Psychoneuroendocrinology (2005) **30**, 92–100

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Diurnal cortisol rhythm and fatigue in breast cancer survivors

Julienne E. Bower[a,b,c,*], Patricia A. Ganz[c,d], Sally S. Dickerson[e], Laura Petersen[c], Najib Aziz[f], John L. Fahey[f,g]

[a]*Cousins Center for Psychoneuroimmunology, UCLA Neuropsychiatric Institute, Los Angeles, CA, USA*
[b]*Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*
[c]*Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center at UCLA, Los Angeles, CA, USA*
[d]*UCLA Schools of Medicine and Public Health, Los Angeles, CA, USA*
[e]*UCLA Department of Psychology, Los Angeles, CA, USA*
[f]*Center for Interdisciplinary Research in Immunology and Disease at UCLA, Los Angeles, CA, USA*
[g]*UCLA Departments of Medicine and of Microbiology, Immunology, and Behavioral Genetics, Los Angeles, CA, USA*

Received 13 November 2003; received in revised form 29 March 2004; accepted 9 June 2004

KEYWORDS
Fatigue;
Cortisol;
Diurnal rhythm;
Cancer survivor

Summary Approximately 30% of breast cancer survivors report persistent fatigue of unknown origin. We have previously shown that cancer-related fatigue is associated with alterations in immunological parameters and serum cortisol levels in breast cancer survivors. The current study examined the diurnal rhythm of salivary cortisol in fatigued and non-fatigued breast cancer survivors. Salivary cortisol measures were obtained from breast cancer survivors with persistent fatigue ($n=13$) and a control group of non-fatigued survivors ($n=16$). Participants collected saliva samples upon awakening and at 1200, 1700, and 2200 h on two consecutive days. Diurnal cortisol slope for each day was determined by linear regression of log-transformed cortisol values on collection time and analyzed using multi-level modeling. Fatigued breast cancer survivors had a significantly flatter cortisol slope than non-fatigued survivors, with a less rapid decline in cortisol levels in the evening hours. At the individual patient level, survivors who reported the highest levels of fatigue also had the flattest cortisol slopes. Group differences remained significant in analyses controlling for demographic and medical factors, daily health behaviors, and other potential confounds (e.g. depressed mood, body mass index). Results suggest a subtle dysregulation in

* Corresponding author. Address: University of California, 300 UCLA Medical Plaza, Room 3306, Box 957076, Los Angeles, CA 90095-7076, USA. Tel.: +310-794-9383; fax: +310-794-9247.
E-mail address: jbower@ucla.edu (J.E. Bower).

hypothalamic–pituitary–adrenal axis functioning in breast cancer survivors with persistent fatigue.

1. Introduction

With advances in detection and treatment, the number of women who survive breast cancer has increased significantly in recent years. Five-year survival rates have climbed to 86%, resulting in an estimated 2 million North American women living in the aftermath of breast cancer (Ries et al., 2003). In most instances, resection and adjuvant therapies cause little permanent impairment and breast cancer survivors enjoy continued health and well-being (Ganz et al., 1998a,b). However, approximately 30% of breast cancer survivors experience persistent fatigue of unknown origin (Lindley et al., 1998; Bower et al., 2000; Servaes et al., 2002). Although symptoms may wax and wane, breast cancer survivors exhibit clear differences from age-matched controls in the frequency and intensity of fatigue and the degree to which fatigue disrupts overall quality of life (Andrykowski et al., 1998; Broeckel et al., 1998).

The mechanisms that underlie post-treatment fatigue in cancer survivors have not yet been determined. Treatment modality is not consistently associated with fatigue in breast cancer survivors (Berglund et al., 1991; Andrykowski et al., 1998; Bower et al., 2000) and there is no indication that these women suffer from residual or recurrent disease. Fatigue is correlated with symptoms of depression, but cannot be explained entirely by mood disturbance (Visser and Smets, 1998; Bower et al., 2000). Although there is much speculation about the role of biological factors in cancer-related fatigue, the few studies to assess biological markers (e.g. hemoglobin, thyroid hormone) among cancer patients and survivors have found only limited evidence for a relationship with fatigue (e.g. Irvine et al., 1994; Knobel et al., 2001; Holzner et al., 2002).

Our research group has focused on the role of the immune system in cancer-related fatigue. This research is based on animal studies demonstrating that peripheral inflammatory stimuli can signal the central nervous system and cause changes in energy as well as sleep, appetite, social behavior, reproduction, and cognition (Maier and Watkins, 1998; Dantzer, 2001). We have previously shown that breast cancer survivors with persistent fatigue show elevations in serum markers of proinflammatory cytokine activity and T lymphocytes relative to non-fatigued survivors, suggesting a chronic inflammatory process (Bower et al., 2002, 2003). In addition, fatigued survivors report behavioral changes consistent with proinflammatory cytokine activity, including depressed mood, decreased social interest, and cognitive difficulties (Bower et al., 2002).

The basis for prolonged inflammatory processes in breast cancer survivors is unclear. One possibility is alterations in physiological systems that regulate immune system activity, such as the hypothalamic-pituitary-adrenal (HPA) axis. Adrenal cortex derived steroids have potent effects on immune cell development, maturation, trafficking, and cytokine production, including production of proinflammatory cytokines (McEwen et al., 1997). In our initial study, fatigued survivors had lower levels of morning serum cortisol than non-fatigued survivors, suggesting some disturbance in HPA axis functioning (Bower et al., 2002). Alterations in HPA activity have been observed in other conditions that involve primary complaints of fatigue, including chronic fatigue syndrome, fibromyalgia, rheumatoid arthritis, and depression (Neeck et al., 1990; Crofford et al., 1994; Deuschle et al., 1997; Catley et al., 2000), making this axis a reasonable candidate for further research.

In healthy individuals, cortisol levels typically peak before awakening then decrease over the course of the day (Posener et al., 1996). This diurnal rhythm is thought to be an important indicator of HPA competence (Sephton and Spiegel, 2003). Circadian patterns of cortisol secretion are altered in cancer patients with advanced disease (Touitou et al., 1995, 1996); indeed, a recent study found that flattened diurnal cortisol slopes were associated with decreased survival time among women with metastatic breast cancer (Sephton et al., 2000). Circadian rhythm disturbance, as assessed by alterations in sleep/activity patterns, has also been associated with symptoms of fatigue in breast cancer patients undergoing chemotherapy (Roscoe et al., 2002). The current study was designed to expand on our previous findings and investigate diurnal patterns of cortisol secretion in breast cancer survivors with persistent fatigue. We hypothesized that survivors who reported more pronounced fatigue would show a flattened diurnal