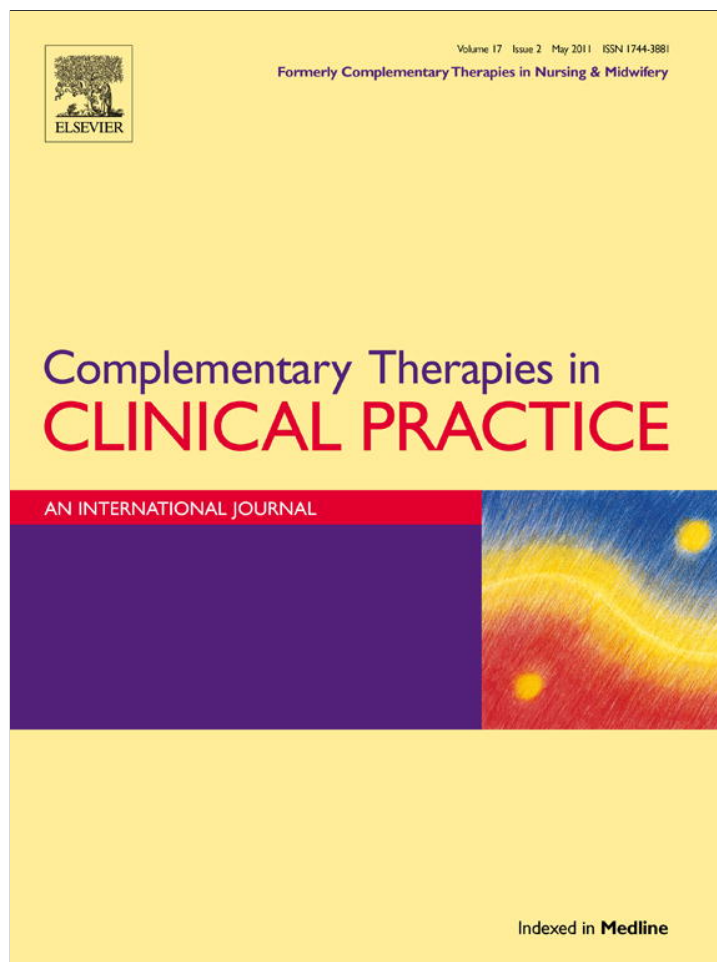


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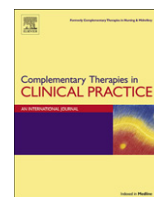
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Changes in the cortisol awakening response (CAR) following participation in Mindfulness-Based Stress Reduction in women who completed treatment for breast cancer

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A B S T R A C T

Keywords:

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Cortisol
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Stress
Cancer
Relaxation

Background: Changes in the cortisol awakening response (CAR) were studied in women participating in a Mindfulness-Based Stress Reduction (MBSR) program after completion of their medical treatment for breast cancer.

Method: Thirty-three women completed questionnaires pre- and post-MBSR pertaining to: stress, depressive symptomatology, and medical symptoms. The CAR was assessed on 3 days pre- and 3 days post-MBSR as a biological marker of stress.

Results: A significant effect on the CAR was found, with cortisol levels showing a prolonged increase after awakening at the post-MBSR assessment period. This was accompanied by significant improvements in self-reported stress levels, depressive symptomatology, and medical symptoms. Furthermore, the change in medical symptoms was negatively correlated with the area under the curve (AUC) at study onset ($r = -.52, p < .002$); i.e., the greater the AUC of the CAR before MBSR, the greater the reduction in medical symptoms after the program.

Conclusions: These results suggest the potential usefulness of employing the CAR as a biological marker in women with breast cancer participating in an MBSR program.

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1. Introduction

The psychosocial program entitled 'Mindfulness-Based Stress Reduction' (MBSR) was designed at the University of Massachusetts Medical Center¹ for patients with chronic pain and other chronic illnesses. It shows promise with regard to helping women who have completed medical treatment for breast cancer to make the transition from patient to survivor status.^{2,3,4,5} In Canada, the psychosocial team at the Tom Baker Cancer Centre in Calgary, Alberta has published numerous studies showing improvements in stress-related symptoms, mood, and quality of life in patients with various types of cancer, and at different stages of disease, after participation in the MBSR program.^{6,7,8,9,10} In fact, Carlson et al.¹⁰ observed that women who were in earlier phases of breast cancer

had steadily declining baseline cortisol levels assessed throughout the day in their home environment after completing MBSR, suggesting that there may be a window of opportunity to offer this program.

