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Diurnal cortisol rhythm and fatigue in breast cancer survivors

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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

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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

cortisol slope relative to non-fatigued survivors, indicating a disturbance in diurnal cortisol rhythm.

2. Method

2.1. Participants

Participants were recruited from a large cohort of breast cancer survivors who participated in a survey study of quality of life between 1994 and 1997 (Ganz et al., 1998a,b). Women were eligible for participation in the original study if they met the following criteria: (1) had been diagnosed with early, resectable breast cancer (stage 0, I, or II at diagnosis); (2) were between 1 and 5 years after initial breast cancer diagnosis; (3) had completed local and/or systemic adjuvant cancer therapy; (4) were currently considered disease-free and were not receiving any cancer therapy other than tamoxifen; (5) had no history of other cancers, with the exception of non-invasive skin cancer and cervical cancer; (6) could read and write English; (7) could provide informed consent; and (8) had no other major disabling medical or psychiatric conditions that would confound evaluation of health-related quality of life.

From this nationwide cohort of 1957 survivors, we contacted 332 women who met our initial eligibility criteria and screened 132 responders for study eligibility. We identified a group of 20 women who reported enduring fatigue and a control group of 20 non-fatigued women to participate in a study on immune mechanisms of fatigue (Bower et al., 2002). Fatigue was assessed using the energy/fatigue subscale of the RAND SF-36 (Ware and Sherbourne, 1992; Hays et al., 1993). Scores on this scale range from 0 and 100, with scores below 50 indicating limitations or disability related to fatigue. Women were considered to be fatigued if they scored below 50 at the initial survey (1–5 years post-diagnosis) and at the immunological assessment (3–7 years post-diagnosis). Non-fatigued control group participants scored above 70 at both assessment points.

Approximately one year later, letters were sent to participants' homes describing the current study and inviting their participation. Women who expressed an interest in the study completed a telephone screening interview to determine eligibility. Exclusion criteria included: (1) breast cancer recurrence; (2) diagnosis with other cancers; (3) history of immunologically-mediated diseases (e.g. autoimmune disease); (4) regular use of immunosuppressive medication; (5)

severe psychological distress in last 6 months; and (6) heavy alcohol use (i.e. >15 alcoholic beverages per week) or substance use. The UCLA Institutional Review Board approved the study procedures, and written informed consent was obtained from all participants.

Of the 40 women in the original sample, two were no longer eligible (one had a cancer recurrence, one moved to another state) and four refused participation (1 fatigued, 3 non-fatigued). Thirty-four (85%) women agreed to participate; however, only 29 (73%) provided analyzable data (one subject never returned saliva samples, three subjects did not provide enough saliva for assessment purposes, and one did not take the samples at indicated times). This yielded a final sample of 13 fatigued and 16 control subjects.

Selected demographic and treatment-related characteristics of fatigued and non-fatigued participants are shown in Table 1. There were no significant differences between fatigued and non-fatigued groups in age, education, income, treatment type, number of years since diagnosis, or presence of other medical conditions (e.g. osteoarthritis, high blood pressure). Fatigued women were significantly less likely to be married or in a comitted relationship (χ^2 ($N = 29$) $= 7.6$, $p = 0.006$), consistent with our previous

Table 1 Demographic and medical characteristics of study participants.

Characteristic	Fatigued BCS	Non-fatigued BCS
Age (mean$\pm$SD)	58.2$\pm$7.3	61.8$\pm$9.2
Ethnicity (N)[†]		
White	13	13
Black	0	1
Asian	0	2
Married or in committed relationship (N)*		
Yes	5	14
No	8	2
Type of cancer treatment (N)		
Surgery only	3	6
Surgery+radiation	6	4
Surgery+ chemotherapy	3	1
Surgery+ radiation+ chemotherapy	1	5
Tamoxifen use (N)	8	7
Years since diagnosis (mean$\pm$SD)	6.8$\pm$0.7	6.3$\pm$1.0

*$p < 0.01$; [†]$p = 0.10$.

reports (Bower et al., 2000, 2002). In addition, there was a marginally significant difference in ethnicity (χ^2 ($N=29$)$=2.7$, $p=0.10$); the three non-White women were all in the non-fatigued group.

