Mindfulness-Based Stress Reduction in Relation to Quality of Life, Mood, Symptoms of Stress, and Immune Parameters in Breast and Prostate Cancer Outpatients

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Objectives: This study investigated the relationships between a mindfulness-based stress reduction meditation program for early stage breast and prostate cancer patients and quality of life, mood states, stress symptoms, lymphocyte counts, and cytokine production. **Methods:** Forty-nine patients with breast cancer and 10 with prostate cancer participated in an 8-week MBSR program that incorporated relaxation, meditation, gentle yoga, and daily home practice. Demographic and health behavior variables, quality of life (EORTC QLQ C-30), mood (POMS), stress (SOSI), and counts of NK, NKT, B, T total, T helper, and T cytotoxic cells, as well as NK and T cell production of TNF, IFN-γ, IL-4, and IL-10 were assessed pre- and postintervention. **Results:** Fifty-nine and 42 patients were assessed pre- and postintervention, respectively. Significant improvements were seen in overall quality of life, symptoms of stress, and sleep quality. Although there were no significant changes in the overall number of lymphocytes or cell subsets, T cell production of IL-4 increased and IFN-γ decreased, whereas NK cell production of IL-10 decreased. These results are consistent with a shift in immune profile from one associated with depressive symptoms to a more normal profile. **Conclusions:** MBSR participation was associated with enhanced quality of life and decreased stress symptoms in breast and prostate cancer patients. This study is also the first to show changes in cancer-related cytokine production associated with program participation.
Key words: psychoneuroimmunology (PNI), meditation, cancer, stress, quality of life, lymphocytes, cytokines.

ANOVA = analysis of variance; **EORTC-QLQ-C30** = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; **FBS** = fetal bovine serum; **IFN-γ** = interferon gamma; **IL** = interleukin; **MBSR** = mindfulness-based stress reduction; **NK** = natural killer; **PBS** = phosphate-buffered saline; **PI** = principal investigator; **PMA** = phorbol 12-myristate 13-acetate; **POMS** = Profile of Mood States; **PTSD** = posttraumatic stress disorder; **QL** = quality of life; **RA** = research assistant; **RBC** = red blood cells; **SOSI** = Symptoms of Stress Inventory; **TNF** = tumor necrosis factor; **WBC** = white blood cells.

INTRODUCTION

Recently, there has been a growth of clinical treatment and wellness programs based on mindfulness meditation and yoga modeled after the mindfulness-based stress reduction (MBSR) program of Jon Kabat-Zinn and colleagues (1) at the Stress Reduction Clinic of the University of Massachusetts Medical Center. Since their initial inception in 1979, there are now over 240 such programs across North America.

MBSR is rooted in the contemplative spiritual traditions in which the experience of conscious awareness is actively cultivated. Within a framework of nonjudging, acceptance, and patience, meditative practice often focuses awareness on the breath leading to a state of relaxation and observant detachment. The body of research investigating MBSR's efficacy for the treatment of health problems has also grown. Studies have shown its efficacy for problems as varied as chronic pain (2, 3) anxiety disorders (4, 5), fibromyalgia (6, 7), epilepsy (8), psoriasis (9), and hypertension (10). Enhancement of health-related quality of life with improved vitality, less bodily pain, fewer role limitations caused by physical health, greater social functioning, and decreased anxiety and depression have been shown recently in a group of mixed diagnosis medical patients (11).

It seemed logical, therefore, to offer the MBSR program to patients diagnosed with cancer, as emotional distress after receipt of a cancer diagnosis is common (12–14). Within the population of cancer patients, there is a growing interest in mind-body medicine and complementary and alternative therapies as well as a desire to be proactive and take initiative in personal care (15, 16). When asked about the cause of their breast cancer, a Canadian sample of women cited "stress" above other possible causal factors such as genetics, diet, and environmental factors (17). Thus, the MBSR program provides not only an efficacious treatment for distress, but fits with the patients' own framework of positive health behavior. Our initial work with MBSR showed improvements in symptoms of stress and mood disturbance in a mixed group of cancer patients (18, 19).

In addition to the demonstrated psychological benefits of the MBSR program, the practice of meditation has been associated with immunological effects. Solberg (20) found that meditation may modify the suppressive influence of strenuous physical stress on the immune system in male athletes. A randomized study of relaxation, meditation, and hypnosis training in asymptomatic HIV-positive men found improved T cell counts in the treatment group which were maintained at a 1-month follow-up (21). QiGong training, a Chinese energy system that combines meditative techniques with other practices, was associated with elevation in CD4 T cells and a higher CD4/CD8 cell ratio in a group of healthy practitioners compared with healthy controls (22).

Many studies have shown that cancer patients have compromised immune function (23), and immune factors have been used to predict disease progression. Levy et al. (24) found that less distress on the Profile Of Mood States predicted a longer disease-free interval in breast cancer patients, but lower natural killer (NK) cell activity predicted recurrence. In a group of breast cancer patients who had recently

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undergone surgery, stress level significantly predicted lower NK cell lysis, diminished response of NK cells to recombinant interferon gamma (IFN-γ), and decreased proliferative response of peripheral blood lymphocytes to plant lectins and to a monoclonal antibody directed against the T cell receptor (25). No psychosocial interventions were provided in these studies.

