Altered Cortisol Response to Psychologic Stress in Breast Cancer Survivors With Persistent Fatigue

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Objective: Fatigue is one of the most common and distressing symptoms experienced by cancer patients and survivors. However, the etiology of cancer-related fatigue has not been determined. In previous studies, we have shown alterations in morning serum cortisol levels and diurnal cortisol rhythms in fatigued breast cancer survivors compared with nonfatigued control subjects. The purpose of the current study was to evaluate cortisol responses to an experimental psychologic stressor in fatigued and nonfatigued survivors. **Methods:** Participants included 27 breast cancer survivors (11 fatigued, 16 nonfatigued). All had completed cancer treatment at least 3 years previously and were currently healthy with no evidence of recurrence. A standardized laboratory stressor, the Trier Social Stress Test (TSST), was administered during a 90-minute afternoon session. Saliva samples and autonomic measures (heart rate, blood pressure) were collected at 15-minute intervals throughout the session. **Results:** Fatigued survivors showed a significantly blunted cortisol response to the stressor compared with nonfatigued survivors, controlling for depression and other potential confounds ($p < .05$). No differences in autonomic measures were observed. **Conclusions:** These results, together with our earlier findings, suggest a dysregulation in hypothalamic–pituitary–adrenal (HPA) axis responsiveness among breast cancer survivors with enduring fatigue. Although the sample size was small, results suggest that attention to the HPA axis may be important for understanding cancer-related fatigue. **Key words:** breast cancer, fatigue, HPA axis, psychologic stress

BDI = Beck Depression Inventory; **HPA** = hypothalamic–pituitary–adrenal; **TSST** = Trier Social Stress Test.

INTRODUCTION

There are a growing number of cancer survivors in the United States, and research on the psychologic and physical sequelae of cancer diagnosis and treatment has taken on increasing importance (1). Fatigue is one of the most common and distressing side effects of cancer treatment (2,3), is elevated in patients with cancer relative to the general population (4), and may endure for months or years after successful treatment completion (5). Among breast cancer survivors (BCS), approximately 30% report persistent fatigue (6–8). The etiology of cancer-related fatigue has not been determined neither psychologic (eg, depression) nor biologic (eg, hemoglobin, thyroid hormone) factors fully account for fatigue symptomatology in patients with cancer (6,9–11).

Fatigue is a prominent component of sickness behavior, a constellation of behavioral changes induced by proinflammatory cytokine effects on the central nervous system (12–14). Preliminary studies suggest that inflammatory processes may be involved in cancer-related fatigue, because fatigued breast cancer survivors show elevations in markers of proinflammatory cytokine activity and increased numbers of circulating T lymphocytes compared with nonfatigued survivors (15,16). Fatigue has also been linked to proinflammatory cytokines and other inflammatory markers among patients with cancer undergoing treatment (17,18). Furthermore, fatigue often co-occurs with other prototypical sickness behaviors in cancer patients and survivors, including depressed mood and sleep disturbance (6,19–21).

There are several mechanisms through which chronic inflammation might develop or persist in patients with cancer, including alterations in immune regulatory systems such as the hypothalamic–pituitary–adrenal (HPA) axis. Adrenal cortex-derived steroids have potent effects on proinflammatory cytokine production and activity (22), and disturbances in HPA axis function have been observed in other chronic inflammatory and fatigue-related disorders (23,24). In previous studies, we found lower levels of morning serum cortisol (15) and flattened diurnal salivary cortisol rhythms (25) in fatigued breast cancer survivors relative to nonfatigued control subjects. The current study was designed to test the dynamic responsiveness of the HPA axis, given evidence that blunted HPA axis responses may be associated with susceptibility to inflammatory disease (26). We used a standardized psychosocial stressor to probe HPA axis activity in fatigued and nonfatigued breast cancer survivors.