2.2. Procedure

Participants collected saliva samples at home using cotton swabs, or 'Salivettes' (Sarstedt, Inc.). Salivary cortisol provides an accurate index of free plasma cortisol (Kirschbaum and Hellhammer, 1989). Subjects were instructed to collect samples upon awakening (though not while still in bed) and at noon (1200 h), 5 p.m. (1700 h), and 10 p.m. (2200 h) for two consecutive days. Subjects were provided with preprogrammed wrist watches which signaled post-waking collection times with an electronic beep, and the importance of collecting samples at designated times was emphasized. Subjects were instructed not to eat, drink, or brush their teeth for at least 15 min before sampling and to refrain from smoking one hour before sample collection (for the one smoker in the study). Self-report questionnaires were also administered on each collection day.

Subjects stored samples in the refrigerator until both collection days were completed and then returned the samples via an express mail delivery service. All samples were received by the laboratory within 2–4 days of collection, and then frozen at −70 °C. Internal studies conducted by our laboratory have shown that saliva samples can be stored at room temperature for at least 7 days with no changes in salivary cortisol values, consistent with findings from other laboratories (Kirschbaum and Hellhammer, 1989).

2.3. Measures

Salivary cortisol. Cortisol levels were assessed by enzyme immunoassay (Salimetrics, State College, PA). This assay has a lower detection limit of 7 ng/dl. The mean intra-assay coefficient was 5.7% (range: 3.9–7.5%) and the mean inter-assay coefficient was 10% (range: 9–11%). All samples from a participant were analyzed in the same assay to minimize variability. Two extreme cortisol values (>950 ng/dl in post-waking samples) were deleted from the data set before analysis.

Examination of individual cortisol levels indicated that 86% ($n=25$) of subjects showed a steady decline in cortisol levels on each collection day, with the most pronounced decline seen between the waking and 1200 h collection.

Two subjects (both non-fatigued) showed a delayed peak at 1200 h on one day of collection, and two subjects (both fatigued) showed a large increase ($>50\%$ of waking value) at 2200 h on one day of collection.

Biobehavioral variables. The energy/fatigue subscale of the RAND SF-36 (Ware and Sherbourne, 1992; Hays et al., 1993) was used to assess fatigue at the time of saliva collection. This measure has excellent reliability and validity and was completed by all study subjects at two prior assessments. Higher scores on this scale indicate higher levels of energy/lower levels of fatigue. Daily health behaviors that may influence cortisol levels were assessed using a brief questionnaire developed by Sephton and colleagues (2000). This measure includes questions about physical activity, stress, pain, sleep quality, and consumption of protein, fat, sugar, alcohol, and caffeine on each sampling day. Medical factors, including type of treatment received (surgery alone, radiation therapy and/or chemotherapy, tamoxifen) and time since diagnosis, were determined from questionnaires completed in the original survey study.

2.4. Statistical analyses

The slope of the diurnal change in cortisol levels was calculated by regressing cortisol values on time of day for each collection day. Smaller slope values reflect more rapid declines in cortisol levels, whereas larger slope values (closer to zero) reflect flatter diurnal rhythms. Because raw cortisol values are typically skewed, the data were log transformed before slopes were calculated, consistent with previous research (e.g. Smyth et al., 1997; Sephton et al., 2000; Catley et al., 2000). Slopes were not calculated for days on which more than one assessment point was missed ($n=1$ day). In addition, slopes were not calculated for days on which subjects reported acute medical problems (i.e. allergy attack; $n=1$ day). Mean cortisol levels for each sampling day were calculated using the log-transformed cortisol values. Area under the curve (AUC) on each sampling day was calculated by trapezoidal estimation using log-transformed cortisol values.

Analyses were conducted using multi-level modeling (HLM 5.02; Raudenbush et al., 2000). This approach accounts for the hierarchical nature of the data (Schwartz and Stone, 1998), in which two days of cortisol collection were nested within each participant. The study was a two-level design; the key outcome measure, cortisol slope, was

a within-subjects (level-1) outcome variable. Mean cortisol level and AUC were also assessed as level-1 outcomes. The key predictor measure, fatigue group, was a between-subjects (level-2) variable, as were the biobehavioral variables.

