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# Stress Management Intervention Reduces Serum Cortisol and Increases Relaxation During Treatment for Nonmetastatic Breast Cancer

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## Abstract

**Objective—**To examine the effects of a cognitive-behavioral stress management (CBSM) intervention, which was composed of relaxation, cognitive restructuring, and coping skills training on late afternoon serum cortisol and relaxation indicators in women who were undergoing treatment for nonmetastatic breast cancer.

**Methods—**Participants ($n = 128$) were randomly assigned to receive a 10-week CBSM group intervention or a 1-day psychoeducation seminar. Serum cortisol was collected and ability to relax was assessed at study entry and again at 6- and 12-month follow-up visits. Data were analyzed using latent growth curve modeling.

**Results—**There was a significant effect of study condition on change across time for both cortisol and perceived ability to relax. Women receiving CBSM had significantly greater reductions in cortisol levels across the 12 months compared with those in the control group, who had no appreciable decline. Women receiving CBSM reported greater increases in ability to relax than controls across time. Perceived ability to relax did not mediate CBSM-related reductions in cortisol.

**Conclusions—**Women who participate in a 10-week CBSM intervention during treatment for breast cancer show decreases in physiological stress in parallel with increases in perceived relaxation skills. This is the first study demonstrating well-maintained reductions in cortisol after a CBSM intervention in cancer patients during and just after treatment.

### Keywords

breast cancer; cortisol; relaxation; stress management

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## INTRODUCTION

Women diagnosed with breast cancer encounter a number of burdens, including anxiety about treatment and prognosis, adjuvant therapy, and disruptions in daily living. Evidence suggests cancer-related stress has a negative impact on health, possibly via neuroendocrine pathways (1). Cortisol, a steroid hormone secreted by the adrenal cortex (2,3), is used to assess hypothalamic-pituitary-adrenal (HPA) axis function and is a reliable measure of physiological stress (4). Cortisol affects multiple physiological processes, including metabolic and immune responses (e.g., suppressing T lymphocyte functions and natural killer cell cytotoxicity) (2,3,5). Women living with breast cancer have higher cortisol levels compared with healthy women, and higher cortisol levels are associated with greater disease severity in women with breast cancer (6,7). Neuroendocrine regulation of cortisol and other adrenal hormones may contribute to cancer progression and health outcomes through multiple mechanisms (1).

There is evidence that breast cancer is associated with greater plasma cortisol increases during a behavioral challenge reactivity task (7). If women with breast cancer are hyperresponsive to stressful challenges, it follows that they may show decreases in cortisol levels if they are taught stress management techniques. Carlson and colleagues (8) measured cortisol levels in breast and prostate cancer patients ($n = 59$) who participated in a mindfulness-based stress reduction program. They found decreases in morning (8 AM), afternoon (2 PM), evening (8 PM), and mean salivary cortisol levels from study entry to 12-month follow-up. This study was limited by its lack of a control group and small sample size.

A study that did include a control group (9) found that women with Stage i or Stage ii breast cancer assigned to a 10-week group-based cognitive-behavioral stress management (CBSM) intervention 4 to 8 weeks post surgery showed reduced late afternoon serum cortisol, compared with those in the wait-list comparison group. Unfortunately, this study was done on a small sample ($n = 34$) and effects were only tested to the point immediately after the last intervention session (approximately 3 months after randomization). Other studies of similar interventions in women with breast cancer are limited in similar ways (10).

In a more recent study, a larger sample of women with Stage 0–III breast cancer were recruited 4 to 8 weeks post surgery, assigned to a similar 10-week CBSM intervention, and followed for 12 months. Results showed decreases in anxiety and negative affect, and increases in positive affect and benefit finding in the CBSM condition, effects that held at the 12-month follow-up (11,12). Latent growth curve modeling (LGM) analyses (13) demonstrated that most of these intervention effects were mediated by participants' confidence in their ability to relax (12). Because prior work shows that CBSM and relaxation lowers cortisol (9,14), we hypothesized that women in this study would also show reductions in cortisol that parallel improvements in relaxation skills.

