, L.M., Wells-Di Gregorio, S., Frierson, G.M., Jim, H.S., Carpenter, K.M., . . . Anderson, B.L. (2005). Traumatic stress, perceived global stress, and life events: Prospectively predicting quality of life in breast cancer patients. *Health Psychology, 24,* 288–296. doi: 10.1037/0278-6133.24.3.288

Gooch, J.L., Lee, A.V., & Yee, D. (1998). Interleukin 4 inhibits growth and induces apoptosis in human breast cancer cells. *Cancer Research, 58,* 4199–4205.

Härtl, K., Engel, J., Herschbach, P., Reinecker, H., Sommer, H., & Friese, K. (2010). Personality traits and psychosocial stress: Quality of life over 2 years following breast cancer diagnosis and psychological impact factors. *Psycho-Oncology, 19,* 160–169. doi: 10.1002/pon.1536

Head, J.F., Elliott, R.L., & McCoy, J.L. (1993). Evaluation of lymphocyte immunity in breast cancer patients. *Breast Cancer Research and Treatment, 26*(1), 77–88. doi: 10.1007/BF00682702

Kang, D.H., Coe, C.L., & McCarthy, D.O. (1996). Academic examinations significantly impact immune responses, but not lung function, in healthy and well-managed asthmatic adolescents. *Brain, Behavior, and Immunity, 10,* 164–181. doi: 10.1006/brbi.1996.0015

Kang, D.H., Coe, C.L., McCarthy, D.O., & Ershler, W.B. (1997). Immune responses to final exams in healthy and asthmatic adolescents. *Nursing Research, 46*(1), 12–19. doi: 10.1097/00006199-199701000-00003

Kang, D.H., Rice, M., Park, N.J., Turner-Henson, A., & Downs, C. (2010). Stress and inflammation: A biobehavioral approach for nursing research. *Western Journal of Nursing Research, 32,* 730–760. doi: 10.1177/0193945909356556

Kang, D.H., Weaver, M.T., Park, N.J., Smith, B., McArdle, T., & Carpenter, J. (2009). Significant impairment in immune recovery after cancer treatment. *Nursing Research, 58*(2), 105–114. doi: 10.1097/NNR.0b013e31818fcecd

Kang, D.H., Weaver, M.T., Park, N.J., Smith, B., McArdle, T., Landers, K., & Carpenter, J. (2011). *Psychological and immune outcomes to an integrated stress management and exercise intervention.* Manuscription in preparation.

Kangas, M., Henry, J.L., & Bryant, R.A. (2002). Posttraumatic stress disorder following cancer. A conceptual and empirical review. *Clinical Psychology Review, 22,* 499–524. doi: 10.1016/S0272-7358(01)00118-0

Kerr, L.R., Hundal, R., Silva, W.A., Emerman, J.T., & Weinberg, J. (2001). Effects of social housing condition on chemotherapeutic efficacy in a Shionogi carcinoma (SC115) mouse tumor model: Influences of temporal factors, tumor size, and tumor growth rate. *Psychosomatic Medicine, 63,* 973–984.

Kiecolt-Glaser, J.K., McGuire, L., Robles, T.F., & Glaser, R. (2002a). Psychoneuroimmunology and psychosomatic medicine: Back to the future. *Psychosomatic Medicine, 64*(1), 15–28.

Kiecolt-Glaser, J.K., McGuire, L., Robles, T.F., & Glaser, R. (2002b). Psychoneuroimmunology: Psychological influences on immune function and health. *Journal of Consulting and Clinical Psychology, 70,* 537–547. doi: 10.1037/0022-006X.70.3.537

Konjevic, G., & Spuzic, I. (1993). Stage dependence of NK cell activity and its modulation by interleukin 2 in patients with breast cancer. *Neoplasma, 40*(2), 81–85.

Lissoni, P., Barni, S., Rovelli, F., & Tancini, G. (1991). Lower survival in metastatic cancer patients with reduced interleukin-2 blood concentrations. Preliminary report. *Oncology, 48,* 125–127. doi: 10.1159/000226910

Llanes-Fernández, L., Arango-Prado Mdel, C., Alcocer-González, J.M., Guerra-Yi, M.E., Franco-Odio, S., Camacho-Rodríguez, R.,

. . . Rodríguez-Podilla, C. (2009). Association between the expression of IL-10 and T cell activation proteins loss in early breast cancer patients. *Journal of Cancer Research and Clinical Oncology, 135,* 255–264. doi: 10.1007/s00432-008-0446-7

