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BRIEF REPORT

Stress Management Skills and Reductions in Serum Cortisol Across the Year After Surgery for Non-Metastatic Breast Cancer

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Abstract Treatment for breast cancer affects psychological adaptation and related neuroendocrine stress indicators. Previously, a 10-week cognitive behavioral stress management (CBSM) group intervention decreased cortisol over 12-months among women receiving treatment for breast cancer. The current re-analysis tested whether changes in stress management skills at 6-month follow-up predict the magnitude of cortisol reductions at 12-months in a time-lagged analysis. Women ($N = 128$) with non-metastatic breast cancer recruited post-surgery were randomized to the CBSM intervention or 1-day psychoeducational seminar. Participants reported perceived CBSM skills and provided late afternoon blood samples for serum cortisol at baseline and 6- and 12-month follow-ups. Improved perceived ability to relax and use cognitive reappraisal skills at 6-months statistically mediated intervention-associated cortisol reduction from 6- to 12-months. This is the first study showing that improved perceived CBSM skills predict the magnitude of cortisol reductions over 1 year in this population and may guide development of more focused interventions.

Keywords Breast cancer · Cortisol · Relaxation · Stress management · Intervention

Multi-modal group-based cognitive behavioral interventions designed to decrease distress and improve quality of life in breast cancer patients as they move through treatment may also improve neuroendocrine and immune function after treatment, as well as longer-term health outcomes (Andersen et al. 2007a, 2008; Lutgendorf et al. 2010). Identifying which aspects of these interventions drive their effects on neuroimmune processes and the

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timing of such effects is essential to developing briefer and more focused interventions and understanding biobehavioral mechanisms underlying the effects of these interventions on optimal recovery from cancer treatment and heath outcomes.

We know that having confidence in stress management skills relates to better quality of life and less depression and anxiety in cancer patients about to begin chemotherapy (Faul et al. 2010). Cognitive behavioral stress management (CBSM) intervention-related improvements in quality of life were mediated by improved stress management skills in men with prostate cancer (Penedo et al. 2006) and women with breast cancer (Antoni et al. 2006a).

CBSM was also associated with decreases in late afternoon cortisol levels and increased confidence in using relaxation skills, though a mediation effect was not established (Phillips et al. 2008). One possible reason the mediation effect was not significant was that most changes in perceived ability to relax occurred between study entry and the 6-month-follow-up (i.e., the short-term post-training period when the women were receiving adjuvant treatment), while changes in cortisol lagged behind these, occurring mostly between the 6- and 12-month follow-up—a period more reflective of recovery from adjuvant therapy (Phillips et al. 2008). Specifically, for the intervention group, cortisol levels were stable from study entry to post-intervention, and then decreased from post-intervention to 12-month follow-up. Ability to relax increased from study entry to post-intervention, then plateaued. That model fit the data when the final time point was freely estimated; the predicted value of the final time point was 5.6 months, indicating much of the change in ability to relax occurred within the first 6 months (Phillips et al. 2008), suggesting the possibility of non-linear change.

While changes in the skills targeted by the intervention may be apparent shortly after its completion, Scheier et al. (2005) found some effects of an intervention delivered to breast cancer patients after adjuvant treatment emerged at 13-month follow-up and were associated with changes in intrusive thoughts. Another trial in breast cancer patients under treatment found a significant indirect effect of psychosocial intervention-related improvements in emotional distress at 4-month follow-up predicting health status at 12-month follow-up (Andersen et al. 2007a). More relaxation practice was associated with fewer physical signs and symptoms and greater reductions in emotional distress at follow-up (Andersen et al. 2007b). It is plausible that these distress and symptom changes were accompanied by neuroendocrine changes reflecting improved stress physiology.

The present study is a re-analysis of the Phillips et al. (2008) study designed to test whether such a lagged effect of CBSM intervention on perceived stress management skills and neuroendocrine functioning was occurring in that trial. This possibility was tested by a lagged mediation analysis, similar to that used by prior researchers (Rogers et al. 2009). Specifically, we assessed whether changes in the mediator (perceived stress management skills) precede changes in the outcome variable (serum cortisol). The aim was to address the question: does perceived ability to implement stress management skills post-intervention predict changes in cortisol from 6- to 12-month follow-up?

Methods

Participants

Participants were women ($N = 128$) diagnosed with non-metastatic breast cancer (Stage 0: $n = 23$, 18%, Stage I: $n = 56$, 43.8%, Stage II: $n = 45$, 35.2%, Stage III: $n = 4$, 3.1%) who participated in the study reported on by Phillips et al. (2008). Women were recruited from doctors' offices prior to beginning adjuvant therapy. They were excluded if they had: metastatic disease, a previous cancer diagnosis (except minor skin cancer), begun adjuvant treatment, a co-morbid major medical condition, or were taking medications with known effects on endocrine functioning. Additional exclusion criteria included panic disorder, suicidality, age over 70, non-fluent in English, and unwillingness to be randomized. Procedures, participant characteristics, and flow diagram with retention rates are described in detail elsewhere (Phillips et al. 2008).

