Original Article

Mindfulness Practice Reduces Cortisol Blunting During Chemotherapy: A Randomized Controlled Study of Colorectal Cancer Patients

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BACKGROUND: The objective of this randomized clinical experiment was to test the influence of a mindfulness meditation practice, when delivered during 1 session of active chemotherapy administration, on the acute salivary cortisol response as a marker of neuroendocrine system activity in cancer patients. **METHODS:** A mindfulness, attention-control, or resting exposure was assigned to 57 English- or Spanish-speaking colorectal cancer patients at 1 county oncology clinic and 1 university oncology clinic at the start of chemotherapy. Saliva samples were collected at the start of chemotherapy and at subsequent 20-minute intervals during the first 60 minutes of chemotherapy (4 samples in all). Self-reporting on biobehavioral assessments after chemotherapy included distress, fatigue, and mindfulness. **RESULTS:** An area-under-the-curve analysis (AUC) showed a relative increase in cortisol reactivity in the mindfulness group after adjustments for biological and clinical measures ($\beta = 123.21$; $P = .03$). More than twice as many patients in the mindfulness group versus the controls displayed a cortisol rise from the baseline to 20 minutes (69% vs 34%; $P = .02$). AUC values were uncorrelated with biobehavioral measure scores, although mindfulness scores were inversely correlated with fatigue ($r = -0.46$; $P < .01$) and distress scores ($r = -0.54$; $P < .01$). **CONCLUSIONS:** Findings suggest that mindfulness practice during chemotherapy can reduce the blunting of neuroendocrine profiles typically observed in cancer patients. Implications include support for the use of mindfulness practice in integrative oncology. ***Cancer* 2017;000:000–000.** © *2017 American Cancer Society.*

KEYWORDS: chemotherapy, colorectal, complementary medicine, cortisol, endocrine, integrative oncology, meditation, mindfulness.

INTRODUCTION

Receiving a diagnosis of cancer and experiencing medical treatment present a threat to self and involve major life role modifications that can be overwhelming for the patient. For example, up to 43% of patients with cancer report significant distress.[1] Patients with cancer endure physical and emotional events during and after treatment that can repeatedly activate a stress response, which involves the mobilization of the biological resources needed to cope with a demand or threat.[2,3] When the brain detects a significant demand, the hypothalamus produces corticotropin-releasing hormone, which stimulates the anterior pituitary to secrete adrenocorticotropic hormone to trigger the adrenal glands atop the kidneys to release the corticosteroid hormone cortisol.[4,5] Chronic activation of this system in patients with cancer, especially those with greater disease severity, has been found to be associated with hypothalamic-pituitary-adrenal (HPA) axis dysregulation, mostly blunting of the diurnal cortisol rhythm.[6-9] Longitudinal observational studies show that a blunted cortisol response in cancer survivors predicts disease progression and decreased survival time for breast, lung, ovarian, and renal cell carcinoma patients after adjustments for important clinical and demographic characteristics.[10-13] These findings in cancer research align with the findings from various other fields showing cortisol blunting after chronic stress exposure.[14-16]

A smaller group of studies have specifically examined the blunting of acute cortisol reactivity in cancer patients and survivors. Giese-Davis et al[17] administered a standardized stressor test (ie, the Trier social stress test) to metastatic breast cancer patients and found acute cortisol reactivity to be blunted for these cancer patients in comparison with a noncancer comparison group at risk for cardiovascular disease. The authors interpreted this as support for HPA axis hyporesponsivity in advanced-cancer patients. Bower et al[18] also observed blunted salivary cortisol reactivity to the Trier social stress test among fatigued breast cancer survivors versus nonfatigued breast cancer survivors. Only 1 study of which we are aware has examined the cortisol reactivity elicited from engaging in clinically prescribed activities. Porter et al[19] conceptualized a mammography exposure as an acute stressor among breast cancer survivors. The selection of this exposure was relevant

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because mammography is often noted as one of the most salient triggers of recurrence fears in cancer survivors, and women without a history of breast cancer generally do not experience significant distress when they are undergoing routine mammography screening.[20] The Porter study showed that breast cancer survivors had blunted cortisol reactivity to an acute cancer-related stressor (mammography) in the years following the completion of treatment. The authors suggested that blunting might have been caused by repeated physiological and psychological efforts by survivors to cope that resulted in fatigue and an inability to mount new acute responses to demand. It remains unknown whether the blunting of acute reactivity in cancer patients can be modified through intervention.