### Current Study

Thus, the current study examined intervention-related changes in serum cortisol among these breast cancer patients over a12-month period, using LGM analyses. We hypothesized

specifically that 1) CBSM intervention would reduce cortisol levels across time (1) and increase perceived ability to relax (2), and 2) perceived ability to relax would mediate intervention-related reductions in cortisol (3).

## METHODS

### Participants

After receiving Institutional Review Board approval from the University of Miami, data collection began in January 1999 and was completed in February 2006. Participants ($n$ = 128) were a volunteer sample of women who were recently diagnosed with breast cancer and recruited from local hospitals and practices in South Florida, and who participated in a substudy of the Coping and Recovery Project (11,12) that was funded by a supplemental award to include serum cortisol data on subjects recruited. Interested persons contacted the research team and completed a phone interview, during which the study was explained and eligibility was determined. Exclusion criteria included a previous diagnosis of cancer (except minor skin cancer), age >70 years, metastatic disease, panic disorder, suicidality, nonfluent English, and unwillingness to be randomized. Participants were also excluded if they had a comorbid major medical condition, were taking medications with known effects on endocrine functioning, or if they began adjuvant treatment before Time 1. Participants were not excluded for taking antidepressants or anxiolytics. These criteria created a reasonably homogeneous sample in terms of disease status and medical treatments, commonality of psychosocial issues, and ability to attend sessions and understand materials presented.

Most participants were White ($n$ = 90, 70.3%) and well educated (mean ± standard deviation (SD) = 15.63 ± 2.61 years). Other subjects included Hispanic, $n$ = 28, 21.9%; Black, $n$ = 10, 7.8%. Mean age was 49.69 ± 7.89 years (range = 25–69 years). Most were married or otherwise partnered ($n$ = 82, 64.1%). Most were nonsmokers ($n$ = 119, 93%). They consumed an average of 2.34 ± 4.05 alcoholic beverages per week; half reported no alcohol use. Average weekly caffeinated coffee consumption was 5.08 ± 6.12 drinks.

Participants were diagnosed with Stage 0 ($n$ = 23, 18.0%), Stage I ($n$ = 56, 43.8%), Stage II ($n$ = 45, 35.2%), or Stage III ($n$ = 4, 3.1%) breast cancer. Nodal involvement ranged from 0 to 19 (0.87 ± 2.40). Sixty women received a mastectomy and 68 received a lumpectomy. Sixty (46.9%) women received chemotherapy and 68 (53.1%) received radiation therapy.

### Procedures

Eligible participants were scheduled for an initial assessment, during which blood samples were obtained. Participants completed questionnaires (by mail) and came in for assessments at study entry (i.e., before the intervention) (Time 1), 6-month follow-up (Time 2), and 12-month follow-up (Time 3). After completing the initial assessment and returning the Time 1 questionnaire, participants were randomized to a 10-week CBSM intervention ($n$ = 65) or a 1-day seminar ($n$ = 63).

**Intervention Group—**Participants met in groups of three to nine breast cancer patients led by two female facilitators trained in the CBSM intervention (11,12). The CBSM intervention

consisted of ten weekly 2-hour sessions. Each session consisted of both stress management techniques (e.g., cognitive restructuring, social support, assertiveness, anger management, coping skills training) and relaxation training (e.g., meditation, abdominal breathing, guided imagery, progressive muscle relaxation). The details of this intervention are described elsewhere (11) and follow a manualized format (15).

**Control Group—**A 1-day psychoeducational group seminar was offered to those randomized to the control condition. The seminar took place at the same location as the 10-week groups and was held at the midpoint of the 10-week CBSM intervention period for each cohort. It consisted of a condensed demonstration of several CBSM techniques used in the intervention and lasted approximately 6 hours.

## Measures

**Ability to Relax—**Participants' perceived ability to relax was measured by the Relaxation subscale of the Measure of Current Mood Status (MOCS) Part A (16). The MOCS instrument and the results of a principal components analysis have been described elsewhere (11). The Relaxation subscale consisted of two items: "I am able to use muscle relaxation techniques to reduce any tension I experience" and "I am able to use mental imagery to reduce any tension I experience." Response options ranged from 0 (I cannot do this at all) to 4 (I can do this extremely well) ($\alpha = 0.66$).

