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# Relationships between serum cortisol, RAGE-associated s100A8/A9 levels, and self-reported cancer-related distress in women with non-metastatic breast cancer

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## Abstract

**OBJECTIVE.—**Elevated inflammation and psychological distress in patients with breast cancer (BCa) have been related to poorer health outcomes. Regulation of the hypothalamic-pituitary adrenal (HPA) axis and signaling of the receptor for advanced glycation end products (RAGE) are important in the inflammatory response and have been associated with increased stress and poorer health outcomes in patients with cancer. This study examined relationships among circulating cortisol, a measure of HPA axis activity and physiological stress; s100A8/A9, a RAGE ligand and emerging cancer-related biological measure; and self-reported cancer-related distress.

**METHODS.—**Patients with BCa (N=183, stage 0–IIIb) were recruited 2–10 weeks post-surgery but prior to receiving adjuvant therapies. Participants provided blood samples, from which serum cortisol and s100A8/A9 levels were determined, and completed a psychosocial questionnaire. Regression analyses, adjusting for age, cancer stage, time since surgery, race, and menopausal status, were conducted examining the relationships between cortisol, s100A8/A9, and cancer-related distress (Impact of Event Scale [IES]–Revised).

**RESULTS.—**Cortisol and s100A8/A9 levels were positively related (β=.218, t(112)=2.332, $p$=.021), although the overall model was not significant. Cortisol levels were also positively associated with IES-Intrusions (β=.192, t(163)=2.659, $p$=.009) and IES-Hyperarousal subscale scores (β=.171, t(163)=2.304, $p$=.022).

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**CONCLUSIONS.—**Patients with higher cortisol levels also reported higher s100A8/A9 levels and more cancer-related distress. The relationship between cortisol and s100A8/A9 supports a link between the stress response and pro-inflammatory physiological processes known to predict greater metastatic risk in BCa. Stress processes implicated in cancer biology are complex and replication and extension of these initial findings is important.

**Keywords**

breast cancer; stress; s100A8/A9; cortisol; biobehavioral

## INTRODUCTION

Cortisol, a marker of physiological stress (1), is a steroid hormone secreted by the adrenal cortex and is considered a reliable measure of hypothalamic-pituitary-adrenal (HPA) axis function (2). Women with BCa have been shown to have higher cortisol levels than healthy controls, and their cortisol levels appear to increase with disease severity (3, 4). Alterations in cortisol levels or regulation may contribute to cancer progression and disease outcomes as cortisol can modulate the immune response and release of proinflammatory cytokines, such that glucocorticoid receptor desensitization can leave inflammatory response cascades relatively unchecked impacting processes involved in cancer (5). Cortisol has also been implicated in chemoresistance in the majority of tumor cells, including breast (6). There is a strong evidence base evaluating how stress processes and distress states relate to general indicators of inflammation and immune function in the context of cancer (7), however, inconsistencies in findings leave debate around how precisely cortisol relates to psychosocial factors in patients with BCa (8).

Also involved in stress-related inflammatory pathways is the receptor for advanced glycation end products (RAGE), a cell surface receptor that is part of the immunoglobulin sub-family of proteins (9). Found on immune and cancer cells, it is activated by ligands such as the heterodimer s100A8/A9 (calprotectin) (10). Evidence suggests elevated leukocyte inflammatory signaling seen in conjunction with elevated stress may be due to effusion of myeloid-derived suppressor cells from the bone marrow with SNS activation (11), which stimulate immune and cancer cells via RAGE (9). Increased RAGE activation, via s100A8/A9 (10), has been linked to greater risk of BCa metastasis because it modifies tumor processes, including increased cell migration and invasion, proliferation, and resistance to apoptosis (9, 12). A growing body of evidence establishes s100A8/A9 as crucial in establishing the “pre-metastatic niche,” a fertile environment for malignant cells from the primary tumor to invade other organs and tissues, facilitating progression from early stage to metastatic breast cancer (9, 13). S100 proteins, and specifically s100A8/A9 in breast cancer, have also been found to mediate chemoresistance, further promoting opportunity for metastasis (14, 15). Identifying and modifying promising prognostic markers such as s100A8/A9 early in the disease course, may impact the cancer trajectory (3, 15, 16).