The hypothalamus-pituitary-adrenal (HPA) axis is the most important neuroendocrine stress system.¹¹ Its secretory products CRH, ACTH and glucocorticoids (cortisol in humans, corticosterone in rodents) are released sequentially in times of increased energy demand, or stress. The regulation of cortisol in humans follows further a strong circadian rhythm – levels are highest in the morning after awakening, and decline throughout the day with the nadir around midnight, to rise again in the early morning hours. A distinct characteristic of the HPA axis is the cortisol awakening response (CAR). The CAR, reflecting the organism's response to the natural stressor of awakening, is a discrete part of the cortisol circadian cycle. In healthy individuals, it is characterized by a sharp rise (between 50 and 75%) of cortisol levels within the first 30 min after awakening.¹² Due to its high intra-individual stability,^{12,13} the CAR may be regarded as a reliable marker of acute reactivity of the HPA axis.¹⁴ Although the CAR appears to be independent of diurnal cortisol secretion, its correlation with the response to standard

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adrenocorticotropin stimulation suggests that it can be considered a marker of adrenocortical reactivity.¹⁴ The CAR is further associated with a number of psychological, mostly stress-related variables (for reviews see Refs. ^{15,16}). In short, it seems that acute stressors lead to an increase in CAR, while chronic, prolonged or traumatic stress seem to be associated with a blunting of the cortisol levels after awakening. The CAR is typically assessed within the first hour after awakening, with three measurements taken at 0, 30 and 60 min after awakening.¹³

Matousek et al.²⁰ reviewed the literature pertaining to cortisol changes following MBSR in various populations and found converging evidence for significant reductions in cortisol post-MBSR^{31,32,33} and at 6-month and 12-month follow-up periods.¹⁰ Interestingly, Carlson et al.³¹ evaluated diurnal salivary cortisol levels pre- and post-MBSR in 59 early stage breast cancer and 10 prostate cancer patients free of concurrent mood and anxiety disorders and reported that approximately 40% of these cancer patients (mostly early stage breast) showed abnormal cortisol secretion patterns both pre- and post-MBSR. Nonetheless, extreme cortisol levels were attenuated, with afternoon elevations of cortisol becoming less prevalent post-MBSR, suggesting that participation in the program may have had beneficial effects on the stress response and on the HPA axis. Since Carlson et al.³¹ sampled salivary cortisol levels only over a single day, we made a point to study cortisol over multiple testing days at each assessment period to see if we could replicate these early findings using CAR. Witek-Janusek et al.³³ also showed reduced late afternoon plasma cortisol levels in early stage breast cancer patients following MBSR – these results were significantly different from a non-randomized control group.

We offered MBSR (please see www.mcgill.ca/wholepersoncare) to women who completed breast cancer treatment starting in autumn of 2006 through the winter of 2009. Our aims were:

- to provide a service for these patients¹⁷;
- to understand the processes underlying benefits¹⁸;
- to investigate the usefulness of employing the CAR as a stress marker before and after the program in women participating in MBSR. This third aim was the primary focus of this paper. Given this novel approach, the analyses are exploratory in nature.

2. Methods

2.1. Procedures

Participants were recruited from university affiliated hospitals and community organizations using posters, pamphlets and e-mail distribution of flyers. Patients were referred by staff at these hospitals or called when they heard about the program from another source (e.g., another participant in MBSR). In the weeks preceding the start of the program, each patient came to the McGill Programs in Whole Person Care office to complete questionnaires via computer administration and be interviewed by the course instructor (PLD) or a clinical psychology post-doctoral student (RHM) to determine eligibility. The study was approved by the Institutional Review Board, Faculty of Medicine, McGill University, Montreal, Canada. Written, informed consent was obtained from all participants.