Mindfulness practice represents a novel learning experience founded on stress-arousal reduction by engaging attention to and awareness of bodily sensations and experiences without judgment or reactivity.[21] The process of mindfulness is commonly defined as "the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment."[22] Programs that aim to cultivate mindfulness, such as the widely disseminated mindfulness-based stress reduction (MBSR) program,[22] are available at some major cancer treatment centers across the nation,[23] and empirical reviews have demonstrated their utility for attenuating subjective states of cancer-related symptoms.[24,25] For context, MBSR and related programs are housed within the broader medical models of mind-body medicine and integrative oncology.[26-28] We have previously observed that a significant proportion of colorectal cancer patients and survivors use integrative health modalities alongside conventional treatment.[29]

Although the current literature is limited to a few studies examining different diseases, preliminary findings suggest that mindfulness practice can influence cortisol profiles in cancer survivors (see the review by O'Leary et al).[30] For example, Carlson et al[31] conducted a multisite randomized controlled trial and assigned distressed breast cancer survivors to a mindfulness-practice intervention, supportive-expressive group therapy, or a brief stress-management control condition. Intent-to-treat analyses indicated that diurnal cortisol slopes were maintained under the mindfulness and group-support conditions, whereas the control group slope showed cortisol blunting. Women in the mindfulness group also reported significantly fewer stress symptoms than women in either the support group or the control group. A separate pre-post, within-subjects study of breast and prostate cancer patients observed that the MBSR program was associated with a shift toward a greater cortisol decline in the afternoon (less blunting), and this change was significantly associated with improved overall global quality of life.[32] Taken together, the initial evidence suggests that mindfulness practice may protect against cortisol blunting in cancer patients and survivors when it is assessed at the level of the diurnal rhythm.

The purpose of this randomized controlled experiment was to examine changes in cortisol reactivity among colorectal cancer patients during the first hour of chemotherapy infusion across a mindfulness exposure versus a control group to ascertain potential changes in cortisol blunting as the primary outcome. The impact of mindfulness practice during chemotherapy on physiological processes relevant to cancer is unexplored, and to date, no study among cancer patients of which we are aware has assessed cortisol at multiple time points across chemotherapy infusion. Our primary research question was whether mindfulness practice could awaken cortisol reactivity as a counter to the blunting previously observed in cancer patients and survivors. Our thinking on the engagement of HPA axis activity during mindfulness practice was guided by literature on the neuroendocrine response to novel learning exposures and states of eustress.[33-36] As such, we hypothesized that exposure to mindfulness practice as novel learning in attention to and awareness of somatosensory states at the start of chemotherapy would yield a relative increase in acute cortisol reactivity. Our exploratory aim was to test for significant associations between cortisol reactivity levels and self-reporting of biobehavioral factors (ie, distress, fatigue, and mindfulness).

MATERIALS AND METHODS

Participants and Procedures

The experimental design was a 2-site randomized controlled study with group intervention exposures and cortisol assessments occurring during an active chemotherapy session. The enrolled participants were 57 English- or Spanish-speaking adult colorectal cancer patients receiving an adjuvant chemotherapy session at a county hospital oncology clinic or a university hospital oncology clinic, both located in East Los Angeles. Potential recruits were identified via referrals made by the site's attending oncologist. When a patient expressed interest in the study, the project staff scheduled a screening session and provided a detailed description of the study. Eligible recruits provided written informed consent before study enrollment. The informed consent process reviewed issues of confidentiality, the patient's right to refuse participation at any

time, time commitments, and potential risks as well as benefits from participation. Recruits were eligible if they were 18 to 89 years old, had been diagnosed with colorectal cancer, were scheduled for a chemotherapy appointment, and were willing to give informed consent, and they were ineligible if their oncologist thought that the patient was too ill to participate or if the patient lacked proficiency in English or Spanish. The University of Southern California institutional review board and clinical investigator support office approved all study procedures (ClinicalTrials.gov identifier NCT02057991). Health Insurance Portability and Accountability Act clearance was also obtained from medical record and chart reviews.