Briefly, participants ranged in age from 25 to 69 years ($M = 49.69$, $SD = 7.89$). The majority were white ($n = 90$, 70%), married ($n = 82$, 64%), and well-educated ($M = 15.63$ years, $SD = 2.61$ years). Sixty (47%) underwent a mastectomy and 68 (53%) a lumpectomy. Sixty (47%) received chemotherapy and 68 (53%) received radiation therapy; 33 (26%) participants received both.

Procedures

Initial assessments were completed prior to randomization (T1). Follow-ups were completed at approximately 6-months (T2) and 12-months (T3) after study entry. Participants completed questionnaires and provided blood samples at the same time of day (4–6:30 p.m.) at each time point. Following data collection at T1, participants were randomized to the 10-week CBSM intervention or 1-day psychoeducation (PE) seminar. There were no differences between those assigned to CBSM or PE in age, education, income, race, marital status, cancer stage, surgical procedure, chemotherapy, radiation therapy, cortisol, or perceived stress management skills ($P > .05$).

CBSM

Participants randomized to the CBSM intervention ($n = 65$) met in groups of three to nine patients for 10 weekly 2-h sessions. Groups were led by two female facilitators (one pre-doctoral and one post-doctoral) trained in the manualized CBSM intervention. The manualized intervention (Antoni 2003) was developed following a biobehavioral conceptualization of the breast cancer experience (Andersen et al. 1994). Each session provided participants with relaxation training and techniques such as cognitive restructuring, coping effectiveness training, anger management, and assertiveness training. Participants were instructed to practice the CBSM skills between sessions, aided by recordings of relaxation and guided imagery. Audiotapes of sessions were reviewed by two clinical psychologists who met weekly with interventionists to ensure fidelity.

PE Control Group

Participants randomized to the control condition ($n = 63$) were offered a 1 day group-based PE seminar, held within the 10-week CBSM intervention period for each cohort. The seminar consisted of heath information and a summary of stress management techniques presented in a lecture format.

Measures

Stress Management Skills

The Measure of Current Status (MOCS) was created to assess possible "active ingredients" of the CBSM intervention (Carver 2005). The MOCS measures participants' current self-perceived ability to enact several skills targeted by the intervention (e.g., relaxation). Response options range from *I cannot do this at all* (0) to *I can do this extremely well* (4). Principal component analyses yielded four components: Relaxation, Awareness of Tension, Getting Needs Met, and Coping Confidence (Antoni et al. 2006a).

Serum Cortisol

Late afternoon (4–6:30 p.m.) serum cortisol measured neuroendocrine functioning. Prior work suggested that PM cortisol elevations predict negative health outcomes in women with breast cancer (Sephton et al. 2000). Serum cortisol levels were measured by competitive ELISA (Diagnostic Systems Laboratories, Webster, TX).

Analyses

Data were analyzed using MPlus software. A time-lagged path analysis was used to test whether intervention-related changes in MOCS components up to T2 mediated change in log-transformed cortisol between T2 and T3. This was done by creating residualized change (Δ) scores (T2 MOCS controlling for T1, and T3 cortisol controlling for T2). Mediation was tested by evaluating the indirect effect of condition on cortisol through the MOCS components using a 95% bias-corrected bootstrap confidence interval based on 5,000 bootstrap samples (Hayes 2009).

Results

Analyses were based on data from the 128 participants who participated in a substudy of the larger Coping and Recovery project and provided blood samples for determining serum cortisol at T1. Comparing these 128 participants to the 112 who did not participate in the cortisol substudy, there were no differences in age, surgical procedure, marital status, or T1 MOCS component scores (P values $> .05$). However, those who participated in the cortisol substudy had less advanced disease than those who did not participate in this substudy ($P = .003$). We had previously established a significant effect of study condition on T1–T3 cortisol slope ($b = -0.01$, $z = -2.27$, $P = .023$) and T1–T3 MOCS-Relaxation slope ($b = 0.07$, $z = 2.17$, $P = .030$) using latent growth modeling (Phillips et al. 2008), indicating differential change across time by condition. The focus here was on investigating the indirect effects of the intervention on changes in cortisol from T2 to T3 through MOCS-components from T1 to T2. Means and standard deviations of key variables are in Table 1.

