

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

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Received 26 November 2006; received in revised form 16 March 2007; accepted 6 April 2007

Available online 22 May 2007

Abstract

Objectives. This study investigated the ongoing effects of participation in a mindfulness-based stress reduction (MBSR) program on quality of life (QL), symptoms of stress, mood and endocrine, immune and autonomic parameters in early stage breast and prostate cancer patients.

Methods. Forty-nine patients with breast cancer and 10 with prostate cancer enrolled in an eight-week MBSR program that incorporated relaxation, meditation, gentle yoga and daily home practice. Demographic and health behaviors, QL, mood, stress symptoms, salivary cortisol levels, immune cell counts, intracellular cytokine production, blood pressure (BP) and heart rate (HR) were assessed pre- and post-intervention, and at 6- and 12-month follow-up.

Results. Fifty-nine, 51, 47 and 41 patients were assessed pre- and post-intervention and at 6- and 12-month follow-up, respectively, although not all participants provided data on all outcomes at each time point. Linear mixed modeling showed significant improvements in overall symptoms of stress which were maintained over the follow-up period. Cortisol levels decreased systematically over the course of the follow-up. Immune patterns over the year supported a continued reduction in Th1 (pro-inflammatory) cytokines. Systolic blood pressure (SBP) decreased from pre- to post-intervention and HR was positively associated with self-reported symptoms of stress.

Conclusions. MBSR program participation was associated with enhanced quality of life and decreased stress symptoms, altered cortisol and immune patterns consistent with less stress and mood disturbance, and decreased blood pressure. These pilot data represent a preliminary investigation of the longer-term relationships between MBSR program participation and a range of potentially important biomarkers. Crown copyright © 2007 Published by Elsevier Inc. All rights reserved.

Keywords: Cortisol; Cytokines; Blood pressure; Heart rate; Meditation; Cancer; Stress; Quality of life; Mood

1. Introduction

Health care delivery has evolved with the advent of more holistic practices and multidisciplinary care of many

chronic and acute diseases. Clinical treatment and wellness programs based on mindfulness meditation and yoga have proliferated. Many are modeled on the mindfulness-based stress reduction (MBSR) program of Jon Kabat-Zinn and colleagues at the Stress Reduction Clinic of the University of Massachusetts Medical Centre (Kabat-Zinn, 1990). MBSR is rooted in contemplative spiritual traditions in which the experience of conscious awareness is actively

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cultivated in specific ways. Attitudes of non-judging, acceptance and patience provide a framework for a meditative practice emphasizing focused awareness of one's own experience, often beginning with breath awareness. Typically, this leads to a state of relaxation and alert observant detachment. We have reported salutary effects of the MBSR program in cancer patients including decreased symptoms of stress, improved mood, better quality of life, better sleep, as well as changes in immune and endocrine parameters (Carlson et al., 2003, 2004; Carlson and Garland, 2005; Speca et al., 2000). To date, however, we have not reported follow-up maintenance of benefit beyond 6-month post-program (Carlson et al., 2001). In our 6-month follow-up we showed that large improvements seen on mood disturbance and stress symptoms from pre- to post-MBSR were maintained, without any return to previous higher levels of distress. The most benefit was seen on subscales of depression, anxiety and anger (Carlson et al., 2001).

The proliferation of reports of MBSR interventions in health care have inspired two general narrative reviews (Bishop, 2002; Baer, 2003) and one meta-analysis (Grossman et al., 2004), all of which have supported the efficacy of MBSR for improving both physical and mental well-being in mixed groups of patients with medical illness. Three recent reviews have summarized the literature on MBSR interventions specifically in cancer patients (MacKenzie et al., 2005; Smith et al., 2005; Ott et al., 2006), concluding that MBSR provides benefit in areas such as mood, sleep quality and reductions in stress.

No other researchers have investigated MBSR effects on biological markers such as cortisol or immune function in cancer patients, but NK cell activity and number increased after MBSR participation in a small group of non-randomly assigned HIV patients compared to a group of patients not interested in meditation; however, no changes in cortisol levels were found (Robinson et al., 2003). Another small trial with heart disease patients also failed to find changes in cortisol levels (Robert McComb et al., 2004). In a workplace sample of healthy volunteers, MBSR increased antibody titers produced in response to an influenza vaccine compared with a wait-list control group (Davidson et al., 2003). Previous MBSR studies in medical populations are rife with methodological problems such as very small samples and high drop-out rates, illustrating the difficulty of conducting such trials in medical settings.

Our previous study reported an intervention with early stage breast and prostate cancer patients on the outcomes of stress, mood, quality of life, immune cell count and intracellular cytokine production, and salivary cortisol (Carlson et al., 2003, 2004). Here, we have followed up with these same patients 6- and 12-months post-MBSR on all the outcome measures previously reported, and we also report previously unpublished results of blood pressure (BP) and heart rate (HR).

Hypertension (high blood pressure) is a reversible risk factor for illnesses such as heart disease, heart failure and stroke (Campbell et al., 1999). This may be an important

consideration in breast cancer patients who have undergone chemotherapy and/or radiation, since the heart muscle is often damaged by the treatments, making these patients more susceptible to future heart disease (Shan et al., 1996; Vallebona, 2000). Thus, it is important to maintain normotensive status in such cancer survivors to decreased future risk. Studies of stress reduction interventions including meditation, biofeedback, relaxation, and cognitive-behavior therapy have found lowered levels of resting systolic and diastolic blood pressure in intervention participants (Blumenthal et al., 2002; Campbell et al., 1999). This finding has been confirmed by three meta-analyses and a review covering the stress reduction literature from 1966 to 1997, including several well-designed RCTs (Spence et al., 1999). The practice of meditation has previously been associated with decreased heart rate (Telles et al., 1998; Travis and Wallace, 1997) slowed respiration (Telles et al., 1998), and lowered blood pressure (Sudsuang et al., 1991; Schneider et al., 1995; Wenneberg et al., 1997), primarily in healthy adult participants. Hence, our study will add to the knowledge base of MBSR on BP and HR in cancer patients, as well as extend our previous findings to 6- and 12-months post-program.