In addition to these observational studies, intervention studies have investigated the effects of psychotherapy on immune system measures, primarily in breast cancer patients. Fawzy et al. (26) provided a 6-week psychosocial intervention to melanoma patients and found significant increases in the percent of lymphocytes and NK cells, indications of increases in NK cytotoxic activity, and a small decrease in the percent of CD4 (helper) T cells. These changes were not observed immediately after the intervention but were evident on a 6-month follow-up assessment. Not all studies of the immune effects of interventions found increases in immune function, however. Breast cancer patients who participated in a 13-week experiential-existential group therapy program evidenced lower percentages of NK, CD4, and CD8 T cells as well as a lower proliferative response to pokeweed mitogen than patients in a waiting-list control condition (27). Richardson et al. (28) found that women with stages I to III breast cancer randomly assigned to either support or imagery sessions did not differ from those in a control condition on measures of NK cell cytotoxicity, IL-1, IL-2m or IFN-γ. Investigation of a two-session presurgical intervention for breast cancer that combined psychoeducation, problem-solving skills, relaxation techniques, and support found that levels of IFN-γ were suppressed in the control group postoperatively but not in the intervention group (29). Again, no changes in NK cell numbers were seen in this study nor in a study of the immune effects of relaxation during chemotherapy for ovarian cancer (30), although those in the relaxation therapy condition did evidence higher numbers of white blood cells and overall lymphocytes compared with the control patients. Of note is the heterogeneity of interventions and techniques investigated in these studies, resulting in a confusing overall picture. There are no studies published to date examining the effects of the MBSR program on immune function in cancer patients.

The pathways by which changes in immune function may translate into disease progression or regression are currently being debated in the literature (31–33). Some researchers question the importance of immunomodulation in cancer progression (33), suggesting that perhaps other pathways such as endocrine activation may be more important. This controversy results in a very exciting field of discovery where any new information may be a valuable addition to our understanding of a very complex puzzle. Based on our previous work and some preliminary research that has shown the effects of meditation on immune function, we sought to extend these observations to the study of the biochemical effects of the MBSR program, specifically its effects on immune cell numbers and function in breast and prostate cancer patients.

The decision to focus on breast and prostate cancer patients was based on the fact that these two cancers have similar good prognoses in the early disease stages and a similar, although often differently expressed, degree of physical and psychological impairment (34–36). Both cancers are also often hormonally dependent and thought to be responsive to psychosocial intervention. Breast and prostate cancer are also the two most prevalent carcinomas reported today in women and men, respectively (37).

METHODS

Subjects

Patients were deemed eligible to participate in the study if they met the following inclusion criteria: 1) age 18 years or older; 2) a diagnosis of stage 0, I, or II breast or early stage (localized) prostate cancer at any time in the past; and 3) a minimum of 3 months since surgery (mastectomy/lumpectomy/prostatectomy/cryotherapy/). Several exclusion criteria were also set: 1) treatment with chemotherapy, radiotherapy, or hormone therapy (except tamoxifen) currently or within the past 3 months; 2) a concurrent DSM-IV Axis I diagnosis; 3) a concurrent autoimmune disorder; and 4) past participation in an MBSR group.

A total of 59 breast and prostate cancer patients were enrolled in the study. One individual did not complete the time 1 measures. Sixteen individuals did not complete the time 2 measures, and of these, seven did not complete the intervention itself: four due to work demands, two due to scheduling difficulties, and one due to lack of interest. As such, data from 42 individuals were available for the pre-post analyses.

Instruments

Demographics and Medical History Form

Demographic information including age, education, marital status, occupation, and current employment status was obtained on a form created for this study. Medical history including type of illness, dates, and treatments were collected. Areas specifically assessed included heart disease, vascular disorders, autoimmune disorders, epilepsy, and psychiatric disorders. All current medications were recorded.

Health Behaviors Form

Health behaviors that could potentially affect the immune and/or endocrine systems were recorded, including amount of coffee, tea, and caffeinated soft-drink consumption (servings/wk); alcohol consumption (servings/wk); smoking (cigarettes/d); exercise (times/wk); average hours of sleep per night; self-rated quality of sleep (poor, adequate, good); and self-rated quality of diet (poor, adequate, good).

Weekly Meditation Form

This form collected daily information on minutes spent in home practice of mediation and yoga from each participant and was collected each week during class.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

This 30-item quality of life questionnaire includes five functional domains of quality of life: physical, role, emotional, cognitive, and social function, and two items assess global quality of life. There are also symptom scales measuring fatigue, pain, nausea and vomiting, dyspnea, sleep disturbance, appetite, constipation, diarrhea, and financial difficulties. It has become the gold standard of QL assessment in clinical trials both in Europe and North America, with much normative data available for comparison (38, 39).

Profile of Mood States (POMS)

The POMS (40) is a 65-item scale which assesses six affective dimensions. It has been widely used in the assessment of mood changes resulting

from a variety of interventions due to its responsiveness and has been used extensively with cancer populations (41).

Symptoms of Stress Inventory (SOSI)

The SOSI (42) was designed to measure physical, psychological, and behavioral responses to stressful situations. The respondent is instructed to rate the frequency with which they experience various stress-related symptoms on a five-point scale ranging from never to frequently during the past week. Ten subscale scores can be calculated.

Procedures

Recruitment

Patients were recruited from the Tom Baker Cancer Center. Patients were recruited primarily with pamphlets and posters around the center, in each of the breast and prostate clinic areas, and were able to self-refer. With the approval and cooperation of the breast tumor group staff, eligible breast cancer patients were also invited to participate in the study (and were given a summary of the research during their clinic visit) or were phoned and invited to participate. If patients were interested in participating, their name was placed on a waiting list administered by the research assistant (RA).

Testing

Once 15 patients were accrued on the waiting list using the recruitment strategy detailed above, they were scheduled for an individual interview with the principal investigator (PI) during the week before the start of the group to further explain the study, determine eligibility, and provide informed consent. During this interview, the Medical History Form and Health Behaviors Form were completed by the PI. A maximum of three patients were assessed daily between 8:00 AM – 10:00 AM (to control as much as possible for time of day) and the blood samples were all taken before 10:00 AM. Appointments were set for 8:00 AM, 8:30 AM, and 9:00 AM. After the 30-minute initial interview with the PI, subjects proceeded to the RA who drew a blood sample of four 7-mL heparinized Vacutainer tubes for immune cell counts and intracellular cytokine assays. The samples were sent to the lab on the same day by 10:00 AM, where the immune assays were conducted that day on the fresh samples. The patients then completed the assessment battery of questionnaires, supervised by the RA who clarified instructions and answered questions, which took approximately 30 minutes.