METHODS

Potential participants were recruited from a large cohort of early-stage breast cancer survivors (27,28). Participants were identified based on their scores on the energy/fatigue subscale of the RAND Health Survey, which was initially completed between 1 to 5 years postdiagnosis as part of the parent study. Scores on this scale range from 0 to 100, with scores below 50 indicating limitations or disability related to fatigue (29). Recruitment letters were sent to 395 women who scored below 50 (fatigued group) or above 70 (nonfatigued group) at the initial assessment and lived in the Los Angeles area. Women ($n = 73$) who returned a response form indicating an interest in the study and who again scored either below 50 or above 70 on the energy/fatigue scale were contacted by phone for additional screening. Exclusion criteria included cancer recurrence, diagnosis with other cancers, history of immune-related diseases, current medical illness or depression, and heavy use of alcohol. Twenty-seven women (11 fatigued, 16 nonfatigued) met all eligibility criteria and completed the experimental session (mean energy/fatigue score for fatigued group = 32.7, standard deviation [*SD*] = 16.9; mean energy/fatigue score for nonfatigued group = 80.3, $SD = 70.4$; t [12.5] = 8.8, $p < .0001$).

The Trier Social Stress Test (TSST) was used to induce activation of the HPA axis (30). The TSST involves preparing and delivering a speech and performing mental arithmetic in front of an audience and is associated with reliable increases in cortisol levels. The 90-minute experimental session

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(15-minute rest period, 30-minute TSST, 45-minute follow up) was conducted in the UCLA GCRC between 4:15 PM and 5:45 PM to capture maximum cortisol reactivity (31).

After the initial rest period, saliva samples and autonomic measures (blood pressure, heart rate) were collected at 15-minute intervals throughout the session (6 assessments total). Autonomic measures were collected once at each assessment point from the same arm using a DINAMAP vital systems monitor (GE Healthcare). Participants also completed self-report measures to assess demographic and medical characteristics, depressed mood (BDI-II), and subjective responses to the task (including ratings of task difficulty, effort, performance, perceived control, perceived threat, and fatigue). All subjects provided informed consent, and the study was approved by the UCLA Institutional Review Board. Salivary cortisol levels were assessed by enzyme immunoassay (Salimetrics, State College, PA). This assay has a lower detection limit of less than 7 ng/dL. The mean intraassay coefficient was 5.5 (range, 4–6%) and the mean interassay coefficient was 8.2 (range, 7–11%). All samples from a participant were analyzed in duplicate in the same assay to minimize variability.

Repeated-measures analysis of variance was used to examine salivary cortisol, autonomic measures, and subjective responses to the task. Primary analyses included all 6 assessment points. Two fatigued participants did not provide adequate saliva to assess salivary cortisol levels at all 6 assessment points. Thus, follow-up analyses were conducted using samples from 3 assessment points: baseline (prestress), 60 minutes poststress, and 75 minutes poststress.

RESULTS

Fatigued subjects were somewhat younger (mean age for fatigued = 55.6 years, SD = 5.3; mean for nonfatigued = 61.1 years, SD = 9.6; t [24] = 1.9, p = .07), had a marginally lower income level (chi-square [5] = 10.4, p = .06), were marginally less likely to be married or in a committed relationship (chi-square [1] = 3.7, p = .06), and reported significantly higher levels of depressed mood (mean for fatigued = 11.9, SD = 10.6; mean for nonfatigued = 5.1, SD = 5.8; t [25] = −2.2, p = .04) than nonfatigued subjects, consistent with our previous research (6,15). In terms of cancer treatment, fatigued subjects were marginally less likely to have received radiation therapy (chi-square [1] = 2.8, p <.10) or chemotherapy (chi-square [1] = 2.8, p <.10) than nonfatigued subjects. There were no significant differences in ethnicity, body mass index, or use of tamoxifen. The average time since diagnosis was 8.4 years (SD = 0.95, range = 6.75–9.92) and did not differ across groups.