2. Methods

2.1. Subjects

Patients were eligible to participate in the study if they met the following criteria: (1) age 18 years or older; (2) a diagnosis of Stage 0, I, or II breast or early stage (localized to the prostate) prostate cancer at any time in the past (using standardized TNM diagnostic criteria) and (3) a minimum of three months since surgery (mastectomy/lumpectomy/prostatectomy/cryotherapy). Exclusion criteria were any of: (1) treatment with chemotherapy or radiation therapy currently or within the past three months; (2) a concurrent DSM-IV axis I mood, anxiety or psychotic disorder (not in full or partial remission); (3) a concurrent autoimmune disorder and (4) past participation in an MBSR group.

2.2. Instruments

2.2.1. 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 of diagnosis and types of treatments were collected. Areas specifically assessed included heart disease, vascular disorders, autoimmune disorders, epilepsy and psychiatric disorders. All current medications were recorded.

2.2.2. Health behaviors form

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

2.2.3. Meditation log

Two different log forms were used during the study: (1) weekly log: this form collected daily information on minutes spent in home practice of meditation and yoga from each participant during the 8 weeks of the intervention, and was collected each week during class; (2) Monthly log: for the

follow-up period, monthly calendars were provided for the entire year to record daily minutes in practice and collected at each follow-up appointment.

2.2.4. European organization for research and treatment of cancer quality of life questionnaire (EORTC QLQ-C30)

(Aaronson et al., 1993): 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. It has become a gold-standard of QL assessment in clinical trials both in Europe and North America, with much normative data available for comparison (Aaronson et al., 1991, 1993).

2.2.5. Profile of mood states (POMS)

(McNair et al., 1971): The POMS 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 (Cassileth et al., 1985).

2.2.6. Symptoms of stress inventory (SOSI)

(Leckie and Thompson, 1979): The SOSI 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 5-point scale ranging from never to frequently during the past week. Ten subscale scores can be calculated, and a total stress score.

2.2.7. Immune and cortisol measures

Patients were recruited in 4 groups of 15 as described in the Procedures section. As a result, time 1 baseline samples for the 3rd and 4th groups were analyzed concurrently with the 6- and 12-month follow-up samples from the 1st and 2nd groups. This ensured that differences observed between different follow-up time points were not the result of changes in staff, reagents or laboratory procedures. Measures of immune cell counts and intracellular cytokine production were assessed as detailed in our previous paper (3). Antibodies directed against specific cell surface determinates were used to determine the proportion of leukocyte subclasses. Specifically, surface cell marker 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. The production of the cytokines interferon gamma (IFN- γ), tumor necrosis factor (TNF), and interleukin (IL)-4 and -10 (IL-10) by stimulated NK and T-cells was determined using three-color flow cytometry with FITC-conjugated anti-CD3 used to identify T-cells, Cy5-conjugated anti-CD56 used to identify NK cells and PE-conjugated anti-cytokine antibodies used to determine the level of cytokine expression in each population. The data were expressed as the percentage of NK or T-cells that were also positive for the specified cytokines.

Salivary cortisol was measured using solid-phase ELISAs according to the manufacturer's instructions on samples collected three times per day (8:00 AM, 2:00 PM and 8:00 PM) at each assessment period, as previously described (Carlson et al., 2004).

2.2.8. Blood pressure

BP was measured at six different points during the study using a mercury manometer: (1) one week prior to starting the program, (2) on the morning of the first meditation session, (3) immediately after the last session (within 1/2 h), (4) one week after the last session, (5) 6-month follow-up and (6) 12-month follow up. At each assessment time, BP and HR were measured twice from each arm with a five minute rest interval between measurements, following the procedures recommended by the Canadian Medical Association (Campbell et al., 1999). Thus, at each of the six time points, the average of four readings was calculated. Because the measures were taken on two different days before and after the program, these measures were also averaged to calculate overall "pre" and "post" BP measures. Therefore, each "pre" and "post" score was averaged from eight measurements for those who provided full data. Axillary node dissection

on one arm made it inadvisable to read BP from that arm for several of the women with breast cancer, so two readings from the other arm were averaged at each assessment time, resulting in the average of four measures for each "pre" and "post" value reported for these women.

2.3. Procedures

2.3.1. Recruitment

Patients were recruited from the Tom Baker Cancer Centre. Patients were primarily recruited with pamphlets and posters around the centre, in each of the breast and prostate clinic areas, and were able to self-refer. If patients wished to participate, their name was placed on a waiting list administered by the research assistant.

2.3.2. Testing

Once 15 patients were accrued on the waiting list they were scheduled for an individual interview with the principal investigator (PI) during the week prior to the start of the group to further explain the study, determine eligibility and provide informed consent. A maximum of three patients were assessed daily between 8:00 and 10:00 h, to control for time of day. Patients then met with the RA who took blood pressure readings following the procedures detailed above. A blood sample was then taken for immune measures, and the patients then completed the assessment battery of questionnaires, supervised by the RA who clarified instructions and answered questions, which took approximately one-half hour. Salivary cortisol salivettes were collected by the participants in their homes the day prior to the first MBSR class, refrigerated overnight, and returned to the first class.

The RA attended the last part of the final meditation class to measure BP at that time and hand out salivettes for salivary cortisol collection. Beginning the week after the completion of the intervention, the same procedure was followed as prior to the intervention, with the patients returning to the hospital to have BP assessed, provide a blood sample and complete the questionnaires. They completed the health behavior form without the assistance of the PI for this assessment and collected salivary cortisol the day before the appointment. All participants were assessed within two weeks of the completion of the intervention.

For the 6- and 12-month follow-up assessments, participants were mailed the questionnaires and the cortisol swabs prior to their appointment and instructed to complete the questionnaires and collect saliva samples on the day prior to coming to the centre for assessment of BP and immune measures.

2.3.3. Intervention

Details of the intervention, including objectives, structure, components and content, have previously been described (Specia et al., 2000). 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 (Kabat-Zinn, 1990). The intervention was provided over the course of eight weekly, 90-min group sessions with a maximum of 15 participants each, plus a 3-h silent retreat on the Saturday between weeks six and seven. The Saturday retreat combined participants from all of our ongoing MBSR groups, and usually consisted of about 40 participants.

In addition, we produced and provided patients with a 52-page booklet containing information pertinent to each week's instruction, a bibliography for those wishing to pursue relevant themes in greater depth, and an audio-tape or CD recording. The recording provided instruction for a sensate focused body scan meditation on one side and a guided sitting meditation on the other. Patients were instructed to practice daily.