Using a 95% bias-corrected bootstrap confidence interval based on 5,000 bootstrap samples, the specific indirect effect of condition on cortisol through MOCS-Relaxation was significant ($P = .02$) (see Table 2). Women assigned to CBSM showed a greater increase in perceived ability to use relaxation between study entry and 6-month follow-up compared to PE controls, and greater confidence in one's ability to relax was associated with decreases in cortisol from 6- to 12-month follow-up.

The indirect effects of the other MOCS components were not significant ($P > .05$), indicating they did not explain the relationship between study condition and changes in cortisol. Because none of these subscales clearly captured the effects of CBSM on cognitive restructuring, a recurring feature of CBSM, we repeated the analysis using a specific item from the MOCS that addresses perceived changes in the ability to re-examine cognitive appraisals about stressors (MOCS-Reappraisal).

Table 1 Means and SD per group

	Intervention M (SD)	Control M (SD)	*t*	*P*
Cortisol				
Cortisol T1	0.90 (0.25)	0.85 (0.18)	−1.12	.260
Cortisol T2	0.90 (0.23)	0.87 (0.22)	−0.53	.595
Cortisol T3	0.84 (0.19)	0.90 (0.21)	1.47	.145
Residualized change (T2–T3)	−0.05 (0.16)	0.05 (0.19)	2.64	.010
MOCS-relaxation				
MOCS-relaxation T1	2.12 (1.00)	2.17 (0.96)	0.29	.773
MOCS-relaxation T2	2.82 (0.87)	2.52 (0.97)	−1.65	.102
MOCS-relaxation T3	2.82 (0.89)	2.45 (0.91)	−2.01	.047
Residualized change (T1–T2)	0.16 (0.82)	−0.17 (0.90)	−1.90	.060
MOCS-reappraisal				
MOCS-reappraisal T1	3.21 (1.19)	3.28 (1.05)	0.36	.723
MOCS-reappraisal T2	3.43 (0.89)	3.14 (0.96)	−1.59	.114
MOCS-reappraisal T3	3.22 (0.85)	3.23 (1.02)	0.04	.972
Residualized change (T1–T2)	0.14 (0.84)	−0.15 (0.81)	−1.76	.081

Table 2 Indirect effects of group assignment on T2 to T3 changes in cortisol through T1 to T2 changes in skills targeted by the intervention

	Point estimate	*SE*	z	*P*	BC 95% CI	
					LL	*UL*
MOCS-relaxation	−.05	.02	−2.31	.02	−.10	−.01
MOCS-reappraisal	−.08	.03	−2.22	.03	−.14	−.01

SE standard error, *BC* bias corrected, *CI* confidence interval, *LL* lower limit, *UL* upper limit

The specific indirect effect of condition on cortisol through MOCS-Reappraisal was significant ($P = .03$) (see Table 2). Women assigned to CBSM reported a greater increase in their ability to stop and reexamine their thoughts to gain a new perspective from study entry and 6-month follow-up compared to PE controls, and greater cognitive reappraisal was associated with decreased cortisol from 6- to 12-month follow-up. Residualized T1 to T2 changes in MOCS-Relaxation and Reappraisal were highly correlated ($r = .89$, $P < .001$), suggesting substantial overlap in perceived confidence across these different skill sets.

Discussion

Prior work found post-intervention decreases in distress had a significant indirect effect on health status at 12-month follow-up in women undergoing treatment for breast cancer (Andersen et al. 2007a). Other work indicated that alterations in hypothalamic pituitary axis (HPA) functioning, reflected in elevated PM cortisol levels, predicted adverse health outcomes in women with breast cancer (Sephton et al. 2000). The present study tested whether increases in confidence in using specific stress management skills after a group-based CBSM intervention explained reduced PM serum cortisol levels at 1 year follow-up among women receiving breast cancer treatment.

As hypothesized, pre- to post-intervention changes in perceived ability to relax statistically mediated 6- to 12-month follow-up reductions in PM cortisol. This finding is consistent with previous work among treated breast cancer patients showing that improvements in quality of life and health status at 12-month follow-up were associated with increased confidence in using relaxation to manage stress (Antoni et al. 2006a; Andersen et al. 2007a, b). These findings are novel in that they demonstrate the potential importance of relaxation training in modulating neuroendocrine stress biomarkers that may explain future health effects (Sephton et al. 2000).

We also found that pre- to post-intervention changes in the MOCS cognitive-reappraisal item (“I can easily stop and re-examine my thoughts to gain a new perspective”) predicted the magnitude of cortisol reductions from 6- to 12-month follow-up. Many breast cancer patients have recurring thoughts about cancer (Jacobsen et al. 1998;

Palmer et al. 2004) and their concerns may remain after completing treatment (Spencer et al. 1999). The finding that CBSM can help cancer patients stop and re-examine their thoughts to gain a new perspective is important. This is the first study to show that these changes strongly predict decreased cortisol levels for up to 12-month follow-up.