After informed consent had been obtained, recruits were enrolled in the study, and research staff met with each participant to collect demographics from a brief, self-report measure. Medical data were also obtained with a brief questionnaire in which treating oncologists reported a patient's diagnosis. This assessment meeting occurred either on the date of the informed consent (all within 3 weeks of the chemotherapy session) or on the date of chemotherapy; this depended on patient availability and clinic scheduling. Research staff obtained medical information from each participant's record or chart (ie, cancer location, grade, and stage). A biostatistician from the clinical investigation support office, blinded to study hypotheses, allocated participants to 1 of 3 exposures in a 1:1:1 ratio. Exposures included 1) standard chemotherapy at rest for the control group, 2) a cancer education module for the attention-control group, and 3) a mindfulness meditation practice video followed by the cancer education module for the active-treatment group. To increase the statistical power and to test for group differences by mindfulness exposure, we collapsed groups 1 and 2 (no mindfulness practice) and compared them with group 3 (mindfulness practice). A test of group contrast showed that area-under-the-curve (AUC) values did not differ between groups 1 and 2 ($P > .05$). The original 3-group design was aimed at testing changes in cancer knowledge, and we categorically refined the groups here to test the effect of exposure to mindfulness practice on salivary cortisol levels. We referred to the videos and protocols in all communications with patients before exposure as educational activities to limit any expectancy effects.

On the date of chemotherapy, participants were instructed to refrain from taking stimulant medications, smoking, eating, drinking, and brushing their teeth at least 30 minutes before their visit to avoid contamination of their saliva. All chemotherapy sessions occurred between 10 AM and 2 PM. At the start of chemotherapy, participants provided a baseline saliva sample, and they provided subsequent saliva samples at 20-minute intervals for the first 60 minutes of chemotherapy (ie, at the baseline and at minutes 20, 40, and 60). All intervention exposures were delivered via a mobile tablet for the purpose of transportability at clinics. At the end of the 60-minute assessment period, participants completed a self-report questionnaire composed of biobehavioral measures (minutes 60-80). At the close of the questionnaire, participants were thanked by the staff and provided with a $10 gift card to acknowledge their time and effort.

Group Exposures

Participants in the standard-care group received routine treatment only as provided at the clinic site. This exposure is best defined as the patient being at rest for 60 minutes while sitting in a chair during chemotherapy. Participants in the cancer education group navigated a 20-minute read-only colorectal cancer educational module on a transportable tablet at the start of chemotherapy and then rested for the remaining 40 minutes of chemotherapy. This educational module is available from the Patient Education Institute (X-Plain Lite) and provides basic information on colorectal cancer disease anatomy, etiology, treatment, and prevention on a touch screen. All video modules and study documents were available in both English and Spanish, as preferred by the participant. Participants in the mindfulness-practice group engaged in 12 minutes of prerecorded audio-video instructions on guided mindful body scan meditation at the start of chemotherapy. The program was developed by David S. Black in collaboration with a teacher trained in MBSR (Eric López Maya) who had more than 6 years of teaching experience. After the mindfulness practice exposure, participants rested for the remaining 8 minutes to reach the 20-minute mark, then completed the 20-minute colorectal cancer educational module, and then had 20 minutes of rest.

Assessments

Salivary cortisol

The measurement of cortisol in saliva reliably reflects physiologically active free plasma cortisol levels in blood because unbound plasma cortisol diffuses easily from blood to saliva.[37] The collection of saliva is a minimally invasive method for repeated measures of biological specimens[38] and thus has high utility for cancer patients in treatment. Research staff timed the 4 saliva collections, including the baseline collection at the start of chemotherapy and subsequent saliva collections at 20-minute

intervals during the first 60 minutes of chemotherapy. Staff provided participants with noninvasive Salivettes (Sarstedt), a commercially available collection device consisting of a dental roll and a centrifuge tube, for the hygienic collection of saliva samples. At the designated collection time, staff asked the participants to remove the cap from the tube and drop the dental roll from the centrifuge tube into their mouth while chewing gently for approximately 1 minute to allow saturation of the dental roll. Participants then spit the dental roll back into the Salivette tube, which was labeled with sample identification numbers and the collection time point (0, 20, 40, or 60 minutes). We stored Salivette tube specimens at −70 °C. At study completion, we sent batched saliva specimens to the Technical University of Dresden (Kirschbaum Laboratory) to be assayed for cortisol quantification via a chemiluminescence immunoassay (IBL, Hamburg, Germany). The interassay coefficient was <.08, and the intra-assay coefficient was < .06 with a lower detection limit of 0.05 nmol/L.