While several key players have been proposed as relevant to the impact of stress factors on inflammatory processes relevant to BCa progression (7, 17, 18), less is known about how stress-related neuroendocrine regulation relates to RAGE activation in

BCa. One identified pathway is that cortisol increases production of s100A8/A9 from polymorphonuclear neutrophils (PMNs) which can lead to reactivation of dormant tumor cells (19). We hypothesized greater cortisol levels would predict greater s100A8/A9 levels in post-surgical patients with BCa as well as higher self-reported cancer-related distress. We also hypothesized a positive association between cancer-related distress and s100A8/A9 levels.

## METHODS

### Participants and Procedures.

This was a secondary analysis of baseline data from an IRB-approved randomized controlled trial registered as National Institutes of Health Clinical Trial NCT02103387. Additional information on trial methodology and primary outcome results can be found in a previously published report (20). From 2006–2013, recently diagnosed BCa patients (stage 0–IIIb) aged 21+ were recruited from clinics and hospitals in South Florida 2–10 weeks post-surgery but before initiating adjuvant therapies to participate in an IRB-approved randomized controlled trial. They were excluded during screening for severe psychiatric illness, non-fluency in English, prior history of cancer (with the exception of nonmelanoma skin cancer), stage IV BCa, other serious chronic medical conditions, and initiation of neoadjuvant or adjuvant therapy (chemotherapy/radiotherapy). Of 739 women approached, 545 were excluded (318 for not meeting study criteria and 227 for participant refusal or nonavailability). Eleven withdrew from the study prior to baseline data collection. Informed consent was obtained from all individual participants included in the study. Participants (N=183) completed a baseline assessment including a psychosocial questionnaire and a blood sample from which serum levels of cortisol and s100A8/A9 were determined. Participants additionally self-reported demographic and medical information, which was later verified through medical chart review by the study team.

### Measures.

A licensed phlebotomist obtained blood samples (35ml) from participants between 4pm and 6:30pm. Cortisol levels in serum were determined with enzyme-linked immunosorbent assay (ELISA, Diagnostic Systems Laboratories, Webster, Texas), inter-assay coefficient of variation (CV) = 6%; intra-assay CV = 5%. Serum s100A8/A9 levels were obtained by an ultra-sensitive ELISA (Calprotectin, Human ELISA; Hycult Biotech Inc, Wayne, PA), inter-assay CV = 4.3%; intra-assay CV = 5.3%. Self-reported cancer-related distress over the past seven days was assessed using the 22-item Impact of Event Scale—Revised (IES-R) (21), which includes three subscales Intrusions (IES-I), Hyperarousal (IES-H), and Avoidance (IES-A). The IES-R has been used in previous studies of stress and stress management in BCa patients (20, 22). Cronbach alpha indicated high reliability (IES-I $\alpha$=.87; IES-H $\alpha$=.83; IES-A $\alpha$=.81).

### Analytic Plan.

Analyses were conducted using the Statistical Package for the Social Sciences-version 25. An alpha level of .05 was used and tests were two-tailed. Consistent with prior reports from this trial, for psychosocial data, outliers (>3 SD from the mean) were winsorized.

Analyses used raw values for physiological data with extreme values of >3 SD from the mean removed (s100A8/A9 N=1; cortisol N=3). Associations were tested with multiple regression. Covariates were selected based on previous research indicating associations with stress adaptation (23) and inflammatory markers (24, 25), and included age, disease stage, days since surgery, menopausal status, and race. All available data were used and analyses used listwise deletion for missing data (see Table 1 for Ns). The study variable with the largest amount of missing data was s100A8/A9 (N=122/183) as this was a post-hoc assay done with cryopreserved serum samples and could only be conducted for participants who had a sufficient amount of remaining intact sample. There were no significant differences ($p$>.05) in demographic or medical variables between participants with s100A8/A9 data and the full sample.