2.4. Data analysis

All data analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 14.1, for the PC in Windows NT.

The demographic, medical history and health behavior variables were described using frequency and descriptive statistics. All continuous variables were tested for normalcy of the distributions at each time period.

Of the health behavior and demographic continuous variables, only alcohol servings/week was significantly positively skewed at both time periods (Skewness >2.0). Therefore, the natural log transformation was applied to this variable, at each time period, which resulted in normal distributions. These transformed variables were subsequently used in all calculations. On the EORTC, SOSI and POMS all variables were normally distributed. All measures of BP and HR also conformed to the normal distribution. Cortisol values were Ln transformed as described in our previous work (Carlson et al., 2004).

To assess effects of the intervention pre, post and over the follow-up and account for missing data, simple mixed-effects models with a heterogeneous compound symmetry correlation structure among repeated measures (Laird and Ware, 1982) were used to compare pre-, post-, 6- and 12-month scores on total scores on the EORTC, POMS and SOSI, immune and cortisol measures as well as systolic and diastolic BP and HR scores, with contrasts to compare the pre-test score and the mean of the post-test scores (contrasts of -3, 1, 1, 1 applied to test sessions 1–4, respectively) and tests in the post-test scores of linear (0, -1, 0, 1 contrast weights) and quadratic (0, -1, 2, -1 contrast weights) trends. These models were first done unconditionally (without covariates), and then using baseline values of health behaviors and disease characteristics as patient-level effects. Because of the limited number of cases and degrees of freedom, adding in all of the health behaviors and disease variables into each model was not statistically viable. Hence, we chose what we felt were the two most important health behaviors (sleep hours/night and exercise times/week), and the disease characteristics of cancer stage and time since diagnosis. These were assessed in each model using interaction terms between each covariate and each time term. As tests of fixed effects in mixed effects models do not have exact *F* distributions, degrees of freedom for these tests were obtained using a Satterthwaite approximation (Satterthwaite, 1946). Valid inference based on the observed data in mixed-effects models requires that the probability that observations are missing depends only on observed covariates or outcomes (the missing at random assumption, Little and Rubin, 1987). Effect sizes on the psychological measures were calculated comparing baseline scores to those at times 2, 3 and 4 using Cohen’s *D* = (Mean time 2 – Mean time 1)/Pooled SD.

To investigate whether BP and HR, or changes in BP and HR were related to values of quality of life, mood or stress symptoms, Pearson product–moment correlations were performed between the BP and HR measures and corresponding psychological scores at each time period.

Similar correlations were also performed between class attendance, home practice and both psychological and BP and HR change scores from baseline to the post-intervention period to assess the possibility of dose–response relationships, and between home practice and BP and HR change scores from baseline to the follow-up assessments. Correlations were carried out only on participants who provided data at each time point.

3. Results

3.1. Subjects

Fifty-nine, 51, 47 and 41 patients provided data at pre- and post-intervention and at 6- and 12-month follow-up, respectively, however not all patients provided full data on each measure at each time-point (see flow diagram Fig. 1). Reasons for drop-outs were recorded as follows: time 2 (*n* = 8), 4 did not complete the MBSR program and withdrew from the study, and 4 did not return to complete the measures; time 3 (*n* = 4), two did not attend appointments to complete measures and two did not return phone calls; time 4 (*n* = 6), three we were unable to contact and three did not return phone calls. Thirty-five patients provided data at all four time points for the immune measures, 33 for the endocrine measures, and 31 provided full data on the psychological measures.

Demographic characteristics of participants at all four assessment times are presented in Table 1. The participants at time 1 were a mean of 54.5 years, SD 10.9 years. Most (*n* = 42) were married or co-habiting 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 five years post-diagnosis. Just over two thirds had

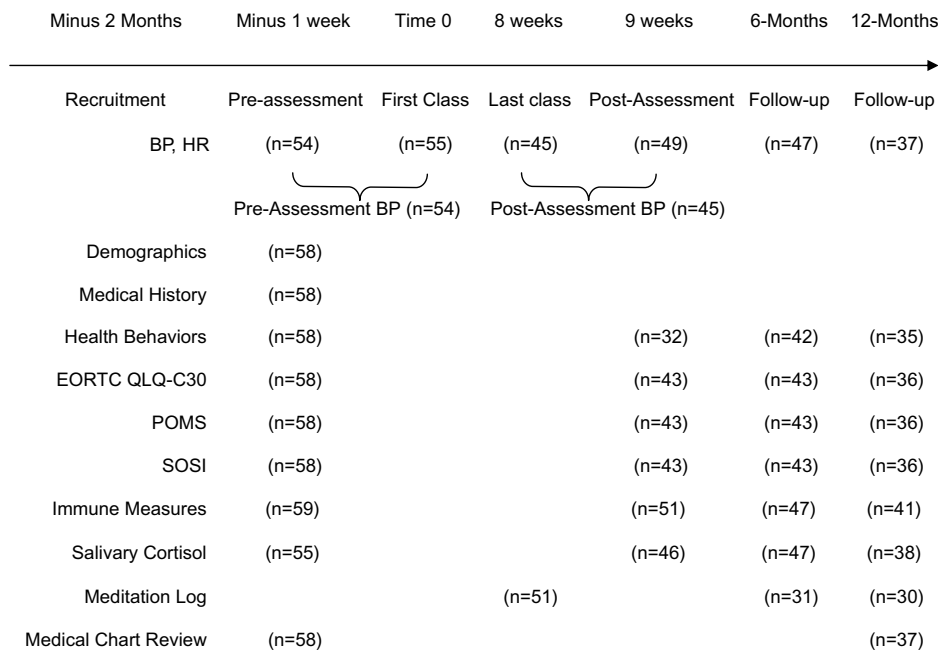


Fig. 1. Study flow chart.