Beginning the week after the completion of the intervention, the same procedure was followed as before the intervention, with the patients returning to the hospital to have blood drawn and to complete the questionnaires. They completed the Health Behavior Form without the assistance of the PI for this assessment. All participants were assessed within 2 weeks of the completion of the intervention (maximum of four each morning).

Intervention

Details of the intervention, including objectives, structure, components, and content, have been described previously (19). Our program was modeled after the mindfulness-based stress reduction program at the Stress Reduction and Relaxation Clinic–Massachusetts Medical Center as described by Kabat-Zinn (1). A few changes have been made to the program since our last publication in order to make our program more consistent with the Kabat-Zinn MBSR format. The intervention was provided over the course of eight (rather than seven) weekly, 90-minute group sessions with a maximum of 15 participants each, and we added a 3-hour silent retreat on the Saturday between weeks 6 and 7. The Saturday retreat combined participants from all of our ongoing MBSR groups and usually consisted of about 40 participants. The program consisted of three primary components: 1) theoretical material related to mindfulness, relaxation, meditation, yoga, and the body-mind connection; 2) experiential practice of meditation and yoga during the group meetings and home-based practice; and 3) group process focused on solving problems concerning impediments to effective practice, practical day-to-day applications of mindfulness, and supportive interaction between group members.

In addition we produced and provided patients with a 52-page booklet containing information pertinent to each week's instruction, including a bibliography for those wishing to pursue relevant themes in greater depth, and an audio tape with a sensate-focused body scan meditation on one side and a guided sitting meditation on the other. Patients were instructed to practice daily. Didactic, inductive, and experiential modes of learning were employed to implement the intervention and to convey the informational content.

Immune Assays

Immune Reagents

Phorbol 12-myristate 13-acetate (PMA), ionomycin, and HEPES were obtained from Sigma Chemicals (St. Louis, MO). Brefeldin A and PermWash were obtained from BD Biosciences (Mississagua, Ontario). Fetal bovine serum, glutamine, beta-mercaptoethanol, and RPMI 1640 were obtained from Gibco BRL, Life Technologies (Grand Island, NY). CalLyse and all antibodies were obtained from Caltag (distributed by Cedar Lane, Hornby, Ontario).

Characterization of Leukocyte Subclasses

Whole blood was drawn into heparinized tubes. One hundred microliters of blood was mixed with 100 μL of phosphate-buffered saline (PBS), and isotype-matched fluorescently conjugated antibodies or fluorescently conjugated antibodies directed against specific cell surface determinates were added. Specifically, CD3 was used to identify T cells, CD19 for B cells, CD4 for helper T cells, CD8 for cytotoxic T cells, CD56 for NK cells, and both CD3 and CD56 for NKT cells. After 20 minutes at room temperature (RT), CalLyse was used according to manufacturer's instructions to fix the white blood cells (WBC) and lyse the red blood cells (RBC). The cells were then spun and resuspended in PBS for flow cytometry (FACS) analysis. Granulocytes, lymphocytes, and monocytes were identified by forward and side scatter properties. Eosinophils were differentiated from neutrophils in an unstained preparation based on autofluorescence. Lymphocytes were gated on and the percent of each lymphocyte subclass was determined based on the percentage of fluorescing cells. Data were acquired using a Becton Dickinson FACScan flow cytometer and data were analyzed using FlowJo software (Mountain View, CA). Lymphocyte results were reported as lymphocyte differentials percent positive for both gated (percent lymphocytes) and ungated (percent WBC). WBC count was reported as total number of cells, and neutrophils, monocytes, lymphocytes, and eosinophils were reported as percent of the WBC count.

Intracellular Cytokine Determination

Production of cytokines from stimulated lymphocytes was performed according to the procedure of Mendes et al. (43). Briefly, 1 ml of whole blood was mixed with 1 ml of stimulation buffer containing 10% fetal bovine serum (FBS), 2 mM of glutamine, 50 μM of β-mercaptoethanol, 10 mM of HEPES (pH 7.4), 50 ng/ml of PMA, 2 μg/ml of ionomycin, and 20 μg/ml of brefeldin A in RPMI 1640 and incubated for 4 hours at 37°C and 5% CO_2. Fluorescein isothiocyanate (FITC)-conjugated anti-CD3 and Cy5-conjugated anti-CD56 were added during the final 20 minutes of incubation. After stimulation, CalLyse was used according to manufacturer's instructions to fix the WBC and lyse the RBC. The WBCs were washed twice with PBS and then resuspended in PermWash from BD Biosciences. After 20 minutes, the cells were spun and resuspended in PermWash containing the appropriate phycoerythrin (PE)-conjugated anticytokine antibody. After 30 minutes at room temperature in the dark, 2 ml of PermWash was added and the cells were spun to remove unbound antibody. The cell pellet was resuspended in PBS and examined using flow cytometry. Data were acquired using a Becton Dickinson FACScan flow cytometer and data were analyzed using FlowJo software. The production of the cytokines interferon gamma (IFN-γ), tumor necrosis factor (TNF), and IL-4 and -10 (IL-10) were measured from both NK (CD56) and T (CD3) cells and reported as percent positive.

Data Analysis

All data analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 10.1, for the PC in Windows NT.

The demographic, medical history, and health behavior variables were described preintervention for the complete sample using frequency and descriptive statistics. The total number of lymphocyte subset cells were calcu-

lated by multiplying the percent of WBC of each cell type by the total number of WBC, then dividing by 100. To calculate the total number of cells expressing cytokines in the functional assays, the percent positive of the gated NK or T cells was multiplied by the percent of lymphocytes each cell type represented, then by the percent of total WBC composed of lymphocytes, then divided by 10,000.