## RESULTS

Participants had a mean age of 54.28 (SD=10.06) and were majority Hispanic (42.2%) or Non-Hispanic White (42.2%). See Table 1 for additional demographic and medical information. There was a significant positive relationship between cortisol and s100A8/A9 (β=.218, t(112)=2.332, $p$=.021), though the overall model controlling for age, stage, time since surgery, menopause status, and race was not significant (F(6, 112)=1.263, $p$=.280, $R^2$=.063, $R^2$ change=.045). The overall multiple regression model testing the relationship between cortisol and the full scale IES, controlling for covariates, was significant (F(6, 160)=4.650, $p$=.<.001, $R^2$=.148, $R^2$ change=.024), and revealed a significant positive association between cortisol levels and IES scores (β=.159, t(160)=2.139, $p$=.034). Similarly, the overall multiple regression model testing the relationship between cortisol and the IES-I subscale, controlling for covariates, was significant (F(6, 163)=5.824, $p$<.001, $R^2$=.177, $R^2$ change=.036), and revealed a significant positive association between cortisol and IES-I (β=.192, t(163)=2.659, $p$=.009), see Figure 1. The overall model testing the relationship between cortisol and IES-H, controlling for covariates, was also significant (F(6, 163)=4.334, $p$<.001, $R^2$=.138, $R^2$ change =.028), and there was a significant positive association between cortisol and IES-H (β=.171, t(163)=2.304, p=.022). Cortisol levels were not related to IES-A scores ($p$>.10). Neither full scale IES nor subscales were related to s100A8/A9 levels ($p$'s>.10).

## DISCUSSION

We documented for the first time that greater circulating levels of cortisol were associated with greater s100A8/A9 levels in BCa patients. The literature suggests that the relationship between cortisol dysregulation and cancer outcomes may be explained at least in part by upregulation of inflammatory processes that facilitate disease progression and metastasis (7, 26–28). The glucocorticoid-resistance model posits that with frequent stress, persistent activation of the HPA axis leads to heightened levels of circulating cortisol, which in turn, causes desensitization of glucocorticoid receptors in inflammatory immune cells like monocytes (29). Since glucocorticoid receptors are responsible for modulation of the immune response including release of pro-inflammatory cytokines, desensitization can leave inflammatory response cascades relatively unchecked (29). The current study examined afternoon levels of serum cortisol, consistent with other prior studies examining stress in

BCa (17, 18). Dysregulated cortisol levels – indexed by flatter diurnal pattern – have been linked to poorer disease outcomes in cancer (30–32), and higher levels of afternoon cortisol can contribute in part to a flatter diurnal cortisol slope. To better understand the extent to which elevations of single-assessment serum levels seen here may or may not be a representation of cortisol dysregulation, future work should investigate other measures of cortisol, such as salivary cortisol collection for diurnal rhythm analysis (33) and assays that assess glucocorticoid sensitivity (34). If results of such investigations are consistent, results would support that adequate management of cancer-related distress could be valuable for BCa patients during this period.

Binding of s100A8/A9 to RAGE receptors facilitates regulation of the nuclear factor-κB and mitogen-activated protein kinase (MAPK) signaling pathways involved in production of pro-inflammatory cytokines. SNS-related neurohormones can stimulate bone marrow to release cells that produce s100A8/A9 (35). As such, we hypothesized that cortisol levels would positively relate to s100A8/A9 levels, which our results supported. Consistent with our results, a recent investigation in a murine lung cancer model showed addition of cortisol to PMNs was associated with the greatest increase in s100A8/A9 compared to other stress hormones such as norepinephrine (19). Importantly s100A8/A9 induced these PMNs to accumulate oxidized lipids and release of these lipids up-regulated fibroblast growth factor and appeared to reactivate dormant tumor cells and formation of new tumor lesions (19). To better understand how stress may relate to cancer outcomes via RAGE-mediated processes, future work should also investigate relationships between s100A8/A9 and other neurohormones in BCa.

Additionally, in line with our hypotheses, cortisol levels were positively related to cancer-related distress. This is in agreement with a large body of existing literature that establishes cortisol as a stress biomarker (36) and prior work that highlights a relationship between cortisol and psychological distress in BCa patients (18, 37, 38). Our results suggested women with BCa who self-reported more cancer-related distress in the form of thought intrusions or hyperarousal after surgery also showed a greater HPA-mediated physiological stress response as measured by serum cortisol levels. Cortisol levels were not related to cancer-related distress in the form of avoidance, consistent with prior work from our group showing intrusions and hyperarousal are the IES subscales that tend to demonstrate relationships with stress and inflammatory processes and greater sensitivity to change through stress-management interventions (20, 39).