**Cortisol—**Serum cortisol was used as a measure of physiological stress. Blood sample for serum assays was collected between 4 PM and 6:30 PM, as this was the time used in our prior work and was a time that participants were able to come in for assessments. In individuals with relatively normal diurnal rhythms, cortisol follows a diurnal cycle, peaking on awakening and decreasing steadily throughout the day (4). Whereas much of the research on cortisol rhythms has been done using salivary cortisol, serum and salivary cortisol profiles are synchronous across 24 hours (17). Therefore, it is important the samples are collected at approximately the same time of day to compare changes in cortisol during an intervention. During assessments, a phlebotomist collected peripheral venous blood via venipuncture in red-topped vacutainer tubes, which contain no anticoagulants and allow for the serum to be separated from cells when centrifuged. Cortisol levels in serum were measured by competitive enzyme-linked immunosorbent assay with kits from Diagnostic Systems Laboratories (Webster, Texas).

## Analyses

A priori power analysis found that, with a sample size of 80 participants per condition, we would have at least 85% power to detect the effects of CBSM intervention over time (18). We compared the two groups at baseline on several biobehavioral variables using $\chi^2$ for categorical variables and *t* test for continuous variables. Control variables were chosen based on prior literature. Intervention effects were tested, using LGM (13). In LGM, a trajectory of change over repeated measurements is computed for each participant and differences in trajectories may then be predicted from other variables. Properties of the trajectories include the intercept (i.e., the starting value) and the slope of change (i.e., over repeated measurements). For this study, intercepts and slopes were modeled as latent variables from

data at Time 1, Time 2, and Time 3. The main predictor was condition (coded 1 for intervention and 0 for control). Loadings for the slope represented the time linked to each assessment (0 for initial assessment, 6 for 6-month follow-up, and 12 for 12-month follow-up). Analyses were conducted, using two-tailed tests.

LGM has two important advantages over repeated-measures analysis of variance. One is its ability to use all available data with full information maximum likelihood, estimating parameters in the presence of missing data (19). Thus, all participants are represented in these intent-to-treat analyses. The other advantage is LGM's flexibility to address nonlinear change (e.g., when an effect plateaus) by estimating the later time point instead of specifying it as in prior work (11,12).

We determined whether the model fit the data by using several indices: nonsignificant $\chi^2$ ($p > .05$), comparative fit index (CFI) >0.95, root-mean-square error of approximation (RMSEA) <0.06, and standardized root-mean-square residual (SRMR) <0.10 (20). Specific effects were tested with the $z$ statistic, with a 0.05 two-tailed significance level. Standardized effect sizes (Cohen's SD) were also calculated (21).

## RESULTS

Analyses were based on $n = 128$ (intervention = 63; control = 65). At Time 2, 21.5% of the control group and 26.9% of the intervention group did not provide data; at Time 3, 24.6% of the control group and 23.8% of the intervention group did not provide data (Figure 1). All participants who completed measures at Time 1 were included in all analyses. Descriptive statistics for intervention and control groups on baseline measures are shown in Table 1. Comparisons between groups revealed that those in the intervention group tended to have undergone chemotherapy ($n = 35$) more than those in the control group ($n = 25$), $\chi^2(1) = 3.75$, $p = .053$. Intervention participants had more positive lymph nodes than control participants: $t(126) = -2.43$, $p = .017$. They also tended to drink less caffeinated coffee than controls: $t(126) = 1.87$, $p = .064$. Because chemotherapy (9), disease severity (6,7,22), and caffeine (23) have been known to affect cortisol, they were included as covariates in all LGM models testing for effects on cortisol.

### Cortisol

First, we tested whether the CBSM intervention predicted decreases in log-transformed cortisol values (controlling for chemotherapy, number of positive lymph nodes, and caffeine). For these analyses, the one outlier (z = 3.65) was substituted with the next highest cortisol value (20). Analyses were also run with the outlier included and excluded with similar results. The model fit the data well: $\chi^2(8) = 3.210$, $p = .92$ (CFI = 1.000, RMSEA = 0.000, SRMR = 0.019). Condition did not predict intercept, indicating no initial differences between groups, a conclusion supported by a group comparison of Time 1 means: $t(126) = -1.08$, $p = .282$. The correlation between intercept and slope was small (0.21, z = 0.37, NS), suggesting there was little covariation between where participants started and how much they changed. This model explained 22% of the variance in cortisol values at Time 1, 37% of the variance at Time 2, and 95% of the variance at Time 3. Condition related significantly to change in cortisol ($z = -2.27$, $p < .05$; Cohen's SD = 0.20), indicating small but

significant differential change over time between the two conditions. Women receiving CBSM had reduced late afternoon cortisol levels over time, whereas controls had no appreciable decline. Compared with the control group, the intervention group demonstrated a small but significant decrease of 0.01 log-units of cortisol per month ($b = -0.01$, $p < .05$) (Figure 2).