2.2. Patients

Women were eligible to enroll if they were 18 years or older, had finished medical treatment for breast cancer, and had no known

endocrine disorders related to cortisol (e.g., Cushing's syndrome). Patients with a concurrent psychiatric disorder (e.g., borderline personality, alcoholism) were excluded because meditation may be contraindicated for them or they may not have been able to participate fully in the program. As program involvement requires a certain degree of commitment, only patients who were able to attend at least 7/9 sessions were included. Those included herein are a subset of a larger study of breast cancer patients ($N = 59$).¹⁷ [We began collecting data for cortisol after the study began when funding became available (in 2009) for this aspect of the work.] Given our aim to provide a clinical service, women who scored high on the depression screening questionnaire were included provided they had adequate resources (e.g., a family doctor) and were able to fully participate (e.g., concentrate during meditation). No women in the analyses were taking antidepressant medications. There were no significant differences in age, stage of cancer, or number of months since completion of breast cancer treatment between the sample of women in the autumn study and those included herein (data not shown).

2.3. Cortisol sampling

Cortisol was collected with the Salivette sampling device (Salimetrics, PA). This noninvasive technique can be used at home and interferes only minimally with normal daily routines. The patients collected saliva 3 times a day for 3 consecutive days at 0, 30, and 45 min after awakening in the morning. Awakening was either spontaneous or by alarm clock. Previous studies have shown that the cortisol response is not affected by this variable.¹² Although it has been shown that the consistency of this measure is dependent on subject compliance, it has also been demonstrated that patient compliance is superior to that of healthy volunteers.¹⁹ Patients were asked to refrain from drinking caffeinated beverages and smoking before saliva sampling. Furthermore, they were instructed not to eat, drink or brush their teeth before the end of the sampling time in the morning.²⁰ Pre-MBSR cortisol collection was performed within the first 5 days preceding the commencement of the 8-week MBSR program while post-MBSR cortisol collection was performed within the 5 days following the completion of the 8-week MBSR program. Cortisol values are reported in nmol/L; data were not transformed.

2.4. Psychosocial measures

2.4.1. Center for Epidemiologic Studies Depression Scale (CES-D)

This questionnaire is a screen for depression and was developed for use with community populations.²¹ Scores range from 0 to 60; a higher score indicates more symptoms consistent with clinical depression. For the population at large, a score of 16 or more indicates a positive screen for depression. The CES-D has been found to have very high internal consistency ($\alpha = .85$ in the general population; $\alpha = .90$ in a patient sample) and moderate test-retest reliability, with all but one correlation between $r = .45$ and $.70$ in these two samples.

2.4.2. Medical Symptom Checklist (MSCL)

The MSCL is a checklist of medical symptoms that the patient has experienced in the past month.²² It consists of a number of physical (e.g., gastrointestinal, respiratory, pain) and psychosocial symptoms (e.g., difficulty relaxing, sexual difficulties). Higher scores are indicative of a greater number of problems. While the reliability and validity of the MSCL have not been determined, research using this questionnaire has consistently demonstrated that post-MBSR, there are significant reductions in medical symptoms for patients with various conditions.^{23,24,25}

2.4.3. The Perceived Stress Scale-10

This 10-item scale was developed to measure the extent to which respondents appraise situations in their life to be stressful during the past month.^{26,27} Each item is scored from 0 to 4. A global score is computed ranging from 0 to 40 with higher scores indicating greater perceived stress. This scale, designed for use in community samples, has been shown to have good internal validity and test-retest reliability.²⁷ The mean score for women in the community is 14.

2.4.4. Mindfulness-Based Stress Reduction program

The MBSR program was provided by the same instructor to groups of about 10–15 women/group, who met weekly for 2.5 h classes for 8 consecutive weeks to learn mindfulness meditation and stress management techniques. They received a home practice manual and 4 CDs created by the instructor to teach the following meditation practices: body-scan, sitting meditation, yoga, and meditation involving visual imagery. At the end of each class, the women were asked to complete specific home practice exercises. Informal practice (awareness of breath; being mindful while engaging in various daily tasks) was also integrated into the home practice. A silent retreat, 6 h in duration, was provided after week 6 to reinforce the meditation practices learned. Group discussions throughout the course focused on the practice itself and how it was being integrated into the participants' daily lives.