Biobehavioral measures

Participants completed a questionnaire inclusive of the following measures, which have been psychometrically validated among various populations, including cancer survivors: 1) the Multidimensional Fatigue Symptom Inventory 7-item General Scale, which is designed to assess the principal manifestations of fatigue with a past-week recall period[39]; 2) the 21-item Depression, Anxiety, and Stress Scale, which is designed to assess a syndrome of distress along 3 axes with a past-week recall period[40]; and (3) the Mindfulness Attention Awareness Scale 6-item short version, which is designed to assess mindful and receptive awareness of present-moment experience with a recall period of current everyday experience per measure instructions.[41,42]

Statistical Analyses

We report descriptive statistics from a chi-square test, a *t* test, and a 1-way analysis of variance to compare the 2 exposure groups at the baseline with respect to sociodemographic and clinical features. For salivary cortisol in nanomoles per liter, we report the area under the curve with respect to increase (AUC_I), the area under the curve with respect to ground (AUC_G), and the area under the curve above the baseline value (AUC_{AB}), as previously detailed.[43,44] Functioning to simplify the repeated assessment of salivary cortisol while reducing multiple-testing error, the AUC represents aggregated data and is derived from a trapezoid formula. Although AUC_G pertains to the total cortisol output, AUC_I and AUC_{AB} pertain to the response sensitivity of the HPA axis/cortisol system. We retained negative AUC_I values to avoid omitting information, and negative AUC_{AB} values were set to zero. With AUC_G, AUC_I, and AUC_{AB} used as outcomes, simple linear and multiple-linear regression models were estimated and adjusted for age, sex, cancer stage, and time since cancer diagnosis with Stata 14.1 (StataCorp LP, College Station, Texas). Square-root transformations of AUC were performed when necessary to ensure the normality and homoscedasticity of residuals in regression models. The multicollinearity of predictors and autocorrelation were checked for all regression models, and no problems were evident. Bivariate correlations were used to test associations between AUC and biobehavioral measure scores. All hypotheses were tested with a 2-sided significance level of $\alpha = .05$.

RESULTS

Study Entry and Sample Characteristics

Sixty-five recruits were approached at the clinic sites and signed the informed consent form. Recruits who showed up for their next scheduled chemotherapy appointment (n = 57) were officially enrolled in the study and were randomly assigned to one of the groups (standard care, n = 21; cancer-education module, n = 19; and mindfulness meditation practice video, n = 17). Combining the standard-care and cancer-education groups (no mindfulness) led to a total of 40. Six participants (1 in the mindfulness group and 5 in the no-mindfulness group) did not provide sufficient saliva during at least 1 collection point, and this made the analytic sample size 51. Table 1 presents descriptive and medical characteristics by exposure group. Scores for all demographic, biological, and clinical measures were equivalent across the groups at the baseline.

Group Exposure Effects on the Cortisol Response During Chemotherapy

Table 2 shows the results for unadjusted and adjusted models testing the impact of mindfulness exposure on cortisol levels. In unadjusted models, mindfulness exposure versus nonexposure predicted a greater aggregated rise in both AUC_I and AUC_{AB} salivary cortisol (AUC_I, $\beta = 118.85$ and $P = .03$; AUC_{AB}, β [square root–transformed] = 4.01 and $P = .03$). Mindfulness exposure versus nonexposure did not significantly predict total cortisol output (AUC_G, β [square root–transformed] = 1.99 and $P = .35$). After adjustments for biological and clinical covariates, the pattern of results for AUC outcomes