All variables were tested for normalcy of the distributions. Of the health behavior and demographic continuous variables, only alcohol servings/wk was significantly positively skewed at both time periods (skewness > 2.0). On the EORTC, only nausea/vomiting and constipation were positively skewed at both time periods. On the SOSI and POMS, all variables were normal. The immune variables of NKT cells both gated and total were significantly positively skewed at both time points. As well, TNF NK and IL-4 NK cell cytokine production were also significantly positively skewed at both times as were IL-10 T cell production at time 2 only. Therefore, the natural log transformation was applied to all of these variables, at both time periods, which resulted in normal distributions for all variables. These transformed variables were subsequently used in all calculations. Untransformed values are reported in the tables.

To evaluate the effects of the intervention, paired-samples *t* tests were used to compare pre- and postintervention scores on the health behaviors, EORTC, POMS, and SOSI subscales and total scores as well as on the immune cell counts and cytokine levels. To analyze change across the two time points, residualized change scores were calculated on each subscale and total score and on the immune variables following the procedure outlined by Cohen and Cohen (44). In this pretreatment of the data, time 2 scores were adjusted for their time 1 values, so that only variance in residual (or regressed) change in the variables was left to be explained.

To investigate whether changes in immune measures were related to changes in quality of life, mood, or stress symptoms, Pearson product-moment correlations were performed between the residualized change scores on each of the immune measures and each of the overall total scores of the psychological measures. Similar correlations were also performed between class attendance, home practice, and both psychological and immunological change scores. To determine if health behaviors or other therapies influenced initial immune parameters, multiple regressions were performed with each of the time 1 immune parameters as the dependent variable, first entering demographic and disease-related variables, followed by caffeine and alcohol consumption, exercise, sleep hours, sleep quality, and diet quality.

RESULTS

Subjects

Demographic characteristics and health behaviors of participants at time one are presented in Table 1. Most participants were 50 years of age or older (mean ± SD, 54.5 ± 10.9 years). Most ($N = 42$) participants were married or cohabiting at the time of study entry. Participants were generally well educated, with a mean of 14.7 years of formal education. They had been diagnosed with cancer a median of 1.1 years previously (range = 3 months–20 years). Six participants were greater than 5 years post diagnosis. About two-thirds had stage II cancer (62.7%), and the remainder had a diagnosis of stage I. Data were collected on the type and timing of the last treatment each patient had received. Radiation was the last treatment for 28 patients; chemotherapy for 7; hormones for 5; 9 patients had no treatment at all; and the type of last treatment was unavailable for 10 patients. The median time for completion of last treatment was 6 months previously, with a range of 3 months to 20 years. Eighteen of the women were currently taking tamoxifen and continued to do so thorough the course of the study.

In order to compare those patients who were more recently diagnosed with those diagnosed further in the past, a split was conducted on the group, comparing those less than 1 year since diagnosis with those greater than 1 year, using independent-samples *t* tests on the variables of QL, health behaviors, SOSI, and POMS scores and immune variables at time 1. This resulted in groups of $N = 26$ for less than 1 year and $N = 33$

TABLE 1. Demographic Characteristics

	Preintervention		Postintervention	
Stage of cancer (*N* (%))				
1	19/56 (32.2)		14/40 (33.3)	
2	37/56 (62.7)		26/40 (61.3)	
Sleep quality (*N* (%))				
Poor	24/58 (40.7)		6/31 (19.4)*	
Adequate	20/58 (33.9)		13/31 (41.9)*	
Good	14/58 (23.7)		12/31 (38.7)*	
Diet quality (*N* (%))				
Poor	5/58 (8.5)		0/31	
Adequate	14/58 (23.7)		8/31 (25.8)	
Good	39/58 (66.1)		23/31 (74.2)	
Smoking status				
Nonsmokers (*N* (%))	52/59 (88.1)		42/43 (97.7%)	
	Mean	SD	Mean	SD
Cigarettes/day				
Smokers (Pre $N = 6$; Post $N = 1$)	14.8	9.7	25.0	0
Alcohol (servings/week)	1.8	3.4	1.8	3.1
Caffeine (servings/week)	17.8	15.2	17.0*	14.4
Exercise (times/week)	4.0	2.5	4.8*	2.3
Sleep (hours/night)	7.1	1.5	7.6	1.4

* Indicates improvement pre- to postintervention, $p < .05$.

for those greater than 1 year post diagnosis. The only two variables that the groups differed on at $p < .05$ were the symptoms of stress Cognitive Disorganization subscale ($t = 2.60$, $p < 0.05$) and the POMS Anger subscale ($t = 2.11$, $p < .05$), with those having more recent diagnoses feeling more confused and angry on these measures. There were no differences in health behaviors, immune measures, quality of life, or other mood or stress subscales or total scores.

Of the 42 patients who completed the time 2 measures, 33 had breast cancer and 9 had prostate cancer. Fourteen patients had stage I cancers and 26 patients had stage II cancers. χ^2 and *t* tests compared the 17 patients with incomplete data with the rest of the sample on all demographic, medical, and psychological variables collected at baseline or preintervention. Participants with complete data were more likely to be married or cohabiting rather than single, divorced, or widowed ($\chi^2(1) = 9.20$, $p < .005$). No other differences on the demographic or medical variables were found. Noncompleters had higher scores than completers on several of the baseline Profile of Mood States (POMS) subscales: depression ($t(56) = 3.6532$, $p < .001$); anger ($t(56) = 2.8783$, $p < .01$); and confusion ($t(56) = 2.1714$, $p < .05$). Such differences are consistent with other research, which has found that cancer patients experiencing emotional and cognitive disturbance seem less likely to comply with medical treatment regimens and participate in research (45). However, no baseline differences on the Symptoms of Stress Inventory (SOSI) were found.

Compliance

The 59 patients in this study attended a median of eight of a possible nine sessions over the 8 weeks (range = 1–9). Seven participants attended four or fewer sessions but the majority (46 patients, 78%) attended seven or more sessions. They also practiced at home as instructed, reporting an average of 24 min/d of meditation and 13 min/d of yoga over the course of the 8 weeks.