Because the correlation between the intercept and slope was of the same magnitude as the effect size for condition's effect on slope, we also ran the model controlling for the influence of the initial value on change over time. When controlling for the effect of the intercept on slope, condition no longer predicted change in cortisol level (z = −1.26, $p = .21$). However, the path regressing slope on intercept was not significant (z = 0.28, NS) and the effect size for condition predicting cortisol slope remained the same ($b = -0.01$, Cohen's SD = 0.20).

### Relaxation

Next, we tested whether CBSM was related to perceived ability to relax. The linear model did not fit the data. When estimating the loading associated with Time 3, the model fit the data well: $\chi^2(2) = 0.20$, $p = .91$ (CFI = 1.000, RMSEA = 0.000, SRMR = 0.009). Time 3 was estimated at 5.6 months, suggesting much of the change in perceived ability to relax occurs within the first 6 months, which is consistent with previous findings (11). Condition did not predict the intercept, indicating no group differences at Time 1. Condition related significantly to slope of MOCSrelax (z = 2.17, $p < .05$; Cohen's SD = 0.44), indicating differential change over time between groups. Those receiving CBSM reported greater ability to relax than controls. The CBSM group demonstrated an increase of 0.07 more units of MOCSrelax per month than the control group ($b = 0.07$, $p < .05$).

### Mediation

To test whether increases in perceived ability to relax mediated effects of the intervention on cortisol, we combined both growth processes for cortisol and MOCSrelax in the same model. Within that model, we incorporated a path from MOCSrelax slope to cortisol slope. In this model ($\chi^2(31) = 35.91$, $p = .25$, CFI = 0.956, RMSEA = 0.035, SRMR = 0.048), the direct effect of condition on cortisol was no longer significant (z = −1.69, NS), suggesting possible mediation.

However, the path from change in MOCSrelax to change in cortisol was not significant (z = 0.419, NS) and a test of the indirect effect was also not significant (z = 0.41, NS). Perceived ability to relax did not mediate CBSM-related reductions in cortisol.

## DISCUSSION

This study tested the effects of a well-established 10-week CBSM intervention on serum cortisol and relaxation indicators over a 12-month period in women who were moving through medical treatment for Stage 0 to Stage III breast cancer. Prior studies with CBSM in breast cancer patients have demonstrated short-term effects in mostly small samples (9,10). Of particular interest here was whether the findings by Cruess and colleagues (9) that a CBSM intervention could reduce serum cortisol in women recruited shortly after surgery for breast cancer could be replicated in a larger sample and over a longer follow-up period.

The first hypothesis—that women in the intervention group would have decreases in cortisol levels across time compared with women in the control condition—was supported. Women who received the intervention demonstrated decreases in cortisol across 12 months. However, caution is in order when interpreting these findings because change in cortisol does contain some influence from the initial value, and a larger sample may be needed to detect the intervention's influence once the initial level is controlled.

The second hypothesis—that women in the intervention group would report increased ability to relax across time compared with women in the control condition—was also supported. Those who received CBSM increased confidence in their ability to relax across time to a greater degree than controls. This is evidence that the intervention is effective at inducing confidence in using specific relaxation skills with such effects peaking by 6-month follow-up and plateauing thereafter. These stress management techniques and maintenance sessions can result in increased confidence in the ability to relax.

The third hypothesis—that perceived ability to relax, previously demonstrated to mediate improvements in quality of life variables (11), would mediate the relationship between study condition and effects on cortisol—was not supported. Although prior research has demonstrated that ability to relax mediated intervention-related changes in psychosocial variables (11), it does not explain the effect on cortisol in this study.