TABLE 1. Sample Characteristics of Randomized Participants

Variable	Controls (n = 40)	Mindfulness Group (n = 17)	*P*
Age, y	54 (7.8)	54 (9.1)	.54
Sex: female, No. (%)	20 (50.0)	8 (47.1)	.84
Ethnicity, No. (%)			.41
Hispanic/Latino	12 (30.0)	7 (41.2)	
Non-Hispanic	28 (70.0)	10 (58.8)	
Primary language, No. (%)			1.0
Spanish	7 (17.5)	3 (17.6)	
English	33 (82.5)	14 (82.4)	
Education, No. (%)			
<9th grade	5 (12.5)	2 (11.8)	
High school/GED	10 (25.0)	5 (29.4)	
Completed vocational school	7 (18.0)	3 (18.0)	
Completed college	18 (45.0)	7 (41.2)	
Time since cancer diagnosis, No. (%)			1.0
≤6 mo	11 (27.5)	4 (23.5)	
>6 mo	29 (72.5)	13 (76.5)	
Cancer stage, No. (%)			
II/III	20 (50.0)	7 (41.2)	.49
IV	19 (47.5)	10 (58.8)	
Unknown	1 (2.5)	0 (0.0)	
MFSI, Mean (SD)	1.43 (1.02)	1.22 (0.89)	.48
DASS, Mean (SD)	0.57 (0.53)	0.56 (0.33)	.96
MAAS, Mean (SD)	5.05 (1.00)	4.93 (1.07)	.70
Cortisol, nmol/L, Mean (SD)			
0 min	12.22 (5.89)	12.28 (7.48)	
20 min	11.42 (5.27)	13.77 (7.59)	
40 min	11.64 (6.25)	13.63 (7.69)	
60 min	9.55 (5.51)	13.01 (7.88)	

Abbreviations: DASS, Depression, Anxiety, and Stress Scale; GED, general educational development; MAAS, Mindfulness Attention Awareness Scale; MFSI, Multidimensional Fatigue Symptom Inventory; mo, months.

remained similar (AUC_I, $\beta = 123.21$ and $P = .03$; AUC_{AB}, β [square root–transformed] = 4.15 and $P = 0.03$; AUC_G, β [square root–transformed] = 2.02 and $P = .34$). Figure 1 shows cortisol increases from 0 to 20 minutes of chemotherapy. At 20 minutes, 34% of the participants (12 of 35) in the control group showed a cortisol increase, whereas 69% of the participants (11 of 16) in the mindfulness exposure did. This difference between the groups was significant ($P = .02$).

Correlation of the Cortisol Response and Biobehavioral Measures

Table 3 shows bivariate correlations between the self-reported biobehavioral measure scores and the cortisol AUC for the total sample. None of the correlations between the cortisol AUC and the biobehavioral measure scores reached statistical significance. The Mindfulness Attention Awareness Scale was significantly anticorrelated with both the Multidimensional Fatigue Symptom Inventory ($r = –0.46$; $P < .01$) and the Depression, Anxiety, and Stress Scale ($r = –0.54$; $P < .01$), whereas the Multidimensional Fatigue Symptom Inventory was significantly correlated with the Depression, Anxiety, and Stress Scale ($r = –0.49$; $P < .01$). All of these significant biobehavioral correlation coefficients were in the range of a large effect size.

DISCUSSION

To better understand the clinical relevance of mind-body practice delivered during chemotherapy, this randomized controlled experiment exposed colorectal cancer patients to mindfulness in the form of a body scan and assessed salivary cortisol profiles during the first 60 minutes of chemotherapy. Results showed that the mindfulness-exposure group in comparison with the control group had significantly greater acute salivary cortisol reactivity during chemotherapy infusion. Findings were evident for 2 AUC approaches (ie, AUC_I and AUC_{AB}) and after adjustments for important biological and clinical measures, including age, sex, cancer stage, and time since diagnosis. More than twice as many patients in the mindfulness group versus the controls displayed a cortisol rise from the baseline to 20 minutes (69% vs 34%). These findings suggest that mindfulness practice during chemotherapy infusion may awaken cortisol reactivity as a counter to detrimental HPA axis blunting, which has been previously observed in cancer survivors and patients.