Health Behaviors

The initial sample reported consuming about 2.5 cups of caffeinated beverages each day. They drank a small amount of alcohol (1.8 drinks/wk) and exercised on average four times a week. They were sleeping an average of 7.1 hours per night but many (40.7%) reported sleep of poor quality. One-third of the sample reported adequate sleep and less than one-quarter reported having good quality of sleep. One-quarter of the patients reported their diet quality as generally adequate and two-thirds rated their diet as good quality. Only 12% of the sample were smokers and, of those, they smoked an average of 15 cigarettes/d.

Post data were available regarding health behavior for 31 of the 42 patients who completed the assessments. The missing data were due to a procedural oversight in that the participants of our first cohort were not asked to provide this data. However, paired-sample *t* tests and χ^2 nonparametric tests investigating changes in health behaviors for those in whom we had pre-post data found that sleep quality improved over the course of the intervention ($\chi^2 = 6.81$, $p < .05$), with 80% of the sample reporting adequate or good sleep on the postassessment. Caffeine servings per week decreased significantly ($t(31) = 2.38$, $p < .05$) and exercise increased ($t(30) = -2.10$, $p < .05$).

Quality of Life

EORTC pre- and post scores are presented in Table 2. Scores are only presented for the sample of 42 patients who completed both the pre- and postintervention questionnaires, on which the paired-samples *t* tests were conducted. Scores for physical and role functioning are not included, as the rate of endorsement of such problems was very low with little variability. Higher scores on the functional subscales indicate better quality of life, and higher scores on the symptom scales indicate higher levels of symptomatology. Changes were seen pre- to post on the overall global quality of life score ($t =$

TABLE 2. EORTC Scores

	Preintervention		Postintervention	
	Mean	SD	Mean	SD
Functional scales (higher scores = higher function)				
Emotional function	66.1	21.2	71.6	20.7
Cognitive function	74.0	20.8	78.5	19.8
Social function	77.4	24.1	82.5	21.5
Global quality of Life	66.3	16.3	71.8*	14.8
Symptom-scales (higher scores = more symptomatic)				
Fatigue	34.4	21.2	31.2	15.8
Nausea	5.6	13.6	4.0	9.6
Pain	23.3	24.7	25.0	27.5
Dyspnea	11.4	16.0	11.4	17.7
Sleep	37.3	28.7	36.5	27.4
Appetite	10.3	21.5	4.0*	10.9
Constipation	8.7	18.1	19.4	53.1
Diarrhea	11.1	27.2	15.1	24.6
Finances	18.2	26.8	15.1	22.3

Improvements pre- to postintervention: *$p < .05$; **$p < .01$.

-2.23, $p < .05$) and in the symptom of appetite loss ($t = 2.72$, $p < .01$), indicating greater overall quality of life and less problems with appetite loss.

None of the correlations between quality of life global change scores and home practice or attendance were significant at the $p < .01$ level.

Mood Scores

Mood scores on the POMS are presented in Table 3. Scores are only presented for the 42 patients who completed both the pre- and postintervention questionnaires, on which the paired-samples *t* tests were conducted. There were no significant changes in any of the POMS scores over the course of the intervention. The Total Mood Disturbance (TMD) score at time 1 was 15.93, which is already quite low, indicating minimal mood disturbance. The change in TMD scores represented a 13% reduction of overall mood disturbance for these participants.

None of the correlations between residualized overall mood disturbance scores and home practice or attendance were significant at the $p < .01$ level.

Stress Scores

Stress scores on the SOSI are presented in Table 4. Scores are only presented for the 42 patients who completed both the pre- and postintervention questionnaires, on which the paired-samples *t* tests were conducted. The mean SOSI total score showed a significant reduction ($t = 3.23$, $p < .01$), representing a decrease in stress symptoms over the course of the intervention. Significant reductions in pre- to postintervention scores were observed in the following SOSI subscales: Peripheral Manifestations ($t = 2.29$, $p < .05$); Cardiopulmonary ($t = 2.08$, $p < .05$); Muscle Tension ($t = 2.71$, $p < .01$); Habitual Patterns ($t = 2.79$, $p < .01$); Depression ($t = 2.32$, $p < .05$); Anxiety ($t = 2.70$, $p < .01$); Emotional Irritability ($t = 1.86$, $p < .05$); and Cognitive Disorganization ($t = 3.26$, $p < .005$). These reductions in scores correspond to reductions in symptoms of stress experienced by participants specific to each of these subscales. These participants achieved a 19.3% mean reduction in total symptoms of stress as measured by the SOSI on completion of the intervention.

None of the correlations between residualized stress change scores and home practice or attendance were significant at the $p < .01$ level.

TABLE 3. POMS Scores

	Preintervention		Postintervention	
	Mean	SD	Mean	SD
Anxiety	5.5	5.7	4.9	6.2
Depression	7.3	8.0	7.1	8.3
Anger	7.3	6.7	6.6	7.4
Vigor	15.9	6.4	15.5	5.9
Fatigue	8.8	6.4	8.3	7.3
Concentration	3.0	5.4	2.6	4.8
Total score	15.9	29.8	13.9	33.0

TABLE 4. SOSI Scores

	Preintervention		Postintervention	
	Mean	SD	Mean	SD
Peripheral manifestations	6.6	4.8	5.4*	4.4
Cardiopulmonary	8.4	6.7	6.7*	6.1
Central-neurological	2.8	2.8	2.4	2.7
Gastrointestinal	5.5	5.0	4.6	4.4
Muscle tension	10.4	7.5	8.7*	7.1
Habitual patterns	18.2	10.5	14.8**	8.6
Depression	8.1	6.3	6.5*	4.9
Anxiety/fear	11.7	8.0	9.2*	7.5
Emotional irritability	5.4	5.1	4.2*	4.3
Cognitive disorganization	5.3	3.6	3.9**	3.3
Total score	82.4	47.6	66.5**	42.6

Fewer symptoms of stress over time (pre- vs post).
* $p < .05$; ** $p < .01$.