Table 1
Demographics across the four time points

	Pre-intervention (<i>n</i> = 59)		Post-intervention (<i>n</i> = 50)		6-Month follow-up (<i>n</i> = 47)		12-Month follow-up (<i>n</i> = 41)	
Type of cancer (<i>N</i> /%)								
Breast	49 (83.1)		42 (84.0)		39 (83.0)		33 (80.5)	
Prostate	10 (16.9)		9 (16.0)		8 (17.0)		8 (19.5)	
Stage of cancer (<i>N</i> /%)								
1	21 (35.6)		18 (36.0)		14 (29.8)		16 (39.0)	
2	38 (64.4)		33 (64.0)		33 (70.2)		25 (61.0)	
Marital status (<i>N</i> /%)								
Married/CL	42 (69.5)		38 (76.0)		35 (74.5)		30 (73.2)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	54.52	10.85	55.86	10.71	54.42	9.89	55.99	10.00
Education (years)	14.71	2.79	14.57	2.74	14.74	3.02	14.71	2.95
Time since diagnosis (years)	2.05	2.96	2.11	3.13	1.90	3.11	1.92	3.14

Stage II cancer (64.4%), with the remainder having a diagnosis of Stage I. Further details of the participants including use of antiestrogen and antidepressant medications are provided in our earlier publication (Carlson et al., 2004).

When the 31 participants who provided full psychological data were compared at baseline to those who did not on demographics and psychological measures using independent samples *t* tests, drop-outs had a lower global QL (58.0 vs. 66.8, $t = -2.57$, $p < .05$), and higher total mood disturbance (35.0 vs. 11.9, $t = 2.8$, $p < .01$). Those who completed the study and the drop-outs were not different on initial stress levels. Nor were they different on any of the demographic or cancer-related variables.

3.2. Meditation practice

The 31 patients who provided complete psychological follow-up data attended a mean 8 of 9 sessions (only 2 attended fewer than 7 sessions). They also practiced at home as instructed, reporting an average of 24 min/day of meditation and 13 min/day of yoga over the course of the eight weeks.

Thirty one patients completed the practice logs at the 6-month follow-up, and reported that they spent a median time of 7.4 h/month doing yoga and/or meditating since the end of the program (about 1/3 yoga, 2/3 meditation). This is approaching 2 h/week. There was a large range, from zero ($n = 3$) to over 59 h/month (almost 2 h/day) in one case. Because of the skewed distribution, the mean was higher at 9.8 h/month (SD 13 h/month). Over the second time period between the 6- and 12-month visits, 30 people provided data, and reported practicing a median of 5.6 h/month, with an even larger range from 0 ($n = 3$) to 73 h/month (mean 9.0 h/month, SD 14.6 h/m).

3.3. Health behaviors

In our previous study we reported sleep quality had improved over the course of the intervention. Caffeine servings per week decreased and exercise increased for those who provided pre- and post-data (Carlson et al., 2003,

2004). Full data at all four time points including the 6- and 12-month follow-up was available for only 23 participants, even though more that this did provide data at each time point (see Fig. 1). Hence, because of the low rate of full data repeated-measures analyses on these variables were not performed, as interpretation may have been difficult with a sample that size, representing less that half of those who began the program.

3.4. Psychological outcomes

The psychological effects of the program on the EORTC, POMS and SOSI subscale scores pre- and post-intervention are fully described in our other papers (Carlson et al., 2003, 2004). Here, we report only global scores for the participants who provided data at each time point using mixed methods. Means for each time period are presented in Table 2 (Means, SDs and effect sizes are presented).

3.4.1. Quality of life

In the mixed-effects model without any covariates, the baseline versus post-comparison was significant ($F[1, 94] = 7.46$, $p < .005$), as was the post-quadratic effect ($F[1, 47] = 5.08$, $p < .05$). This indicates that the pre-intervention value was different (lower QL) than the average of the three post-intervention values, and the post-values themselves changed in a quadratic pattern, decreasing then increasing. When the covariates were added to the model the main effects were no longer significant, but none of the interactions between the time effects and covariates were significant either.

None of the correlations between quality of life global change scores and home practice or attendance were significant at the $p < .05$ level from pre- to post-intervention, or at the 6- and 12-month follow-up assessments (all $p > .10$).

3.5. Mood scores

None of the contrasts were significant in the mixed-effect model without covariates for the POMS total mood disturbance score. The TMD score at time 1 was 15.93, which is

Table 2
QL, mood and stress scores for participants with all four assessments ($n = 31$)

Measure	Time 1 (pre-MBSR)		Time 2 (post-MBSR)		~ES1 <i>D</i>	Time 3 (6-month follow-up)		ES2 <i>D</i>	Time 4 (12-month follow-up)		ES3 <i>D</i>
	Mean	SD	Mean	SD		Mean	SD		Mean	SD	
EORTC QLQ C-30 global QL	68.82	15.51	72.58	13.64	0.26	70.16	18.85	0.08	73.12	13.73	0.29
POMS TMD	11.87	27.16	11.81	33.20	0.00	11.56	34.09	0.01	7.26	32.16	0.16
SOSI total score	81.58	50.05	68.16	44.28	0.28	66.65	48.27	0.30	62.58	44.52	0.40

~ES1 = (Mean time 2 – Mean time 1)/Pooled SD; ES2 = (Mean time 3 – Mean time 1)/Pooled SD; ES3 = (Mean time 4 – Mean time 1)/Pooled SD.

already quite low, indicating minimal mood disturbance. No significant interaction emerged with the addition of the covariates. None of the correlations between changes in overall mood disturbance scores pre- to post-intervention and home practice or attendance or at the 6- and 12-month follow-up assessments were significant at the $p < .05$ level (all $p > .10$).

3.6. Stress scores

There was a strong effect comparing baseline to the post-intervention average scores ($F[1,85] = 16.30$, $p < .001$), indicating that stress scores decreased over the intervention and stayed low for the follow-up period (Fig. 2). Linear and quadratic effects across the post-scores were not significant. The ES went from $d = 0.28$ at post-intervention to $d = 0.30$ at 6-month and $d = 0.40$ after a year, a moderate-sized effect. When the health behaviors and disease variables were added as interaction terms, no interactions emerged, but the effect washed out the significance of the previous decrease in stress symptoms after the intervention.

None of the correlations between stress change scores and home practice or attendance pre- to post-intervention, or at the 6- and 12-month follow-up assessments were significant at the $p < .05$ level (all $p > .10$).