TABLE 2. Prediction of the Salivary Cortisol Area Under the Curve in Nanomoles per Liter: Unadjusted and Adjusted Estimates

	β	SE	*t*	*P*[a]	95% CI
AUC_I					
Unadjusted model					
Group (REF: control)	118.85	52.98	2.24	**.03**	12.38, 225.31
Adjusted model[b]					
Group (REF: control)	123.21	54.33	2.27	**.03**	13.72, 232.70
Age	2.13	3.13	0.68	.50	−4.18, 8.44
Female	−17.81	51.03	−0.35	.73	−120.65, 85.04
Cancer stage (REF: stage II/III)	36.31	51.37	0.71	.48	−67.22, 139.84
Time since diagnosis (REF: < 6 mo)	−80.98	56.01	−1.45	.16	−129.27, 103.46
AUC_{AB}[c]					
Unadjusted model					
Group (REF: control)	4.01	1.82	2.20	**.03**	0.34, 7.68
Adjusted model[b]					
Group (REF: control)	4.15	1.85	2.24	**.03**	0.41, 7.88
Age	0.03	0.11	0.27	.79	−0.19, 0.24
Female	−1.19	1.74	−0.68	.50	−4.69, 2.32
Cancer stage (REF: stage II/III)	−3.01	1.91	−1.58	.12	−6.86, 0.83
Time since diagnosis (REF: < 6 mo)	2.31	1.75	1.32	.20	−1.22, 5.84
AUC_G[c]					
Unadjusted model					
Group (REF: control)	1.99	2.11	0.94	.35	−2.25, 6.22
Adjusted model[b]					
Group (REF: control)	2.02	2.09	0.97	.34	−2.19, 6.22
Age	−0.16	0.12	−1.36	.18	−0.41, 0.08
Female	−3.07	1.96	−1.56	.13	−7.01, 0.88
Cancer stage (REF: stage II/III)	1.16	1.97	0.59	.56	−2.81, 5.14
Time since diagnosis (REF: < 6 mo)	−3.07	2.15	−1.43	.16	−7.41, 1.26

Abbreviations: AUC_{AB}, area under the curve above the baseline value; AUC_G, area under the curve with respect to ground; AUC_I, area under the curve with respect to increase; CI, confidence interval; REF, reference group serving as contrast; SE, standard error.
[a] Bold *P* values are significant at $P < .05$.
[b] A participant was missing cancer stage data, so the analytic sample was reduced by 1.
[c] Square-root transformation for the area under the curve.

Our findings add to the knowledge garnered from previous studies that have examined cancer-related HPA axis dysregulation. Specifically, previous results have indicated the occurrence of cortisol blunting in terms of acute reactivity and diurnal rhythm in cancer patients as well as cancer survivors.[17,18] Our findings are specifically pertinent to a previous study that showed acute cortisol blunting in response to a recommended medical procedure (mammography) among cancer survivors.[19] Because such blunting might be caused by repeated physiological and psychological efforts to cope with demand, it appears that mindfulness practice might offer a unique mechanistic route to activate acute cortisol reactivity during the prescribed medical treatment of chemotherapy, which can be a stressful event for patients. Our findings suggest that the blunting of acute cortisol reactivity during cancer treatment is malleable to psychobehavioral intervention, and this is an opportunity for new advances in integrative oncology specific to mind-body interventions provided to patients during chemotherapy.

Although research on the effects of mindfulness practice on cortisol profiles is scant at present,[30] initial work shows that cancer patients exposed to a mindfulness intervention are protected from the diurnal cortisol blunting observed in controls.[31] Interestingly, the mindfulness group in the Carlson study reported corresponding and relative reductions in stress symptoms. A quasi-experimental study also showed a mindfulness intervention exposure to be associated with profiles that suggested significantly less diurnal cortisol blunting. Again, this change was significantly associated with improved overall global quality of life.[32] Our findings uniquely add to this work by showing that mindfulness exposure can also awaken cortisol reactivity as a counter to neuroendocrine blunting during chemotherapy infusion. As such, this study provides the initial evidence and methodological framework for investigating the effect of mindfulness on acute cortisol reactivity during routine medical treatment for cancer.