Evaluating patterns of change, the intervention group demonstrated a delayed decrease in cortisol levels whereas the control group had a steady increase across 12 months. Though there were no differences between groups at T1, the groups changed differentially across time in the expected directions. However, by T3 the between-group difference in average cortisol was not statistically significant, suggesting more work with a larger sample is needed to understand the clinical significance of the cortisol findings. From T1 to T2, MOCS-Relaxation improved in both groups, then from T2 to T3, it stabilized for the intervention group and decreased for the control group. From T1 to T2, MOCS-Reappraisal increased in the intervention group and decreased in the control group, then from T2 to T3, the intervention group returned to its initial level and was roughly equal to the control group. Results suggest these variables may follow separate, non-linear trajectories.

The indirect effects for MOCS-Relaxation and Reappraisal were significant, but these components were highly correlated, suggesting overlap in perceived confidence across different skill sets. Thus, contrasting the two indirect effects was not appropriate (Preacher and Hayes 2008). It is plausible that being able to reexamine one's appraisals about stressors may also impact one's ability to relax. More work is needed to understand the inter-relationship between these skills.

With respect to relaxation training, 45 min of each of the ten 2-h sessions involved some form of relaxation training or a related anxiety reduction technique. Participants not only had more in-session exposure to relaxation skills than any one of the other intervention components, but were also instructed to practice their relaxation skills daily. All of this exposure likely optimized their perceived confidence in using relaxation skills. With respect to cognitive restructuring, while only two sessions formally addressed the mechanics of cognitive appraisals, we did carry over the notion of addressing cognitive appraisals as we introduced new techniques such as coping effectiveness training, anger management and assertion training (Antoni 2003). This integration and repetition could account for the strong influence that perceived cognitive appraisal skills played in explaining our cortisol effects. We found no evidence that a number of other specific skills targeted by CBSM were affected by the intervention, which is consistent with previous findings (Antoni et al. 2006a). One possible reason for the lack of intervention effects components, such as awareness of tension, asking for support, coping abilities, may be that the each received less coverage than either relaxation or cognitive reappraisals, which both permeated the program.

More research is needed to better understand the impact cognitive restructuring and relaxation skills have on stress physiology and peripheral cortisol levels among women with breast cancer. Since changes in both perceived relaxation and cognitive reappraisal skills were very highly correlated in this study, it is plausible that they both reflect a general improvement in self-efficacy or "buy-in" of the value of the intervention. The question also arises whether an intervention that focuses on only cognitive restructuring or only relaxation techniques can lead to reductions in cortisol. This would require a "dismantling" study that compares well-matched interventions systematically varying in specific techniques provided (e.g., relaxation only vs. cognitive behavioral only vs. education only). Such a study is underway in our lab.

It is crucial to keep in mind that we measured *perception* of ability to use specific CBSM skills, not skill acquisition or usage. Future work should include measures of the frequency of use of these skills and effectiveness of their implementation. The timing of the follow-up measurements was somewhat arbitrary. The amount of exposure to specific CBSM components may be important. Thus replication with more frequent measurements points with a larger sample is needed to establish the evolution of cortisol changes after the intervention and the role of repeated practice. Most participants were well-educated, middle-class Caucasian women; thus, results cannot be generalized to minority women of lower socio-economic status. Participants with higher stage disease were less likely to participate in the cortisol substudy and those with metastatic disease were not included in this study; thus, results cannot be generalized to those with advanced disease, who have often been the focus of prior studies of cortisol regulation and health outcomes (e.g., Sephton et al. 2000).

In this study cortisol was measured with a single blood draw collected between 4-6:30 p.m.. As cortisol levels may fluctuate due to stressors in the environment (Yehuda 2003), future studies should sample cortisol throughout the day so changes in circadian rhythms can be examined across the intervention and at follow-up. More work is needed to understand whether CBSM can restore neuroendocrine circadian rhythms among cancer patients. Beyond effects on future health, the normalization of circadian cycles may also be associated with more proximal effects on sleep, fatigue, and depression thereby contributing to symptom management (Antoni et al. 2006b; Miller et al. 2008).

In summary, this study was the first to establish that improvement in the specific skills targeted by a 10-week CBSM intervention statistically mediated reductions in cortisol over long-term follow-up among women moving through treatment for non-metastatic breast cancer. Specifically, improved perceived ability to use stress management skills post-intervention (i.e., confidence in ability to relax and make cognitive re-appraisals) may explain reductions in cortisol from 6- to 12-month follow-up. Changes in perceived skills targeted by a psychosocial intervention may be evident post-intervention, while their effects on physiological changes may be detectible months after the intervention when participants have completed adjuvant treatment and/or had time to rehearse the skills they learned and integrated them into their lives. These findings may guide the development of more focused and possibly briefer interventions for this population.

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