3.7. Biological outcomes

3.7.1. Cortisol measures

The mixed-effects models found decreases in Ln cortisol comparing baseline to post-intervention values across the

follow-up at all time periods: 8:00 AM ($F[1,122] = 13.28$, $p < .001$), 2:00 PM ($F[1,82] = 4.30$, $p < .05$), 8:00 PM ($F[1,129] = 16.27$, $p < .001$) and across average cortisol levels ($F[1,88] = 19.85$, $p < .001$). In addition to these decreases after the intervention, there were continued downward linear effects for cortisol at 8:00 AM ($F[1,38] = 21.33$, $p < .001$), 2:00 PM ($F[1,43] = 22.32$, $p < .001$) 8:00 PM ($F[1,49] = 27.07$, $p < .001$) and for average cortisol values ($F[1,28] = 32.50$, $p < .001$) across the year of follow-up. See Fig. 3 for a depiction overall mean cortisol values. However, cortisol slope did not change significantly across time points. Evening cortisol levels at time 4 were associated with stress scores ($r = .366$, $p < .05$), but no other CRT values were significantly associated with concurrent stress levels or home meditation practice.

When the interaction terms were added to the models, the time effects on 8:00 AM, 2:00 PM, 8:00 PM and mean cortisol were washed out, but the main effect for baseline versus post-mean cort values persisted ($F[1,54] = 3.94$, $p < .05$). The only significant interactions were between the baseline versus post-intervention change and time since cancer diagnosis at 8:00 AM ($F[1,58] = 4.46$, $p < .05$), such that the decrease in cortisol after the intervention was less for those who had been living with cancer for a longer period of time. As well, the interaction between stage of disease and the post-quadratic effect on the cortisol slope was significant ($F[1,80] = 6.01$, $p < .05$), indicating that the decrease in cortisol daily slope over the follow up was attenuated in those with more advanced cancer.

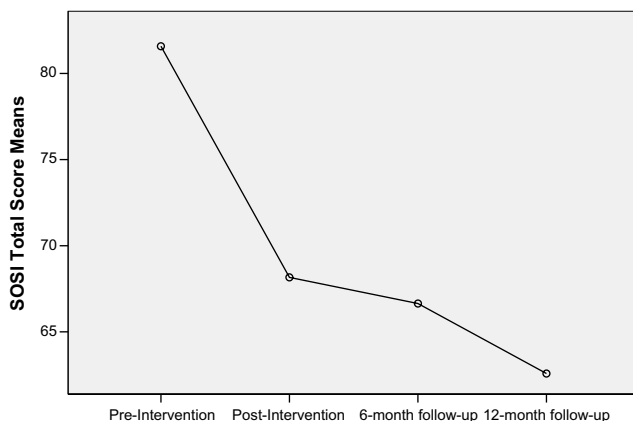


Fig. 2. Symptoms of stress inventory scores.

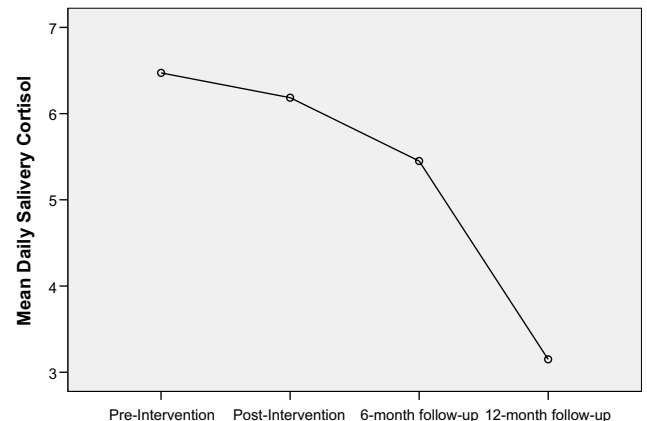


Fig. 3. Mean daily salivary cortisol values across time.

3.8. Immune measures

3.8.1. Cell counts

Over the course of the year, the number of monocytes at the baseline compared to the post-assessment average decreased over time ($F[1,79] = 6.74, p < .01$), while eosinophils increased ($F[1,155] = 21.31, p < .001$). Eosinophils also continued to increase linearly across the follow-up assessments ($F[1,64] = 6.19, p < .05$). Lymphocytes, neutrophils and overall white blood cell counts did not change significantly. The main effects for monocytes and eosinophils were washed out by the addition of the interaction terms in the model, but no one interaction term was significant.

3.8.2. Lymphocytes

Within the lymphocyte subtypes (Table 3), NK cells (CD56+) showed a significant quadratic effect across the three post-intervention values, increasing then decreasing over time ($F[1,74] = 5.85, p < .05$). NKT cells showed both a linear ($F[1,80] = 6.68, p < .05$) and quadratic ($F[1,116] = 4.39, p < .05$) effect, increasing across the post-intervention follow-up assessments. B cells (CD19+) changed in two ways, increasing comparing baseline to the post-intervention scores ($F[1,142] = 6.06, p < .05$) and linearly increasing over the follow-up ($F[1,108] = 7.00, p < .05$). Within the T-cell populations, total T-cells (CD3+) showed all three significant time effects, decreasing comparing baseline to the average of the post-scores ($F[1,115] = 4.81, p < .05$), and both linearly ($F[1,83] = 5.91, p < .05$) and quadratically ($F[1,33] = 4.33, p < .05$) over follow-up. T-helper cells (CD4+) decreased then increased quadratically from times 2–4 with a small effect ($F[1,130] = 3.94, p < .05$), and T-cytotoxic cells (CD8+) were higher at baseline compared to all three follow-up periods ($F[1,129] = 12.76, p < .001$), and also decreased linearly across follow-up assessments ($F[1,89] = 4.95, p < .05$).

When the interaction terms were added to the models of lymphocyte counts, the main effects on B cells, total T-cell, and helper T-cells were no longer significant, but the quadratic effect on cytotoxic T-cells post-intervention inter-

acted with sleep ($F[1,108] = 9.2, p < .005$) such that those with less baseline sleep showed greater decreases in cytotoxic T-cells over the follow-up period.