Interestingly, self-reported cancer-related distress was not directly related to s100A8/A9 levels. In the current study, the IES was selected to represent psychological distress. This scale was chosen as it distinctly captures both the physiological (hyperarousal; IES-H) and the cognitive component of distress (intrusions; IES-I), and has been shown to be influenced by stress management interventions in BCa (20, 22). It is possible, however, that other indicators of psychological adaptation (e.g., depressive symptoms) not assessed here and/or examination of associations between s100A8/A9 and psychological wellbeing in a metastatic sample as opposed to early stage (0-IIIb) would have yielded different relationships with s100A8/A9. In fact, a recent publication reported lower levels of social and family well-being and higher levels of depressive symptoms were related to greater

s100A8/A9 in women with metastatic breast cancer (40). The examination of distress in BCa is of great importance with one study categorizing 40% of BCa patients assessed as highly distressed (41). The current study, however, did not specifically select for distressed patients and participants on average endorsed being bothered by symptoms “a little bit” over the past week. Similarly, there was variation in cortisol and s100A8/A9 levels. Mean levels of s100A8/A9 in this study, as expected, were greater than mean levels in prior reports with non-cancer samples (42, 43) and lower than mean levels in non-metastatic breast cancer patients with high distress (39) and patients with metastatic breast cancer (40). It would be valuable in a future study to determine if a significant relationship would emerge between distress and s100A8/A9 in a distressed sample.

Finally, it is possible that the IES measure of cancer-related distress assessed during the recently diagnosed period captured acute distress that better relates temporally to cortisol compared to s100A8/A9, which may be more related to longer-term psychological status, assessed with measures of depression or social and family wellbeing (38). This post-surgical period was chosen for collection of inflammatory measures, as surgery-related inflammation has likely resolved and adjuvant treatments have not begun. This is additionally a time of particular interest in psycho-oncology as women often have elevated distress during this period (44). This may not necessarily be representative of the biopsychosocial processes at play throughout the disease trajectory. Future work should involve longitudinal designs to gain better insight into how these variables relate over time and potential mechanisms at work.

To note, the current sample was comprised of largely middle-class, well-educated, and highly motivated women who were willing to be part of a research study. While a strength of the study was that over 50% of the sample identified as an ethnicity other than non-Hispanic white, only English-speaking patients were able to participate. Also of note, psychosocial data were collected via self-report which is subject to potential participant recall and reporting biases. Furthermore, other demographic or medical variables not included in this study may influence relationships examined here, such as anti-inflammatory treatments, NSAID use, or acute illness. As this study was cross-sectional in nature, no claims can be made concerning causation nor temporality of relationships. Bi-directional relationships exist in stress and inflammatory pathways, and the relationship seen here between cortisol and s100A8/A9 could be independent of stress perceptions via self-reports.

Since this was the first investigation of the associations of cortisol with s100A8/A9 and cancer-related distress, and because the relationship between the two variables but not the overall model was significant, replication is needed before conclusions can be confidently drawn. While the variables examined here are part of the biopsychosocial model of stress in disease (7, 45), inflammatory pathways involved are numerous and complex and more work is needed characterizing the psychological, neuroendocrine, and immunologic variables and networks involved. Despite limitations, this study adds to the literature by demonstrating that among BCa patients in the post-surgical period, greater cortisol levels are associated with greater s100A8/A9 levels, an emerging inflammatory biomarker known to promote processes mediating BCa metastasis.

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Dr. Antoni is a consultant for Blue Note Therapeutics and Atlantis Healthcare and receives a small royalty from APA and Oxford Press for books he wrote on stress management. Dr. Taub is a consultant for Blue Note Therapeutics. This study was funded by NCI R01CA64710 and Sylvester Cancer Center. Dr. Taub is funded by NCI T32CA193193.

## Acronyms:

| | |
|---|---|
| **BCa** | breast cancer |
| **IES-I** | Impact of Event Scale – Intrusions |
| **IES-H** | Impact of Event Scale – Hyperarousal |
| **HPA** | hypothalamic-pituitary adrenal |
| **RAGE** | receptor for advanced glycation end product |
| **ELISA** | enzyme-linked immunosorbent assay |
| **PMNs** | polymorphonuclear neutrophils (PMNs) |