2.5. Statistical analyses

Paired sample *t*-tests were performed to determine whether changes in outcome variables were statistically significant from pre- to post-MBSR. To determine the magnitude of change experienced by women for each outcome, effect sizes (ES) were calculated. To calculate the effect size we used the following formula from Cohen²⁷

$$d = \frac{\bar{X}_1 - \bar{X}_2}{s}$$

where \bar{X}_1 is the mean for one population, \bar{X}_2 is the mean for the other population, and *d* is a standard deviation based on either or both populations. To analyze the cortisol increase after awakening for the 3 sampling days, a three-factor within-subject ANCOVA was computed with repeated measures on all factors (pre/post-MBSR assessment: 2 levels; day: 3 levels; time: 3 levels). Since depression could potentially affect cortisol regulation this was controlled for by entering CES-D scores as covariates.

In addition, we investigated the association between the cortisol response patterns and the outcome variables, namely stress, depressive symptomatology, and medical symptoms. For that purpose, we computed the area under the curve with respect to increase (AUC_i) to analyze the linear relationship between each independent outcome variable and cortisol awakening levels.²⁸ For all correlation analyses, cortisol levels were transformed into a single value by first calculating the area under the curve (AUC) for each day and then calculating the mean from the three individual cortisol (day) values. This new variable was then used in partial correlations to compute the relationship between the AUC cortisol response after awakening and the outcomes, while controlling for levels of depression. All statistical analyses were performed using SPSS.

Cortisol was analyzed using a time-resolved fluorescence immunoassay with proven reliability and validity.²⁹ For this sample, the intra- and inter-assay variance was below 6% and 8%, respectively.

Table 1
Patient characteristics.

Variables	N(%) or Mean ± SD (range)
Sociodemographic	
Age, years	55.9 ± 10.8 (28–72)
Ethnicity (Caucasian %)	11 (73.3%)
Maternal language (French-speaking %)	5 (21.7%)
Maternal language (English-speaking %)	17 (73.9%)
Education, degree	
High school	3 (9.1%)
College	7 (21.2%)
Bachelors	15 (45.5%)
Masters	6 (18.2%)
Ph.D.	2 (6.1%)
Marital status (%)	
Married	15 (65.2%)
Single	3 (13.0%)
Separated or divorced	4 (17.4%)
Widowed	1 (4.3%)
Employment status (working %)	20 (68.9%)

3. Results

3.1. Patients

Thirty-three patients provided written consent to enroll in this aspect of the study and completed the screening interview. Participant demographics are shown in Table 1. The average age of the participants was 55.9 years (SD = 10.8). All had a high school education or above, with 7 having a college degree (21.2%), 15 having an undergraduate degree (45.5%), 6 having a Master's degree (18.2%), and 2 with a PhD degree (6.1%). Most women presented with early stage breast cancer (*n* = 25; 75.8%), either being diagnosed with Stage 1 (*n* = 13; 39.4%), or Stage 2 (*n* = 12; 36.4%). The stage of 5 (15.2%) women was unknown (all stages were based on self-report as we did not have access to medical records), either because the patients did not know their stage (*n* = 3) or because they could not be reached after the completion of the study for this information (*n* = 2). Time since completion of breast cancer treatment was, on average, 34.9 months (SD = 72.9; range 2–340).

3.2. Attendance

The average number of MBSR classes attended was 8.2/9 (SD = 1.2); attendance was 90.7%.

3.3. Changes in outcomes pre- to post-MBSR

As shown in Table 2, results of paired samples *t*-tests revealed significant reductions in depressive symptomatology (*p* < .0001), perceived stress (*p* < .0001), and medical symptoms (*p* < .0001) over time. These remained significant following correction for multiple testing (Bonferroni correction with $\alpha = .05$ and 3 tests yielded a corrected *p* = .0167). The current results from the subset

Table 2
Pre- post-MBSR outcomes.

Variable	Pre-program Mean (SD)	Post-program Mean (SD)	Difference	d value	t value	p value
Depression	15.58 (9.03)	8.55 (6.00)	7.03	.93	5.17	.0001
Perceived stress	17.76 (5.76)	13.88 (5.92)	3.88	.67	4.57	.0001
Medical symptoms	19.96 (11.78)	11.24 (8.21)	8.72	.87	5.88	.0001

Bonferroni correction = α/n where $\alpha = .05$ and *n* = number of tests (3) = .0167.