3.8.3. Cytokines

The largest magnitude changes were seen in terms of cytokines. The percentage of T-cells expressing these cytokines is also detailed in Table 3. Within the T-cell population, IFN- λ decreased substantially over the course of the year both compared to the baseline pre-intervention value ($F[1,72] = 28.98, p < .001$) and across the three follow-up assessments both linearly ($F[1,77] = 70.52, p < .001$) and quadratically ($F[1,100] = 19.93, p < .001$). A similar pattern was seen for T-cell TNF production, comparing baseline to post-intervention average scores ($F[1,70] = 28.42, p < .001$), across follow up in a linear trend ($F[1,69] = 72.28, p < .001$) and less strongly in a quadratic trend ($F[1,86] = 12.58, p < .001$). IL-4 showed the same pattern with the strongest effect being a follow-up linearly decreasing trend ($F[1,67] = 66.84, p < .001$), followed by a decrease from baseline to follow-up ($F[1,62] = 29.42, p < .001$) and a quadratic trend ($F[1,138] = 4.84, p < .05$). The typical pattern of these decreases is shown for IFN- λ in Fig. 4. For NK cells, production of IFN- λ also decreased linearly across the follow-up assessments ($F[1,64] = 11.30, p < .01$) as did IL-4 ($F[1,65] = 4.08, p < .05$), and IL-10 showed a quadratically decreasing effect ($F[1,123] = 18.03, p < .001$) (Table 4).

With health behaviors and disease variables added as covariates, significant time effects on T-cell production of IFN- λ were still present for the linear decrease post-intervention ($F[1,77] = 8.14, p < .01$). An interaction between exercise and the change in T-cell IFN- λ from pre- to post-intervention appeared ($F[1,93] = 4.42, p < .05$), in that those who had exercised more showed a larger decrease in IFN- λ over time. Changes in T-cell production of IL-4 continued to be significant, but only for the linear decrease over the follow-up period ($F[1,118] = 8.04, p < .005$). Changes in T-cell TNF were no longer significant. For NK cells, time effects on IFN- λ production

Table 3
Immune cell subtypes and cytokine expression for participants with all four assessments ($n = 40$)

	Time 1		Time 2		Time 3		Time 4	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Lymphocytes								
Total lymph (% WBC)	28.45	9.46	29.86	7.27	29.99	7.37	29.35	7.95
CD3 (% lymph)	70.22	9.10	69.90	7.56	66.85	12.72	67.76	8.51
CD4 (% lymph)	45.77	10.56	44.74	10.49	44.52	9.97	45.46	10.95
CD8 (% lymph)	26.00	7.34	25.70	7.14	24.25	7.33	24.13	8.26
CD19 (% lymph)	12.56	6.27	12.82	6.58	13.80	6.59	13.98	6.92
CD56 (% lymph)	9.34	4.34	9.87	4.48	10.21	5.81	8.45	4.78
Cytokines (% of T-cells)								
IFN- γ	27.58	17.35	27.52	14.51	11.31	9.00	10.75	8.72
TNF	42.08	24.47	44.40	22.84	20.37	16.35	15.17	12.32
IL-4	3.17	2.82	3.16	2.76	0.99	1.48	0.27	0.34
IL-10	2.60	1.87	3.09	2.38	2.82	4.18	2.34	3.10

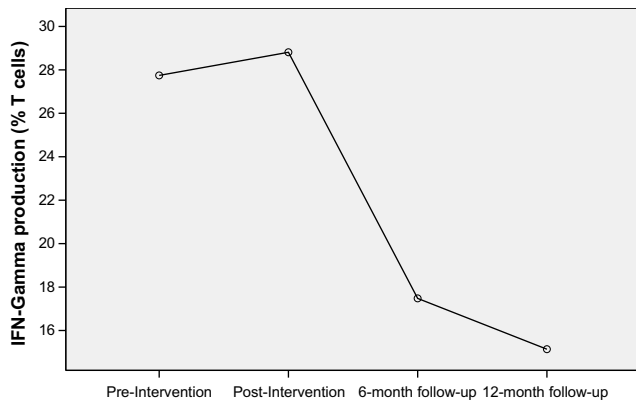


Fig. 4. Mean IFN- λ T-cell production across time.

became non-significant without any significant interaction terms. For TNF, an interaction appeared between duration of illness and the pre-intervention versus post-intervention time effect ($F[1,81]=9.43$, $p<.01$), such that people who had been diagnosed with cancer for a longer period of time showed more of a decrease in NK cell production of TNF in response to the intervention. The same interaction was apparent for IL-4 ($F[1,137]=8.78$, $p<.005$); those with a longer duration of cancer showed more of a decrease in NK cell production of IL-4 from pre- to post-intervention. The effects of time on IL-10 were washed out by the addition of the covariates.

Pearson product-moment correlations were performed between T-cell cytokine production and stress levels as well as home meditation and yoga practice at each time point for participants with full data. Two outliers with extreme scores on home practice were removed from the analysis to create normal distributions. At time 1 (pre-intervention) higher TNF production was associated with higher stress levels ($r=.385$, $p<.05$), and at time 3, IL-4 production was correlated with total stress scores ($r=.369$, $p<.05$). There were no associations between immune measures and home practice at any time point.

3.8.4. Blood pressure and heart rate

Values for BP and HR are presented for each time period in Table 3. Because this data has not yet been published for the pre- and post-assessments, more detailed analyses are presented for this outcome. The pre- and post-assessment measures were averaged as detailed in the data analysis section and compared using paired-samples t tests on SBP, DBP and HR. The overall SBP pre and post-measures were different from one another, indicating an overall decrease in SBP ($t[1,44]=2.02$, $p<.05$) from 119.7 to 117.6 mm Hg. None of the other measures changed pre- to post-intervention.

The mixed-effects models found a significant effect comparing baseline to the average of the follow-up assessments for SBP ($F[1,85]=6.32$, $p<.05$), indicating that the change over the course of the intervention was also significant when compared to the average of the follow-up measures. Overall resting heart rate decreased both from baseline across the follow-ups ($F[1,90]=4.17$, $p<.05$), but also continued a linear decrease over the three follow-up assessments ($F[1,67]=5.86$, $p<.05$) from about 72 beats per minute at pre-intervention to 68 beats after one year. When effects of health behaviors and disease variables were added to the equations, the baseline to post-intervention change in SBP was washed out by an interaction with duration of illness ($F[1,88]=5.46$, $p<.05$) such that those living with cancer longer showed smaller decreases in SBP after the intervention. With the addition of the covariates, the time main effects in the model were no longer significant for HR.