Analyses were first conducted to determine whether any of the potential confounding variables (i.e. health behaviors, medical factors) were significant predictors of cortisol slope. Next, the primary analyses examined whether fatigue group was a significant predictor of cortisol slope, controlling for relevant confounds. Analyses also examined whether fatigue group was a significant predictor of mean cortisol and AUC. Finally, to identify when aberrations in the diurnal rhythm may have occurred, analyses were conducted with cortisol samples at each collection point (e.g. 2200 h sample) as the outcome measure, again controlling for relevant controls. Regression coefficients were estimated using restricted maximum-likelihood and robust standard errors to adjust for non-normality of the data.

3. Results

As expected, women classified as fatigued at the initial assessments continued to report higher levels of fatigue at time of saliva collection. Mean scores on the energy/fatigue subscale of the SF-36 were 52.7 (SD=15.1) for fatigued women and 80.3 (SD=11.5) for non-fatigued women (recall that lower scores on this scale indicate less energy and greater fatigue). Current fatigue was highly correlated with fatigue at the original survey ($r=0.75$, $p<0.0001$) and at the immunological assessment ($r=0.80$, $p<0.0001$), indicating that this behavioral state was consistent across assessment points.

Analyses were first conducted to identify biobehavioral variables associated with cortisol slope, including daily health behaviors (i.e. daily physical activity, stress, pain, sleep quality, and daily consumption of protein, fat, carbohydrate, sugar, alcohol, and caffeine) and treatment-related factors (i.e. time from diagnosis, type of cancer treatment). Only time from diagnosis and consumption of sugar significantly predicted cortisol slope ($B=-0.0026$ (0.00095), $t(27)=-2.69$, $p=0.012$; $B=-0.0031$ (0.0013), $t(27)=-2.34$, $p=0.027$, respectively). Thus, these variables were included as controls in all analyses.

Fatigued breast cancer survivors had significantly flatter cortisol slopes than non-fatigued survivors, $B=0.092$ (0.036), $t(25)=2.57$, $p<0.018$ (mean slope for fatigued group$=-0.0014$,
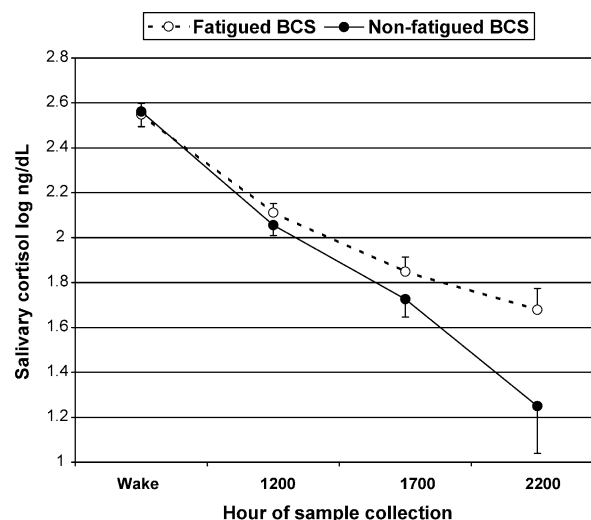

Figure 1 Means of log-transformed salivary cortisol values at four times of day for fatigued and non-fatigued breast cancer survivors. Fatigued survivors had significantly flatter cortisol slopes than non-fatigued survivors, with a significant elevation in cortisol levels at 2200 h.

SD=0.0006; mean slope for non-fatigued group$=-0.0021$, SD=0.0013). For illustrative purposes, mean levels of log-transformed cortisol at each assessment point in fatigued and non-fatigued BCS are shown in Fig. 1. Approximately 25% of the between-person variation in slope could be accounted for by fatigue group. In addition, fatigue severity showed a linear association with cortisol slope, such that higher levels of current fatigue were associated with flatter slope values, $B=-0.0023$ (0.00095), $t(25)=-2.44$, $p=0.022$. Mean daily cortisol levels and AUC did not differ between the two fatigue groups ($B=8.02$ (23.84), $t(25)=0.34$, $p=0.73$; $B=12244.19$ (24086.52), $t(24)=0.51$ $p=0.62$, respectively). To rule out the possibility that group differences in cortisol slope were driven by the few days with aberrant cortisol rhythms ($n=4$ days), analyses were conducted excluding those collection days and showed the same pattern of results.