Results suggest that these women are able to maintain reductions in cortisol well into the postadjuvant therapy period. This is the first demonstration of well-maintained reductions in cortisol after a psychosocial intervention in breast cancer patients under medical treatment. Given that perceived relaxation ability does not explain the effects of the intervention on cortisol, it may be a combination of relaxation and other CBSM-taught skills (e.g., cognitive restructuring) or nonspecific factors (e.g., group support and other processes) that singly or together promote better stress management and improved HPA-axis functioning.

One limitation of this study is that participants were highly educated and the majority were White, middle-class women. Results cannot be generalized to more diverse populations, those with other forms of cancer, metastatic disease, or women >70 years old. Another limitation is the fact that this sample was self-selected to participate. Those who decided to participate in a stress-management research study may have been initially aware of the importance of practicing stress-management and they were less distressed.

Another study limitation is the way in which serum cortisol was measured. At each time point, cortisol was measured with a single blood draw collected between 4 to 6:30 PM. The exact time of collection was not recorded; thus, caution is in order due to slight variations at the beginning and end of this window. Because of moment-to-moment fluctuations in cortisol due to stressors in the environment, a single sample may not represent the best method for estimating cortisol levels (24). One solution would be to sample cortisol various times throughout the day, using repeated saliva samples outlining the diurnal cycle. One advantage of such an approach is that one can then examine changes in diurnal slopes of cortisol output across the intervention and at follow-up.

Although there is no current evidence linking late afternoon cortisol levels to health outcomes in cancer patients, there is evidence that flatter cortisol slopes are associated with higher mortality in women with metastatic breast cancer (22). Sephton and colleagues found that those with flatter slopes had higher cortisol levels at 5 PM, with mean cortisol values being nearly three times higher in the flat versus the steep slope groups. It is unclear whether these findings hold for women with early stage breast cancer.

Future work should examine whether CBSM is associated with the “normalization” of the diurnal circadian rhythm in this population. Further work is also needed to better delineate which intervention elements account for its effects on cortisol. Determining whether CBSM-associated skills versus nonspecific group factors account for the cortisol effects observed here require “dismantling” designs that compare well-matched interventions systematically varying in specific techniques provided (e.g., relaxation only versus cognitive behavioral only versus group support only). It is also unclear whether our measure of confidence in using relaxation is a marker for actual relaxation skills, general self-efficacy, or general buy-in of the importance of using the skills taught in the intervention. Fine-grained analyses of adherence and accuracy in completing CBSM homework assignments as well as in-session relaxation-induced physiological changes (25) may provide some insight into these issues.

### Summary

Group-based CBSM intervention significantly decreased late afternoon serum cortisol levels and enhanced breast cancer patients’ confidence in their ability to relax. Although the effects on cortisol were small, they persisted up to a year after study entry, a point by which women had completed adjuvant therapy. Thus, this study provides support that CBSM is clinically useful in producing significant and durable psychosocial and physiological changes in breast cancer patients.

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## Glossary

| | |
|---|---|
| **CBSM** | cognitive-behavioral stress management |
| **MOCS** | Measure of Current Mood Status |
| **MOCSrelax** | relaxation subscale of the MoCS |
| **LGM** | latent growth curve modeling |
| **HPA** | hypothalamic-pituitary-adrenal |