TABLE 5. Immune Measures

	Preintervention		Postintervention	
	Mean	SD	Mean	SD
White blood cells (10^6)	5.56	2.25	5.28	1.97
Neutrophils (% WBC)	56.88	10.90	55.91	9.28
Monocytes (% WBC)	7.50	2.29	6.81*	2.42
Lymphocytes (% WBC)	28.81	8.69	30.09	6.96
Eosinophils (% WBC)	1.99	1.13	2.37*	1.32
NK gated (% lymph)	9.44	4.39	9.88	4.87
NK total count (10^6)	0.14	0.08	0.15	0.11
NKT gated (% lymph)	3.11	10.12	2.81	4.43
NKT total count (10^6)	0.04	0.11	0.04	0.08
B gated (% lymph)	13.80	6.31	13.82	6.90
B total count (10^6)	0.22	0.16	0.22	0.16
CD3 gated (% lymph)	69.33	8.56	69.37	7.85
CD3 total count (10^6)	1.04	0.40	1.06	0.42
CD4 gated (% lymph)	43.78	11.47	44.51	11.32
CD4 total count (10^6)	0.67	0.30	0.66	0.33
CD8 gated (% lymph)	26.70	8.66	26.04	8.33
CD8 total count (10^6)	0.41	0.23	0.38	0.19
IFN-γ NK (% lymph)	4.56	6.17	3.17	4.55
IFN-γ NK total count (10^6)	0.07	0.09	0.04	0.06
IFN-γ T (% lymph)	27.21	16.20	21.39**	19.03
IFN-γ T total count (10^6)	0.44	0.31	0.34*	0.35
TNF NK (% lymph)	4.82	9.83	5.78	10.94
TNF NK total count (10^6)	0.07	0.12	0.09	0.16
TNF T (% lymph)	42.03	24.20	40.39	23.51
TNF T total count (10^6)	0.69	0.51	0.62	0.45
IL-4 NK (% lymph)	2.62	7.96	2.34	4.47
IL-4 NK total count (10^6)	0.04	0.10	0.03	0.07
IL-4 T (% lymph)	3.12	2.59	12.74**	16.52
IL-4 T total count (10^6)	0.05	0.05	0.17**	0.25
IL-10 NK (% lymph)	14.96	15.09	9.79*	12.52
IL-10 NK total count (10^6)	0.20	0.19	0.15	0.21
IL-10 T (% lymph)	3.03	2.02	3.90	5.85
IL-10 T total count (10^6)	0.05	0.04	0.05	0.06

Indicates changes pre- to postintervention.
* $p < .05$; ** $p < .01$.

Immune Cell Counts and Cytokine Production

Immune cell counts pre- and postintervention and change scores are presented in Table 5, along with intracellular cyto-

kine production values. Values of lymphocyte cell counts are represented both as percentage of lymphocytes and as absolute cell numbers. Values for cytokine production from NK or T cells are represented as percentage of the cells, expressing the cytokine within that population of lymphocytes, and as absolute cell numbers expressing cytokine.

Numbers of monocytes decreased significantly ($t = 2.26$, $p < .05$), whereas eosinophils increased ($t = -2.23$, $p < .05$). T cell production of IFN-γ decreased, whether measured as a percentage of lymphocytes ($t = 3.00$, $p < .01$) or as total cell expression ($t = 2.18$, $p < .05$). IL-4 production in T cells increased significantly by percentage of lymphocytes ($t = -3.84$, $p < .001$) and total cell numbers ($t = -3.13$, $p < .01$). NK cell production of IL-10 decreased as well over the course of the intervention ($t = 2.22$, $p < .05$).

None of the correlations between the psychological change scores and the immunological change scores were significant at the $p < .01$ level.

Relationships Between Health Behaviors and Immune Variables

Regression equations were performed using each of the immune measures as the dependent variable, regressing the predictor variables of alcohol servings per week, caffeine servings per week, smoking status, exercise times per week, sleep hours per night, sleep quality, and diet quality in one block, after first entering the demographic and disease variables of age, years of education, cancer stage, duration of illness, tamoxifen use, and time since last treatment as a block. The overall ANOVA was significant for the total number of white blood cells ($F(13,43) = 2.06$, $p < .05$), with being a smoker ($t = 2.8$, $p < .01$) and exercising more ($t = -2.5$, $p < .05$) predicting greater white blood cell count, accounting for 30.7% of the variance in white blood cells over and above that accounted for by the first block of variables. Total B cell counts were also affected ($F(13,43) = 2.83$, $p < .01$), such that being a smoker ($t = 2.59$, $p < .05$); sleeping fewer hours per night ($t = -2.52$, $p < .05$); and more time since the end of treatment ($t = 2.48$, $p < .05$) were predictive of higher B cell counts, accounting for 41.1% more of the variance in B cells than the demographic and cancer history variables. In CD3 total cell numbers, only longer duration of illness was a significant predictor of higher cell counts ($F(13, 43) = 2.77$, $t = 3.22$, $p < .01$).

In CD8 cytotoxic T cells, the overall ANOVA was also significant ($F(13,42) = 2.07$, $p < .05$), where more caffeine servings per week ($t = 2.19$, $p < .05$); more exercise times/wk ($t = 3.24$, $p < .01$); and fewer alcohol servings/wk ($t = -2.40$, $p < .05$) were associated with a higher percent of CD8 lymphocytes. For the overall CD8 cell counts ($F(13,42) = 2.96$, $p < .01$), only a longer duration of illness was associated with higher cell counts ($t = 3.76$, $p < .001$).