Correlations at each of the four common assessment periods between BP and HR values and the total scores of the POMS, SOSI and EORTC were significant between HR and the SOSI total ($r=.28$, $p<.05$) and POMS total ($r=.38$, $p<.01$) at pre-intervention, and between HR and SOSI total at 6- ($r=.44$, $p<.01$) and 12-month ($r=.37$, $p<.05$) follow-ups. This indicates that elevated resting HR was related to reporting more symptoms of mood disturbance pre-intervention, and of stress at three separate test times.

Table 4
BP and HR measures

		Systolic BP	Diastolic BP	HR
1. One week pre-first class	Mean	120.7 ^a	78.4	72.7
	SD	15.3	10.0	8.6
2. Immediately pre-first class	Mean	116.4 ^a	73.5	74.0
	SD	12.7	8.7	7.9
3. Immediately post-last class	Mean	118.8 ^a	76.5	70.4
	SD	14.5	8.4	8.6
4. One week post-last class	Mean	114.7 ^a	75.2	74.5
	SD	11.9	8.8	8.0
5. 6-Month follow-up	Mean	115.4	76.3	71.4
	SD	10.5	8.1	8.8
6. 12-Month follow-up	Mean	116.3	74.3	68.6
	SD	12.8	8.0	7.2

^a Average of assessments 1 and 2 SBP higher than average of assessments 3 and 4, $p<.05$.

4. Discussion

The results of this pre–post intervention and one-year follow-up study indicate that this 8-week mindfulness-based stress reduction program was effective in decreasing symptoms of stress in this group of breast and prostate cancer patients, and maintaining these improvements over a year of follow-up. The effect-size was moderate ($d = 0.40$), which typically represents the lower range of clinically significant improvement. These improvements were independent of the amount of subsequent home practice of meditation and yoga. Improvements were also seen across the year in global QL scores, but not to the same extent as for stress symptoms. However, no significant changes were seen on mood disturbance scores of these patients, which may be explained by the low level of initial mood disturbance. These results are similar to those observed in the patients who provided pre- and post-intervention data (Carlson et al., 2003). Participants who dropped out of the program or did not complete full follow-up assessments were more distressed at baseline than those who provided full data, so it may be the case that optimal benefit will accrue for those with mild-moderate levels of distress, rather than for those with very low or very high levels. This has been suggested by many other researchers as the optimal target population for psychosocial group interventions (e.g. Goodwin et al., 2001; Ross et al., 2002).

Cortisol levels also continued to decrease over the follow-up period, with all of the morning, afternoon and evening as well as mean cortisol values decreasing both from pre- to post-intervention, and also decreasing linearly across the year of follow-up. The most robust finding after controlling for a number of health behaviors and disease characteristics was the decrease in the mean daily cortisol value. There was also less of a decrease in cortisol levels over time in people who had a higher stage of cancer and had been living with the illness for a longer period of time, perhaps indicating that stress-related changes in cortisol are more possible earlier in the survivorship period for those with less disease burden. However, due to the single data of salivary cortisol collection and known day-to-day variability in cortisol production (Kirschbaum and Hellhammer, 1994), these findings should be verified with more rigorous cortisol data collection methods involving multiple days of testing at each assessment period. Indeed, a recent report comparing test-retest reliability of cortisol slopes in older participants (average age 61.5 years, 88% female) concluded that minimally two and preferably three days of salivary testing be utilized (Kraemer et al., 2006). The correlations between slopes on two different days supporting this conclusion were in the 0.5–0.6 range. As a result, in our more current protocols this method is being used.

Nonetheless, if abnormal or elevated cortisol levels are a marker of poor prognosis in cancer patients, as suggested by previous work (Sephton and Spiegel, 2003; Sephton

et al., 2000), this effect, if verified, could prove significant. Indeed, although very few follow-up studies have been conducted on the effects of meditation on disease course, pre-hypertensive patients who participated in meditation interventions an average of eight years previously benefited from a decrease in death rates due to cancer of 49% compared to randomized control groups (Schneider et al., 2005). This was even larger than the decrease in cardiac mortality of 30%, and represents a very large reduction in cancer mortality risk in this sample of 202 relatively healthy participants. The only other long-term follow-up of a meditation intervention was in a small sample of patients with irritable bowel syndrome, who showed continued reductions in pain and bloating over the year (Keefer and Blanchard, 2002).

In terms of immune function, we observed interesting downward trends in the T-cell production of pro-inflammatory cytokines. Pro-inflammatory cytokines have been associated with increased stress levels (Anisman and Merali, 2003) and are elevated in patients with depression and heart disease (Joynt et al., 2004; O'Connor and Joynt, 2004). Administration of pro-inflammatory cytokines (IFN- α) for treatment of melanoma relapse produces depression in up to 50% of patients (Capuron and Miller, 2004). Based on these and other lines of evidence, several recent reviews highlight the putative role of pro-inflammatory cytokines in the etiology of depression, possibly through altering HPA axis reactivity, down regulating serotonin precursors, and impairing processes of neurogenesis (Raison et al., 2006; Hayley et al., 2005; Hayley and Anisman, 2005; Schiepers et al., 2005). Consistent with these hypotheses, higher levels of proinflammatory cytokines were associated with greater self-reported stress symptoms (which are highly correlated with mood disturbance) on follow-up assessments in this study.

Despite these associations between cytokines and stress levels, there were no consistent relationships between home meditation or yoga practice and changes in cytokines. This in combination with the lack of associations between stress scores and meditation practice may suggest a more general pattern of recovery from the stress of cancer diagnosis and treatment, rather than one specifically due to the meditation practice. It may also be the case that once improvements were instigated through the MBSR program, they were self-sustaining and further formal meditation practice was not necessary. Indeed, a large component of the MBSR program involves instilling attitudes of non-judging, acceptance and patience, which may allow people to live more at ease even without formal daily practice. Another important part of the program is practicing “mini” meditation exercises that take only several seconds to minutes (such as slowing and counting breaths), and what is known as “informal” practice throughout the day, which includes awareness of patterns of stress reactivity. It may be that this more mindful approach to life was responsible for some of the changes observed in these participants. These questions remain to be explored in further research.

The continual drop of cytokine production observed over the 6- and 12-month follow-up was not directly related to decreases in stress, as most of the stress reduction occurred immediately following MBSR program participation. It is possible that changes in cytokine production could reflect improvement in disease status at the 6- and 12-month follow-up time points, continued physiological recovery from the effects of treatment, or a delay in the effects of stress reduction. There was no disease recurrence in any of the patients who provided cytokine data at all time points and no new treatments were started or current treatments remained the same (for those taking tamoxifen). Future studies examining longitudinal cytokine profiles of patients who do not choose to participate in mindfulness meditation could help to determine how these patients compare.