Little is known about the mechanistic processes underlying how mindfulness affects a blunted cortisol profile; however, content reviews are just beginning to uncover the biological significance of mindfulness practice and its function in disease processes (see the review by

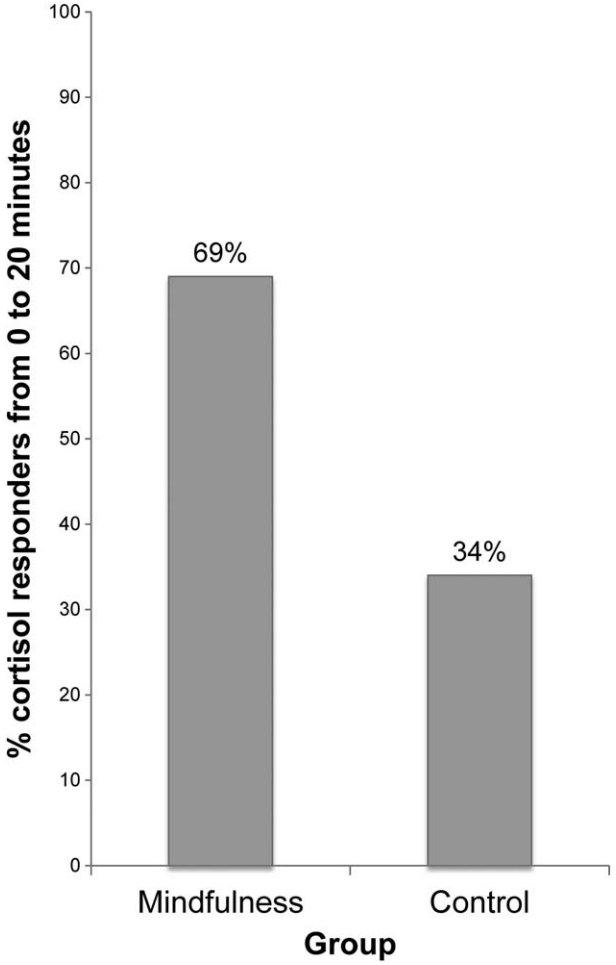

Figure 1. Cortisol responders (nmol/L) by group exposure ($P = .02$ for group difference). The 20-minute mark is presented because it had the highest mean cortisol value for any group during the entire assessment period. The timing of this cortisol peak is similar to previously reported trajectories induced by acute stressors.[45] A representation of all data collection points is shown in the area-under-the-curve analysis in Table 2.

TABLE 3. Bivariate Correlations Between Cortisol in Nanomoles per Liter and Biobehavioral Measure Scores

Variable	AUC_I	AUC_{AB}	AUC_G	MFSI	DASS	MAAS
AUC_I	1					
AUC_{AB}	0.83[a]	1				
AUC_G	0.16	0.42[a]	1			
MFSI	−0.07	−0.10	−0.11	1		
DASS	0.08	0.01	0.03	0.49[a]	1	
MAAS	0.09	0.07	0.11	−0.46[a]	−0.54[a]	1

Abbreviations: AUC_{AB}, area under the curve above the baseline value; AUC_G, area under the curve with respect to ground; AUC_I, area under the curve with respect to increase; DASS, Depression, Anxiety, and Stress Scale; MAAS, Mindfulness Attention Awareness Scale; MFSI, Multidimensional Fatigue Symptom Inventory.
[a] $P < .001$.

Black and Slavich).[46] As an initial exploration of the topic, we suggest that mindfulness practice represents a novel learning experience founded on stress-arousal reduction, a process that engages attention to and awareness of bodily sensations and experiences without judgment or reactivity.[21] This leads directly to the involvement of the HPA axis in novel learning exposures and states of eustress, which are linked with positive outcomes rather than negative outcomes.[33-36] Thus, mindfulness exposure might exact a demand to recruit attentional resources and learning faculties in a manner that is detectable via acute cortisol reactivity yet does not translate physiologically into making the patient experience the demand as a stressful or negative event. This notion was partially supported by our finding of equal distress levels reported at the conclusion of chemotherapy across groups.