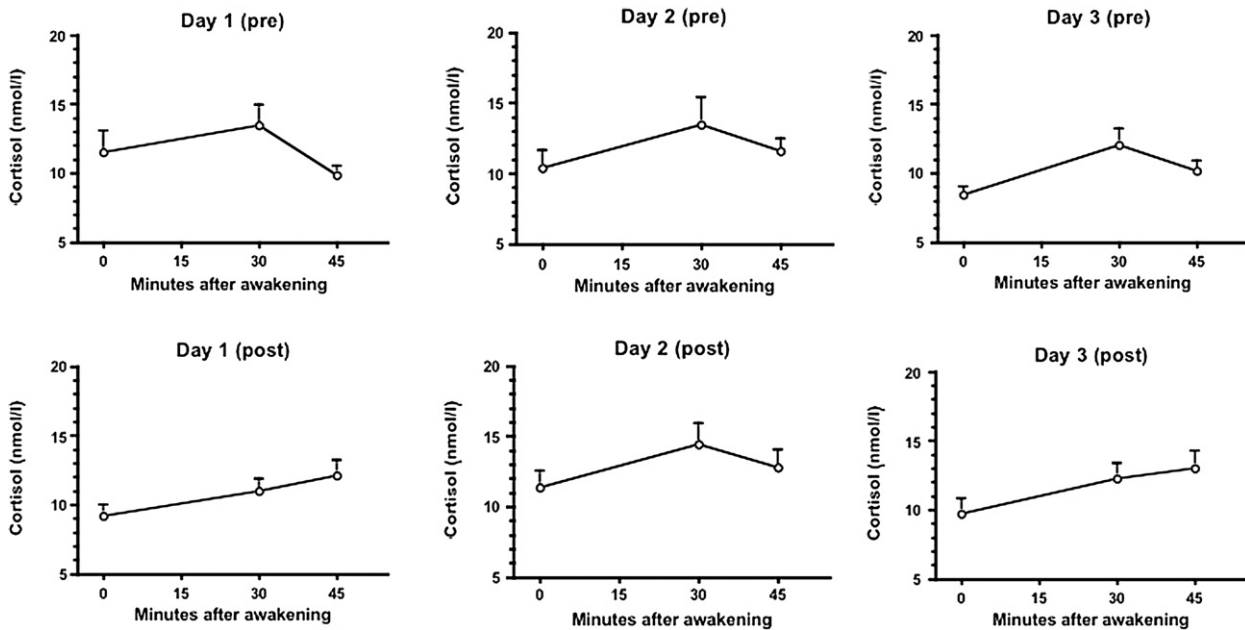


Fig. 1. Changes in CAR for 3 days pre- and post-MBSR. Matousek et al.¹⁷

of participants who provided cortisol are in line with the results for the full sample ($N = 59$) for the psychosocial measures.¹⁷

3.4. Changes in CAR

Fig. 1 shows the early morning free cortisol levels on the 3 days for both visits. Early morning free cortisol levels showed a significant effect of awakening across pre- and post-MBSR assessment periods (time $F(2,64) = 3.03; p = .05$). Free cortisol levels increased from between 8 and 10 nmol/L at the time of awakening to between 11 and 13 nmol/L 30 min thereafter on all 3 days at pre- and post-MBSR. The effect size for the cortisol increase after awakening on days 1, 2 and 3 of pre-MBSR was $f^2 = .25$, explaining 21% of the variability in the early morning free cortisol levels ($\omega^2 = .21$), according to the formulas provided by Cohen.³⁰ After controlling for depression, the effect of awakening was no longer significant (time $F(2,64) = 1.74, p = .19$), indicating that depressive symptomatology impacted on the rise of cortisol after awakening. The repeated measures factor 'day' was not significant ($F < 1, p > .20$) indicating that the CAR was stable across the 3 days within each session.

Further, we observed a significant difference for session, indicating that the CAR increased significantly from pre- to post-MBSR

($F(2,64) = 4.03, p = .05$). This finding was more pronounced when depressive symptomatology was controlled for statistically ($F(2,64) = 7.16, p = .012$). Newman Keuls post-hoc tests indicated that the effect of session came from a stronger increase at the level of 45 min after awakening at the second session (see Fig. 2).