We also saw decreases in SBP in patients over the course of the intervention, which were maintained over follow-up, but attenuated in people who had been living with cancer for a longer period of time. This decrease is especially striking given that participants entered the study with essentially normal BP levels (average less than 120/80), and had resting HRs in the low 70 s. Thus, it would not be expected that very dramatic changes would be associated with participation in the MBSR program. This SBP decrease in our participants of an average of 6 mm Hg is consistent with other research. Wenneberg and colleagues recorded an average decrease of 9 mm Hg in ambulatory DBP in normotensive male volunteers after four months of meditation (Wenneberg et al., 1997). In a group of African Americans with initially high BP, decreases of 10/6 mm Hg were seen in resting SBP and DBP, respectively (Schneider et al., 1995). As well, in a group of Thai college students who practiced meditation intensively for two months, SBP decreased about 5 mm Hg, and DBP decreased about 6 mm Hg (Sudsuang et al., 1991). Similarly, SBP decreased over 3-month in groups of elderly nursing home residents randomly assigned to either transcendental meditation (TM) or mindfulness meditation, compared to relaxation and no treatment controls (Alexander et al., 1989). Barnes et al. also found that even during a single meditation session, experienced TM practitioners' SBP dropped 3.0 mm Hg, whereas for healthy non-meditating controls SBP increased 2.1 mm Hg during eyes-closed relaxation (Barnes et al., 1999). These studies all point to potentially beneficial effects of meditation on BP in a variety of groups of healthy subjects of varying ages, and support the magnitude of the findings of the current study.

There were, however, no associations between changes in BP over time and meditation practice, so we were similarly unable to document any "dose-dependent" changes in BP related to the amount of home practice. There was also a relationship found between age and SBP, in that older participants tended towards higher SBP. This is consistent with very commonly observed increases in BP with advancing age (van Boxtel et al., 1996; Tanaka et al., 2001).

HR was lowest when measured immediately following the last class, which is likely an indication of the immediate effect of the preceding meditation session, potentially an indication of activation of the relaxation response (Benson, 1975). Similarly, decreases in HR occurred during TM sessions in two studies of healthy volunteers who were experienced in TM techniques (Travis and Wallace, 1997; Telles et al., 1998). Another interesting finding was that resting HR was related to self-reported symptoms of stress at several time points. This may be an indication of psychological stress resulting in physiological manifestations in the form of increased HR. One may argue the possibility that completion of the questionnaires and thinking about symptoms of stress in close temporal proximity to the autonomic measures may have elevated HR. Procedurally, however, at the first assessment patients had their BP and HR taken prior to completing the questionnaires, and for the other three test sessions, patients completed the questionnaires at home some time before having their HR measured, and in all cases sat quietly for at least five minutes before the measurements, which argues against that possibility. It may be the case, then, that people who subjectively feel that they are experiencing high levels of stress also tend to have a higher resting HR even when not directly thinking about their stress.

The major methodological limitation of this study is the lack of a control or comparison group. Overall, this limits our ability to infer causation of any changes observed to participation in the MBSR program. For example, it is possible that stress and/or BP levels could have been artifactually elevated prior to program participation due to the novelty of beginning a new treatment program and being in the hospital setting (i.e. "white-coat hypertension"). This is part of the reason that we chose to take several pre- and post-measures, and conducted analyses on the mean scores of participants. Nonetheless, the results reported here must be considered preliminary and hypothesis generating. Nonspecific factors such as expectancy and the therapeutic alliance also cannot be controlled in a single-group design and may play an important role in the beneficial results found. Another issue related to the non-specificity of the intervention is that even if the beneficial effects were due to the intervention and not laboratory induced, 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.

Another obvious limitation of this approach is the multiple statistical comparisons that were conducted, as there were a high number of outcome measures employed. This elevates the chances of Type I error—falsely identifying significant findings in their absence—but in the context of a hypothesis-generating study such as this there is typically a higher tolerance for this type of error. Future

hypothesis-testing studies can further investigate promising relationships identified in this research. Due to the relatively small sample size, there is also the danger of Type II error—failing to identify significant relationships that are present. Indeed, because of sample size limitations we were not able to test for several comparisons of interest, such as between the men and women (there were only 10 men at baseline) or to include other potentially important covariates such as cancer treatments, marital status or other health behaviors. This study suffers from some degree of both lack of power and a large number of analyses, so the results must be considered in this light.

In summary, this study confirmed our previous findings of decreases in stress symptoms after participation in an MBSR program which were maintained over a one year follow-up. Cortisol levels continued to drop on average, and pro-inflammatory cytokine production decreased over the full year of follow-up. SBP decreased somewhat pre- to post-intervention overall in these already normotensive individuals, and HR decreased immediately following a meditation session. HR and cytokine levels were also associated with self-reported stress symptoms. Changes seen in these patients were moderate. This may have been due to the high levels of patient functioning at the start of the study, but could also indicate that this type of program is only moderately effective for early stage breast and prostate cancer patients who are three months or more post-treatment. Nonetheless, these data are intriguing for a preliminary uncontrolled study of the immune, endocrine and autonomic effects of the MBSR program in cancer patients. Future studies of this nature would benefit from a randomized control group and from screening for moderately distressed individuals at the start of the program. Such individuals are more likely to benefit in terms of improvements in stress symptoms, mood and quality of life, as well, perhaps, in enhancement of autonomic functioning.

Acknowledgments

This study was supported by the Canadian Breast Cancer Research Initiative. Dr. Linda Carlson was a Terry Fox Postdoctoral Research Fellow of the National Cancer Institute of Canada during the time the study was conducted. She is currently a Canadian Institutes of Health Research New Investigator. Dr. Kamala Patel is an Alberta Heritage Foundation for Medical Research Senior Scholar and holds a Canada Research Chair. Heartfelt thanks to all the men and women who participated in the study, whose enthusiasm continues to inspire us. Special thanks to research nurse Ms. Lori Tillotson for her tireless efforts in assuring the smooth running of the study, and research assistant Ms. Jodi Cullum for data input and management.

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