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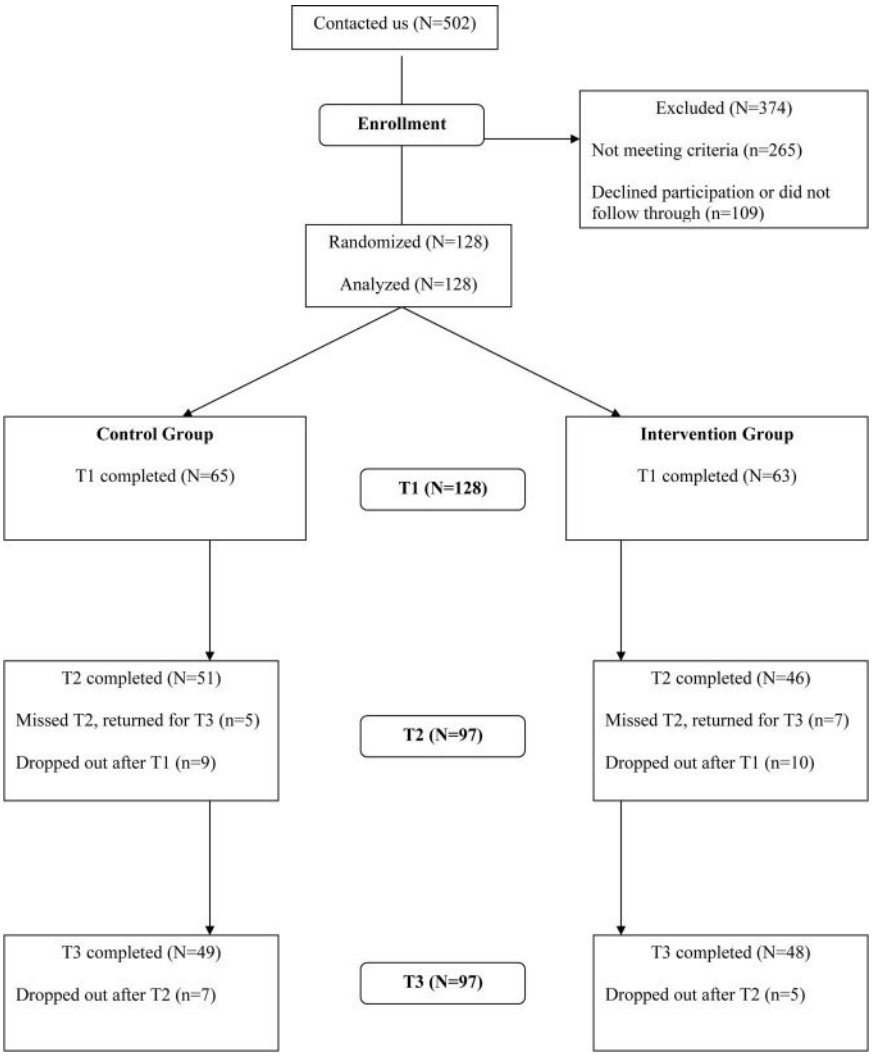


**Figure 1.**
Experimental design and flow diagram of participants. T = time.

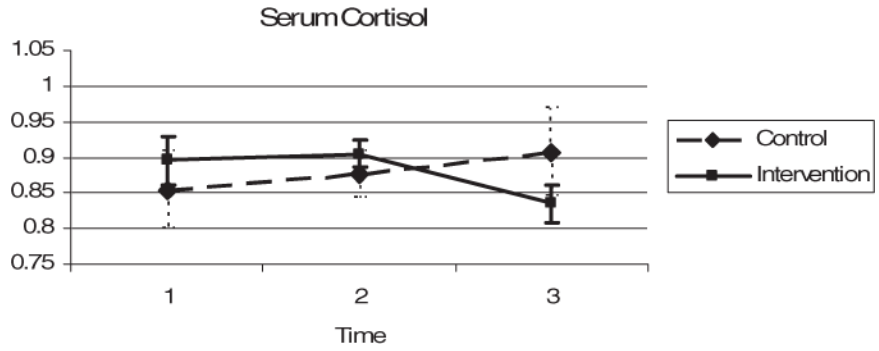


**Figure 2.**

Mean values and 95% Confidence Intervals for log-transformed serum cortisol values at time points 1, 2, and 3 for women assigned to the control and intervention group.

**TABLE 1**

Baseline Measures by Group

| Measure | Intervention Group | | | | Control Group | | | |
|---|---|---|---|---|---|---|---|---|
| | Mdn | IQR | M | SD | Mdn | IQR | M | SD |
| Positive lymph nodes | 0.00 | 1.00 | | | 0.00 | 0.00 | | |
| Caffeine | 1.00 | 7.00 | | | 5.00 | 10.00 | | |
| Cortisol | | | 0.90 | 0.25 | | | 0.85 | 0.25 |
| MOCSrelax | | | 2.12 | 1.00 | | | 2.17 | 0.96 |

Mdn = median; IQR = interquartile range; M = mean; SD = standard deviation; MOCSrelax = Relaxation subscale of the Measure of Current Mood Status.