There was a significant increase in salivary cortisol in response to the stressor (time effect: F [5,115] = 12.4, p <.001), a significant main effect for group (F [1,23] = 5.4, p = .03) and a significant group-by-time interaction (F [5,115] = 4.5, p = .001). As shown in Figure 1, salivary cortisol levels for nonfatigued women increased by more than 4-fold after the TSST, whereas fatigued women showed a negligible change over this period. Main effects for group, time, and the group-by-time interaction remained significant in analyses with 3 assessment points.

Analyses were conducted to control for factors that differed between fatigued and nonfatigued subjects and may influence HPA axis responsiveness. The fatigue group-by-time interaction remained significant in analyses controlling for potential demographic and medical confounds (ie, age, income, marital

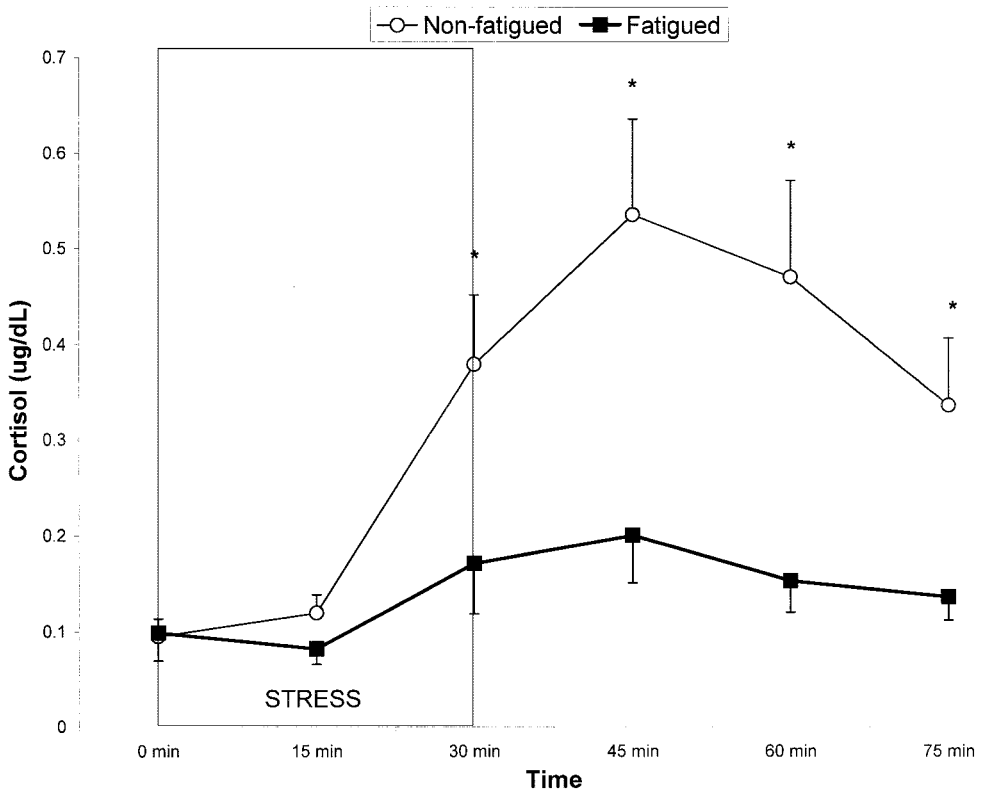

Figure 1. Mean salivary free cortisol levels before, during, and after experimental psychologic stress in fatigued and nonfatigued breast cancer survivors. The stressor occurred during the first 30 minutes indicated on the graph. Error bars represent 1 standard error. *p <.05.

status, cancer treatment) and depressive symptoms (ie, BDI-II scores) (F [5,85] = 4.6, p = .001). Two of the fatigued women reported cigarette use in the past week; removal of these subjects from the data set yielded the same pattern of results.