Luecken, L.J., & Compas, B.E. (2002). Stress, coping, and immune function in breast cancer. *Annals of Behavioral Medicine, 24,* 336–344. doi: 10.1207/S15324796ABM2404_10

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

Palesh, O., Butler, L.D., Koopman, C., Giese-Davis, J., Carlson, R., & Spiegel, D. (2007). Stress history and breast cancer recurrence. *Journal of Psychosomatic Research, 63,* 233–239. doi: 10.1016/j.jpsychores.2007.05.012

Palmer, S.C., Kagee, A., Coyne, J.C., & DeMichele, A. (2004). Experience of trauma, distress, and post-traumatic stress disorder among breast cancer patients. *Psychosomatic Medicine, 66,* 258–264. doi: 10.1097/01.psy.0000116755.71033.10

Peters, C., Lötzerich, H., Niemeier, B., Schüle, K., & Uhlenbruck, G. (1994). Influence of a moderate exercise training on natural killer cytotoxicity and personality traits in cancer patients. *Anticancer Research, 14*(3A), 1033–1036.

Pross, H.F., & Lotzová, E. (1993). Role of natural killer cells in cancer. *Natural Immunity, 12*(4–5), 279–292.

Reiche, E.M., Nunes, S.O., & Morimoto, H.K. (2004). Stress, depression, the immune system, and cancer. *Lancet Oncology, 5,* 617–625. doi: 10.1016/S1470-2045(04)01597-9

Robinson, F.P., Mathews, H.L., & Witek-Janusek, L. (2003). Psychoendocrine-immune response to mindfulness-based stress reduction in individuals infected with the human immunodeficiency virus: A quasi-experimental study. *Journal of Alternative and Complementary Medicine, 9,* 683–694. doi: 10.1089/107555303322524535

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

Sephton, S.E., Sapolsky, R.M., Kraemer, H.C., & Spiegel, D. (2000). Diurnal cortisol rhythm as a predictor of breast cancer survival. *Journal of the National Cancer Institute, 92,* 994–1000. doi: 10.1093/jnci/92.12.994

Sinkovics, J.G., & Horvath, J.C. (2005). Human natural killer cells: A comprehensive review. *International Journal of Oncology, 27*(1), 5–47.

Su, F., Ouyang, N., Zhu, P., Ouyang, N., Jia, W., Gong, C., . . . Song, E. (2005). Psychological stress induces chemoresistance in breast cancer by upregulating mdr1. *Biochemical and Biophysical Research Communications, 329,* 888–897. doi: 10.1016/j.bbrc.2005.02.056

Tabachnick, B.G., & Fidell, L.S. (2000). *Using multivariate statistics* (4th ed.). Boston, MA: Allyn and Bacon.

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

Toi, M., Bicknell, R., & Harris, A.L. (1992). Inhibition of colon and breast carcinoma cell growth by interleukin-4. *Cancer Research, 52,* 275–279.

Vicari, A.P., & Trinchieri, G. (2004). Interleukin-10 in viral diseases and cancer: Exiting the labyrinth? *Immunological Reviews, 202,* 223–236. doi: 10.1111/j.0105-2896.2004.00216.x

Vivier, E., Tomasello, E., Baratin, M., Walzer, T., & Ugolini, S. (2008). Functions of natural killer cells. *Nature Immunology, 9,* 503–510. doi: 10.1038/ni1582

Von Ah, D., Kang, D.H., & Carpenter, J.S. (2007). Stress, optimism, and social support: Impact on immune responses in breast cancer. *Research in Nursing and Health, 30*(1), 72–83. doi: 10.1002/nur.20164

Webber, K.H., Tate, D.F., Ward, D.S., & Bowling, J.M. (2010). Motivation and its relationship to adherence to self-monitoring and weight loss in a 16-week Internet behavioral weight loss intervention. *Journal of Nutrition Education and Behavior, 42,* 161–167. doi: 10.1016/j.jneb.2009.03.001

Whiteside, T.L., & Herberman, R.B. (1995). The role of natural killer cells in immune surveillance of cancer. *Current Opinion in Immunology, 7,* 704–710. doi: 10.1016/0952-7915(95)80080-8

Witek-Janusek, L., Albuquerque, K., Chroniak, K.R., Chroniak, C., Durazo-Arvizu, R., & Mathews, H.L. (2008). Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. *Brain, Behavior, and Immunity, 22,* 969–981. doi: 10.1016/j.bbi.2008.01.012

Yang, H.C., Brothers, B.M., & Andersen, B.L. (2008). Stress and quality of life in breast cancer recurrence: moderation or mediation of coping? *Annals of Behavioral Medicine, 35,* 188–197.