DISCUSSION

The results of this pre-post intervention study indicated that this 8-week mindfulness-based stress reduction program was effective in decreasing symptoms of stress and improving overall quality of life in this group of breast and prostate cancer patients. Stress symptoms improved on 8 of the 10 symptoms of stress subscales, including anxiety and depression, emphasizing the breadth of stress-related symptoms that were significantly alleviated over the course of this intervention. No change was seen on the POMS scores of these patients, which may be explained by the low level of initial mood disturbance. In fact, the initial level of total mood disturbance in this sample was similar to the postintervention level of distress reported in our previous samples (18, 46). This low level of mood disturbance could be explained by the study inclusion criteria that patients be in early stage disease and at least 3 months posttreatment. The period of diagnosis and active treatment is often associated with greater distress and, because our previous group was very heterogeneous with respect to both type and stage of cancer and treatment regimen, it is not overly surprising to see these differences. With such low initial levels of mood disturbance in the current sample creating a floor effect with significant variance in scores, it would be difficult to attain statistically significant improvements. Consistent with the lower scores on the POMS, initial scores on the SOSI were somewhat lower in this group of patients compared with our previous study group but still significantly higher than the postintervention scores. However, the postintervention scores were quite similar in both groups. This indicates that the end point for both groups was similar in terms of both stress symptoms and mood but that the current group began with somewhat less distress.

Also of note was the finding that certain health behaviors changed over the course of the program, most notably sleep quality, which improved in many patients. Over 40% of the sample reported poor sleep before the program, whereas under 20% of those for whom post data were available continued to report poor sleep quality. The total number of hours of sleep increased by one-half hour per night as well, although this difference was not statistically significant. Improvements were also seen in exercise times/wk (which increased from four to five) and servings of caffeine (which decreased from 18 to 17). Exercise has been associated with many quality of life and biological benefits for cancer patients (47, 48) and also may reduce risk for the development of breast cancer (49). Considering that one goal of the study was to encourage regular yoga exercises, it is heartening that the exercise frequency did seem to increase somewhat. Indeed, patients reported practicing an average of 13 minutes of yoga and 24 minutes of meditation daily, very close to the targets we set of 45 minutes of daily home practice.

In terms of the immune results, no changes in numbers of any of the lymphocyte subtypes (NK, T, or B cells), or overall lymphocyte numbers, were seen. This is consistent with a number of other studies of psychosocial interventions that found no change (28–30), or decreases (27), in NK cells. Similarly, in the Fawzy et al. (26) melanoma study, effects on the immune system were not seen until 6 months postintervention. We will be able to investigate the possibility of

finding a similar effect in follow-up assessments which are currently underway.

Unexpectedly, a decrease in IFN-γ from T cells was observed pre- to postintervention along with the decreases in stress symptoms, whereas decreases in IFN-γ are generally associated with increases in stress (50, 51). However, the main difference between the cytokine profile of stress and depression is that IFN-γ is often *increased* from baseline in depression whereas it is decreased under stress (52). Increases in IFN-γ and other Th1-type cytokines are associated with proinflammatory effects. The cytokine pattern of depression is very similar to that of cancer, leading researchers to suggest a high degree of similarity between the pathobiochemistry and immunology of cancer, cancer pain, and depression (52). This may indicate that the decreases in IFN-γ in this sample represent a shift away from a depressive/carcinogenic cytokine profile.

Decreases in NK production of IL-10 were also seen pre- to postintervention. There is evidence associating elevated IL-10 levels with depression in cancer patients. Cancer treatment incorporating IL-2 therapy alone or in combination with IFN-α is associated with the appearance of depressive symptoms in a large proportion of patients (53–55). This effect seems to be mediated by the activation of the cytokine network, specifically of IL-6, soluble receptors of IL-2 (sIL-2R), IL-1 receptor antagonist, and IL-10 (56). All of the cytokines that were reliably elevated during IL-2 administration are not only activated by IL-2 but are also seen to be elevated in depressed patients (57–59). Of all the cytokines that were elevated during IL-2 treatment, only IL-10 levels were strongly and reliably associated with changes in depressive symptoms over the course of the treatment in a sample of renal cell and melanoma cancer patients (60). Treatment for depression with selective serotonin reuptake inhibitor medication also resulted in decreases in the levels of IL-10 in depressed patients (58). This seems to indicate that the decreases in levels of IL-10 concomitant with our program may be an indication of decreases in depressive symptoms, consistent with the decreases in IFN-γ. Although mood disturbance on the POMS did not decrease significantly, scores on the depression subscale of the SOSI did significantly decrease.

Another unexpected but promising finding was the greater than three-fold increase in T cell production of IL-4 cytokine. IL-4 and IL-10 produced from T cells are known as Th2 cytokines and generally have antiinflammatory effects, whereas TNF and IFN-γ are Th1 (proinflammatory) cytokines. A recent study of the effects of examination stress on cytokine production found a significant decrease in levels of IL-4 production 48 hours post exam compared with 30 days earlier, during an academically unstressful time (61). In another study, men with PTSD had lower levels of IL-4 than matched healthy control subjects (62). Therefore, if stress is related to decreased production of IL-4 as indicated by these studies, it may be the case that the increases in IL-4 levels seen in this population are associated with the decreases in stress symptoms that were also observed. Most interestingly, recent reports have identified IL-4 as inhibiting growth and contributing to apoptosis, or cell death, in breast cancer cell lines (63), leading researchers to suggest that IL-4 treatment be considered for adjuvant immunotherapy of breast cancer (64). In fact, phase I clinical trials of IL-4 are currently underway (65). If the MBSR program is a natural way to increase IL-4 levels, this may prove beneficial for fighting cancer, at least for women with breast cancer. The overall pattern of immune changes, with increases in eosinophils and T cell production of IL-4, and decreases in IFN-γ, are consistent with a shift away from a proinflammatory or T helper (Th) type 1 response to an antiinflammatory (Th2) environment. This Th2 environment may be more beneficial in terms of cancer-fighting properties.