Both groups showed significant changes in autonomic measures in response to the stressor, including increases in blood pressure (time effect for systolic: F [5,105] = 10.8, p <.001; time effect for diastolic: F [5,105] = 7.3, p <.001) and heart rate (time effect: F [5,105] = 6.6, p <.001). There were no significant effects of group and no group-by-time interactions on these parameters, although there was a trend for a different pattern in heart rate response (group-by-time interaction: F [5,105] = 2.0, p = .09). The fatigued women had an elevated heart rate at baseline relative to the nonfatigued women and, as a result, did not show the same increase in heart rate in response to the stressor. Heart rate at subsequent assessments was comparable for fatigued and nonfatigued groups.

Perceptions of the stressor were assessed by self-report to address the possibility that subjective responses to the task may have differed across groups, accounting for physiological differences. There were no significant differences in perceptions of task difficulty, effort, perceived control, or perceived threat (all p's >.25). Fatigued women did report significantly lower levels of energy throughout the session (F [1,23] = 11.6, p = .002), and there was a significant fatigue group-by-time interaction (F [4,92] = 2.6, p = .04); fatigued subjects reported decreased energy by session end, whereas nonfatigued subjects reported increased energy.

DISCUSSION

Results from this study document a blunted HPA response to psychologic stress among breast cancer survivors with persistent fatigue. Fatigued survivors showed only a small increase in salivary free cortisol in response to a standardized stress task, whereas nonfatigued survivors showed the robust increase in cortisol levels observed in healthy individuals (30,31). Fatigued participants' blunted response could not be accounted for by demographic or treatment-related differences between groups, or by differences in subjective responses to the task. Although fatigued survivors reported elevated depressive symptoms relative to nonfatigued survivors, differences in cortisol reactivity remained significant in analyses controlling for depression. Furthermore, the pattern of cortisol alterations seen in fatigued survivors can be contrasted with that observed in depressed patients, who show elevated levels of cortisol across the day (32,33) but do not show differences in cortisol responses to stress (34,35). Both fatigued and nonfatigued participants showed a similar pattern of autonomic responses to the task, suggesting that the alterations in HPA axis function may be specific to that system.

In a previous study, we found flattened diurnal cortisol slopes in fatigued breast cancer survivors relative to nonfatigued controls (25). Exploratory analyses conducted in the subsample of women who provided samples for both studies (n = 17) revealed a negative correlation between stress-induced changes in cortisol and diurnal cortisol rhythms (r = −0.42, p<.10), such that women with flatter slopes showed a more blunted stress response. Both circadian cortisol rhythms and cortisol responses to stress reflect the ability of the HPA axis to turn on and off in response to internal and external cues. In animal models, failure to generate an appropriate glucocorticoid response to pharmacologic or physiological stimuli is associated with increases in inflammation (26). There is also evidence of HPA axis dysregulation among individuals with inflammatory and autoimmune diseases, including blunted cortisol response to a comparable stressor in patients with atopic dermatitis (36). Of note, the TSST is known to elicit increases in proinflammatory cytokines (37), which could persist in the absence of cortisol modulation. Thus, it is possible that the observed alterations in HPA axis function may influence fatigue symptomatology through effects on inflammatory processes. On the other hand, HPA axis alterations may also occur secondary to behavioral changes that co-occur with cancer-related fatigue, including sleep disturbance and reduced activity (38,39).

This study focused on highly selected group of breast cancer survivors who reported significant fatigue for years after cancer treatment. Results require replication in a larger, more representative sample of patients with cancer-related fatigue. In addition, prospective studies are required to explicate the complex interrelationships among HPA axis function, inflammatory processes, and fatigue in patients with cancer.

There is growing interest in HPA axis function among patients with cancer (40), with some evidence that HPA dysregulation is associated with disease progression in women with metastatic breast cancer (41). Results from this study provide preliminary evidence that alterations in HPA function are also relevant for behavioral symptoms experienced by patients with cancer, and suggest that attention to this system may be important for understanding cancer-related fatigue.

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