The results did not lend support to our exploratory aim, which was to test for significant associations between cortisol reactivity levels and self-reporting of biobehavioral factors (ie, distress, fatigue, and mindfulness). Here it is important to note that the interpretation of our results is limited by our smaller sample size and the past-week recall period for fatigue and distress. However, we did find that mindfulness scores reported on the same day as chemotherapy for the full sample were significantly anticorrelated with fatigue and distress scores with a large bivariate effect size, which does corroborate findings in the previous literature for colorectal cancer patients.[47] These correlations also lend possible support for the future use of mindfulness practice to bolster mindfulness skills to support a reduction in fatigue and distress in cancer patients during the course of their chemotherapy treatments. Such intervention efforts have generally proven beneficial for cancer survivors and lead to biologically relevant changes in immune function,[24,48-50] yet little is known about effects on cancer patients during their clinical treatment.

The strengths of our study include the fact that it is the first experiment of which we know to examine the effect of mindfulness exposure on cancer-relevant physiological markers during chemotherapy infusion. We enrolled colorectal cancer patients, a significant proportion being Hispanic/Latino, from 2 oncology clinics, and these are all features that further the generalizability of our findings. The repeated measurement of cortisol and the use of validated biobehavioral self-report measures lend support to the future replication of this study. Furthermore, the use of a prerecorded video and its delivery on a transportable tablet allowed exposure standardization

across participants and could lead to future integration of the protocol into routine oncology care. Because a video intervention is readily available and transportable, dissemination efforts have translational value for clinical oncology. The use of a body scan as the mindfulness practice is a straightforward and solid model for novices unfamiliar with mindfulness. Limitations of the study include the smaller sample size and the lack of biobehavioral measurements before chemotherapy due to time constraints. We referred to all study activities and protocols as educational activities to support masking of exposures, yet historical and expectancy biases are possible for those with previous meditation experience. It is possible that the body scan induced relaxation; thus, future experiments may benefit from offering different mindfulness exposures (eg, breath awareness and open monitoring awareness) and comparing them with relaxation-focused exposures to better determine whether mindful awareness or relaxation is the mechanism of action. The mindfulness exposure was 32 minutes long, whereas the education exposure was 20 minutes long; this makes the exposure time a possible explanation for some of the change observed in cortisol; thus, future research is warranted to match the time of exposures across all conditions. Moreover, future studies will benefit from the repeated measurement of self-reported variables during chemotherapy that align with saliva collection to determine whether chemotherapy induces changes in statelike distress, fatigue, and other biobehavioral measures.

In conclusion, our findings show that mindfulness practice may awaken acute cortisol reactivity as a counter to the HPA axis blunting that is often observed in cancer patients, specifically during chemotherapy infusions. The longer term impact of this awakening remains unknown, yet it is understood that cortisol blunting in cancer patients is predictive of adverse health outcomes and reduced survival. Pending future replication and advancement of these findings, patient engagement in mindfulness practice appears to be relevant to cancer-related physiology during chemotherapy, and this might have implications for treatment responses and longer term cancer survivorship outcomes.

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CONFLICT OF INTEREST DISCLOSURES

Heinz-Josef Lenz reports the following: working on an advisory board for Boehringer Ingelheim; working on an advisory board for, giving lectures for, and receiving clinical trial support from Roche/Genentech; working on an advisory board for, giving lectures for, and receiving clinical trial support from Merck; receiving clinical trial support from Novartis; working on an advisory board for, giving lectures for, and receiving clinical trial support from Bayer; working on an advisory board for and receiving clinical trial support from Taiho; and working on an advisory board for and receiving clinical trial support from Bristol-Myers Squibb.

AUTHOR CONTRIBUTIONS

David S. Black: Project conceptualization, methodology, investigation (Principal Investigator), resources, data visualization, supervision, funding acquisition, and lead of manuscript writing. **Cheng Peng**: Statistical analysis, data curation, supportive writing. **Alix G. Sleight**: Statistical analysis, data curation, supportive writing. **Nathalie Nguyen**: Statistical analysis, data curation, supportive writing, and project administration. **Heinz-Josef Lenz**: Project supervision, resource allocation, and manuscript writing support. **Jane C. Figueiredo**: Project conceptualization, methodology, investigation, resources, supervision, funding acquisition, and supportive writing.

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