3.5. Associations between CAR and outcomes

In addition, we investigated the association between the cortisol response patterns and the outcome variables. These included stress, depressive symptomatology, and medical symptom using partial correlations to compute the relationship between the AUC cortisol response after awakening and the outcomes, while controlling for depressive symptomatology using the CES-D scores. These partial correlations were not significant except for a significant negative correlation between the Medical Symptom Checklist (MSCL) difference scores (post-MBSR - pre-MBSR) and the AUC₁ at pre-MBSR ($r = -.52, p < .002$). As shown in Fig. 3, lower cortisol awakening responses before MBSR were associated with less improvement in MSCL scores from pre- to post-MBSR (i.e., in terms of alleviation of symptoms). However, this result did not withstand a Bonferroni correction, suggesting modest effect sizes of the MBSR program on this aspect of the cortisol awakening response.

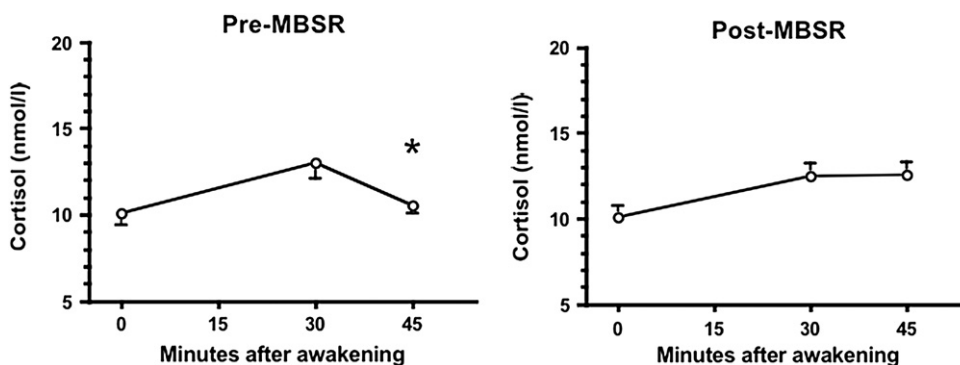


Fig. 2. CAR increased significantly pre- to post-MBSR. Matousek et al.¹⁷

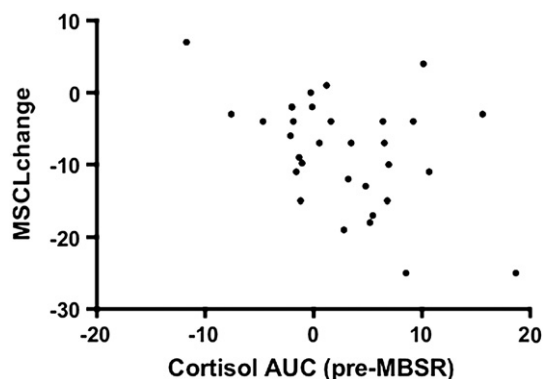


Fig. 3. Associations between CAR and changes in medical symptoms. Matousek et al.¹⁷

4. Discussion

The main purpose of this study was to examine changes in the CAR in women who had completed medical treatment for breast cancer and took an 8-week MBSR program. Results revealed that the MBSR program was associated with the CAR, with cortisol levels showing a prolonged increase after awakening at the post-MBSR assessment period.

To the best of our knowledge, only one other study investigated the effects of participation in an MBSR program on CAR. Marcus et al.³² studied 21 patients receiving treatment for substance abuse in a therapeutic community; they found significant reductions in salivary cortisol levels from pre- to post-MBSR, such that the increase in cortisol on awakening post-intervention was less than the increase prior to the intervention. In contrast, we found that cortisol levels showed a prolonged increase after awakening at the post-MBSR assessment period. One thing to consider when comparing these opposite findings is the population under investigation. Our sample consisted exclusively of women following treatment for breast cancer living in the community; these women could be considered to have been exposed to a prolonged or chronic stressor related to the aftermath of their cancer and/or its treatments. If this is the case, the CAR changes we observed are in line with Chida and Steptoe's review¹⁵ which indicated that following chronic stressors, the CAR might be blunted. Thus, it is possible that the women in our study may have exhibited a blunted CAR at baseline as a function of their exposure to the stressful experiences associated with cancer. In the absence of a normal control group, we can only speculate about the meaning of the CAR profile with regard to post-MBSR profiles seen. Nonetheless, if we compare our results to those of Wust et al.,¹³ who combined data from four separate studies with a total of 509 adult subjects in an effort to compile reliable information on normal values for the free cortisol response to awakening, we see that the mean values at 0, 30 and 45 min from awakening in our sample of breast cancer patients was lower than the values found in their healthy controls (theirs: CAR₀: 15.12 ± 9.13 nmol/L; CAR₃₀: 22.31 ± 9.33 nmol/L; CAR₄₅: 20.33 ± 8.89 nmol/L versus ours: CAR₀: 10.09 ± 1.59 nmol/L; CAR₃₀: 12.99 ± 0.81 nmol/L; CAR₄₅: 10.53 ± 0.92 nmol/L), suggesting that the women in our sample had blunted CAR values pre-MBSR. Of course, we acknowledge the difficulty of comparing raw numbers of cortisol across assays, although the analyses of our study were performed in the same laboratory as that of Wust et al., and the method used produces inter-assay variability consistently below 12%; thus, even taking these differences into account our results still point to a blunted CAR. Therefore, the increases in the CAR observed in our sample post-MBSR would be in keeping with what one might expect had the CAR been lower than normal to begin