Also of note was the finding that certain health behaviors were related to lymphocyte counts but not to measures of cytokine production. Greater caffeine intake related to slightly (but not significantly) lower CD4, but significantly higher CD8 cell counts, which would result in a lower CD4/CD8 ratio. This ratio of helper to cytotoxic T cells is considered an important indicator of the ability of the immune system to respond to tumor burden in cancer patients (66). Therefore, the effects of caffeine in lowering this ratio could be detrimental to the cancer patients' ability to fight tumors. Unexpectedly, exercise was also related to higher CD8 levels. This profile is sometimes seen after acute bouts of strenuous and prolonged endurance exercise, but the usual effect of chronic moderate exercise is enhancement of immune function, particularly NK cell activity (67). However, the effects of exercise on lymphocyte subsets remains controversial, particularly in the case of cancer patients (67, 68). Longer duration of illness, as measured by time since diagnosis, was related to higher cytotoxic and total T cell counts. Similarly, time since the completion of treatment was related to higher total B cell numbers. These relationships confirm that some immune parameters continue to improve as patients recover from disease and treatment. Because we had such a wide range of values for duration of illness, this relationship was possible to detect. However, over the course of the 2 months of the intervention, as mentioned below, the effects of resolution over time are likely minor. Few of the other health behaviors, or disease and treatment characteristics including tamoxifen use and type of treatment, were related to baseline immune measures.

The significance of these findings in terms of disease status or progression is essentially unknown at present. The most commonly cited immunological indicator of disease progression has been NK cell cytotoxicity, as NK cells are cytotoxic to tumor tissue in vitro (32), and reductions in NK cell activity have been noted in cases of tumor progression and metastasis (23) and in patients with greater tumor burden (50). However, other mechanisms suggested for the effects of stress on cancer progression include alterations in DNA repair and/or cell death (50), changes in health behaviors (33), as well as neuroendocrine and central nervous system pathways (eg, chronic autonomic arousal resulting in hypothalamic-pituitary-adrenal axis dysregulation) (31–33, 69). Further studies with large enough samples to adequately investigate immune, endocrine,

and autonomic parameters, and subsequent disease progression, will undoubtedly shed more light on this complicated question.

The major methodological limitation of this study is the lack of a control or comparison group. It could be argued that the observed changes may have occurred spontaneously as part of the cancer recovery trajectory or healing of the immune system and recovery of QL as a matter of natural history. However, some of the immune changes seen are contrary to what would be expected as effects of surgery or chemotherapy. Although chemotherapy, radiotherapy, and, to a smaller extent, surgery most certainly do downregulate NK cell cytotoxicity and lymphocyte counts (70, 71), reports of return to pretreatment levels indicate that recovery seems to occur within our 3-month inclusionary cutoff for most forms of treatment, and some lymphocyte subpopulations are not adversely affected at all (70–72).

The patients in this sample were an average of 2 years post diagnosis, with a median time of about 14 months post, so it is unlikely that any significant return to normal lymphocyte levels would still be occurring in this sample of patients. Compared with a sample of healthy community women who were an average age of 55.6 years (27), similar to the age of our population, our subjects had similar, or slightly higher, percentages of CD3 (65% of healthy controls vs. 69% of this sample); CD4 (37% vs. 43%); CD8 (24% vs. 26%); and NK (8% vs. 9%) cells preintervention. This is in contrast with the compromised percentages seen in the women with breast cancer who participated in the same study from which the control data were drawn (27). Similarly, another report that found no difference in lymphocyte percentages between treatment and control groups of ovarian cancer patients postintervention reported almost identical lymphocyte percentages (29%) and WBC counts to the pre-scores in our sample (30). As well, others (73) indicated lymphocyte percentages in the treatment group postintervention that were similar to, if not slightly lower than, the pre-scores of our group (24% vs. 29% in our sample). Similar findings are reflected in the QL scores, which represent a quite high initial QL in this group of patients. Compared with a Swedish normative sample of the same age range whose average global QL score was 77 (74), our patients scored an average global QL preintervention of 66. This is higher than other patient groups that have reported scores in the 50s (38). This may indicate that, similar to the floor effects seen in the POMS mood disturbance scores, our participants had essentially healthy levels of lymphocytes and relatively good QL before participation in the intervention, making it more difficult to incite enhancement of these already quite healthy levels. Nonetheless, without a formal randomized control group for comparison, the influence of outside factors on the outcome measures cannot be precluded and no definitive cause-effect relationships established between participation in the MBSR program and the concurrent changes in immune function and psychological scores observed.

Another issue related to the nonspecificity of the intervention is that, even if the beneficial effects were due to the intervention and not natural history or recovery, the relative importance of the different components of the program cannot yet be ascertained. Whether the most effective components are the meditation, yoga, social support, group processes, professional attention, or other factors will have to await further "dismantling" studies of MBSR. In all likelihood, the most useful aspects vary from person to person depending on the individual's needs, background, and personality.

In summary, this study confirmed our previous findings of decreases in stress symptoms after participation in an MBSR program and further demonstrated small improvements in overall quality of life of these early stage breast and prostate cancer patients. Sleep quality, a common problem for cancer patients, improved over the course of the intervention, and other health behaviors such as exercise and caffeine consumption also improved. T cell production of IL-4 increased and IFN-γ decreased, whereas NK cell production of IL-10 decreased. These changes in the immune profiles of these patients are consistent with a shift in the balance from a Th1 (proinflammatory) to a Th2 (antiinflammatory) environment and behaviorally associated with a shift away from a depressive pattern to one more consistent with healthy immune function. Changes seen in these patients were moderate, due perhaps to the high levels of psychological and immunological functioning of patients at the start of the study. Future studies of this nature may benefit from screening for more distressed individuals at the start of the program, as those individuals are more likely to benefit in terms of improvements in stress symptoms, mood, and quality of life as well, perhaps, in enhancement of immune parameters.

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