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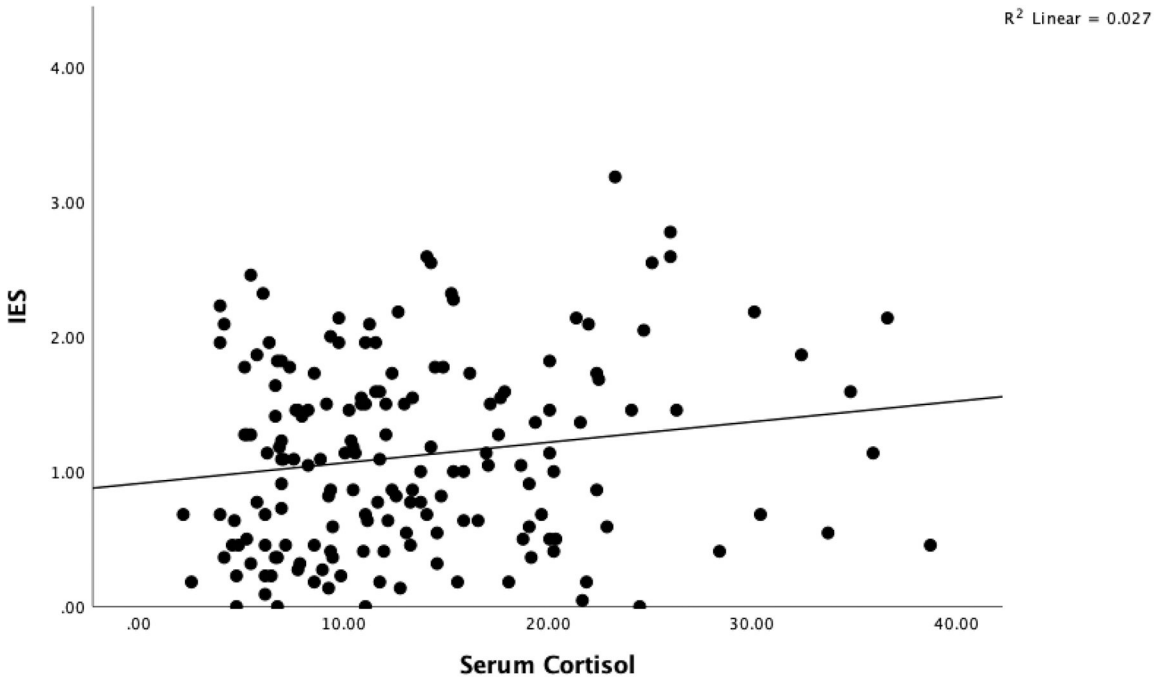


**Figure 1.**
Scatterplot of simple regression for serum cortisol levels and IES-I scores.

**Table 1.**

Sample Characteristics

| Variable | N | Mean (SD) or Count (%) |
|---|---|---|
| Age (years), range=28–80 | 183 | 54.28(10.06) |
| Surgery to baseline (days) | 183 | 37.42(22.3) |
| BMI (weight/height*703) | 154 | 26.91(5.34) |
| Premenopausal (yes/peri or post) | 178 | 57 (32.0%) |
| Household income (thousands) | 183 | 100.61(67.89) |
| Education (years) | 179 | 15.49(2.99) |
| Married/partnered (yes/no) | 183 | 117(63.9%) |
| Employed (yes/no) | 183 | 129(70.5%) |
| Race/Ethnicity | 183 | |
| *Non-Hispanic White* | | 76(42.2%) |
| *Hispanic* | | 76(42.2%) |
| *Black* | | 16(8.9%) |
| *Other* | | 12(6.7%) |
| Stage | 182 | |
| *0* | | 35(19.2%) |
| *I* | | 94(51.6%) |
| *II* | | 44(24.2%) |
| *III* | | 9(4.9%) |
| Positive Nodes (yes/no) | 183 | 37(21.6%) |
| Hormonal Status | | |
| *Her2 neu* (yes/no) | 143 | 17(11.9%) |
| *ER Positive* (yes/no) | 164 | 141(86.0%) |
| *PR Positive* (yes/no) | 159 | 122(76.7%) |
| *ER or PR Positive* (yes/no) | 158 | 137(86.7%) |
| Surgery | 183 | |
| *Lumpectomy* | | 89(48.6%) |
| *Mastectomy* | | 94(51.4%) |
| Study Variables | | |
| *Serum s100A8/A9* (ng/mL) | 122 | 3936.06 (3079.66) |
| *Serum Cortisol* (nmol/L) | 177 | 13.39 (7.50) |
| *IES-I* (0–4 range) | 179 | 1.31(.86) |
| *IES-H* (0–4 range) | 179 | .8491(.77) |