with (pre-MBSR) and then moved towards normalization after the program.

While it is unclear whether good health is associated with larger or smaller CARs,³⁴ further (albeit indirect) support for the interpretation that higher post-MBSR CARs may be indicative of benefit stems from the concomitant improvements in all three outcome variables. Indeed, the women in our sample consistently showed marked reductions in perceived stress, medical symptoms, and depressive symptoms. However, the women with the lowest CAR pre-MBSR did not display as sharp a reduction in medical symptoms as women with initially higher cortisol levels. One possibility is that the women who did not display marked reductions in medical symptoms post-MBSR were suffering the greatest amount of exhaustion, inhibiting improvements in medical symptoms through participation in MBSR.

Given that cortisol is often viewed as a physiological marker of stress, we were curious about a possible association between the CAR and changes in stress or depressive symptoms. We failed to find an association between cortisol levels and self-report indices of either mood or stress consistent with results from other MBSR studies.^{10,32}

Carlson et al.³¹ suggested that decreases in cortisol levels after stress management programs in breast cancer patients have been related to self-report indices of stress only for those with high levels of cortisol at the onset of the program. Indeed, when they subdivided their sample by initial mean daily cortisol levels, they found that those with initially elevated cortisol levels showed significant decreases in cortisol over time, whereas those with lower initial levels displayed increases in their cortisol levels over time. The authors interpreted this to mean that participation in the MBSR program could lead to normalization of the HPA axis functioning. However, they could not rule out the possibility of it being a statistical artifact related to regression to the mean.

A number of limitations prevent us from drawing firm conclusions. First, the lack of a control group makes it impossible to draw firm conclusions about the cortisol changes observed. Furthermore, the CAR is usually measured at 0, 30 and 60 min after awakening to reflect the entire dynamic of the CAR (increase and decrease) over the first hour after awakening. While we measured the CAR at 0, 30, and 45 min after awakening, interestingly and somewhat unexpectedly, the main findings in the current study occurred with the 45 min measure. We cannot know if stronger effects would have emerged if we had included a 60-min measure instead. Finally, the manner in which depression was controlled for in the current study was not optimal. While it was not possible for ethical reasons to exclude women who screened positive for depressive symptoms when providing the MBSR program, it would have been better to have a subgroup with clinical depression. Limitations in budget and sample size precluded doing so, but it is recommended to have a large enough sample to be able to study the effects of depression separately. Even so, controlling for depression as we did showed that the main effect (i.e., changes in CAR from pre- to post-MBSR) was strongly affected by depressive symptoms, leading to stronger effect sizes in our statistical analysis.

Overall, the results of the present study indicate that MBSR is associated with psychological and physiological improvements following medical treatment for breast cancer. While self-reports of stress and depressive symptoms were not associated with the CAR pre- or post-MBSR, the greater the CAR at the onset of the program, the greater the drop in self-reported medical symptoms in response to the program.

These results suggest the potential usefulness of employing the CAR as a biological marker in women with breast cancer participating in an MBSR program. Future studies using larger sample sizes are needed to determine the value of using this marker alone

or in conjunction with other biological measures to identify which participants might benefit most from taking an MBSR program.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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