Additional analyses were conducted to control for depressed mood, which is elevated in these fatigued survivors (Bower et al., 2000, 2002) and may be associated with alterations in HPA axis function (Deuschle et al., 1997). We also controlled for demographic and physical factors on which the fatigued and non-fatigued groups differed, including body mass index, marital status, and ethnicity. None of these factors (including depressed mood) was independently associated with cortisol slope, and controlling for these factors did not influence the association between fatigue and cortisol slope.

Flattened cortisol slopes may reflect slower declines, abnormal elevations in afternoon or evening cortisol levels, and/or to a lack of peaks throughout the day (Sephton et al., 2000). We conducted follow-up analyses to better characterize the rhythm alterations observed in this sample. Comparison of individual collection points revealed that the fatigued women had significantly higher cortisol levels at the 2200 h assessment compared to non-fatigued women ($B = 0.62$ (0.23), $t(24) = 2.63$, $p = 0.015$), and marginally significantly higher cortisol levels at the 1700 h assessment ($B = 0.18$ (0.10), $t(25) = 1.82$, $p = 0.081$), as shown in Fig. 1. There were no significant differences between groups at waking or 1200 h ($p > 0.20$). Overall, this pattern of results suggests that the 'flatter' cortisol slope in fatigued survivors was due primarily to a slower decline in cortisol levels from morning to evening.

4. Discussion

This study examined the hypothesis that breast cancer survivors with persistent fatigue would show alterations in diurnal cortisol rhythms. As predicted, we found that fatigued breast cancer survivors had a significantly flatter cortisol slope than non-fatigued survivors, with a less rapid decline in cortisol in the evening hours. Higher levels of fatigue were associated with flatter slope, suggesting a linear association between symptom severity and disturbance in diurnal cortisol secretion. The difference in cortisol slope could not be accounted for by health behaviors during the time of cortisol collection, demographic or treatment-related factors, or other potential confounds such as body mass index and depressed mood. We found no association between mean cortisol levels or area under the curve and fatigue, highlighting the importance of cortisol slope rather than average or total daily cortisol as a correlate of fatigue.

Previous studies have examined HPA axis function in disorders characterized by fatigue, including chronic fatigue syndrome, vital exhaustion, depression, fibromyalgia, and rheumatoid arthritis. There is some evidence of cortisol rhythm alterations in these disorders, including flattening of diurnal slope and altered evening levels (McCain and Tilbe, 1989; Neeck et al., 1990; MacHale et al., 1998; Nicolson and van Diest, 2000; though see Catley et al., 2000; Gaab et al., 2002). To our knowledge, this is the first study to show an association between diurnal cortisol rhythm and fatigue in breast cancer survivors. These findings

add to our previous research suggesting alterations in HPA axis function among BCS with persistent fatigue (Bower et al., 2002). In contrast to our earlier results, we did not find differences in morning cortisol levels in this study; instead, fatigued women showed elevated cortisol levels in the evening hours compared to non-fatigued participants. This difference may be attributable to differences in the timing and other characteristics of sample collection (e.g. length of fasting prior to collection, saliva vs. blood).

How might alterations in circadian cortisol patterns be linked to symptoms of fatigue? Diurnal changes in cortisol are known to modulate the number and function of immune cells in peripheral blood (Kronfol et al., 1997), and flattened cortisol rhythms have been associated with disturbances in immune function (e.g. suppression of natural killer cell function) among breast cancer patients (Touitou et al., 1996; Sephton et al., 2000). Alterations in cortisol rhythms may also disrupt the suppressive effects of cortisol on proinflammatory cytokine production (Petrovsky et al., 1998), potentially leading to elevations in circulating cytokines and subsequent increases in fatigue. Of note, there is evidence that disruptions in circadian rhythm may be more relevant for immune status than total cortisol output (Sephton et al., 2000), perhaps because rhythm alterations indicate a loss of regulatory competence (Sephton and Spiegel, 2003).

On the other hand, it is possible that chronic inflammatory processes and associated behavioral symptoms might drive changes in cortisol rhythm. For example, daytime fatigue may disrupt the evening cortisol decline via changes in circadian rest and activity patterns (Roscoe et al., 2002). Further, if alterations in cortisol rhythm and other circadian patterns interfere with sleep (Vgontzas and Chrousos, 2002), this may trigger next-day elevations in proinflammatory cytokines and fatigue (Vgontzas et al., 1999, 2002; Irwin, 2002), creating a positive feedback loop. Our current research is examining fatigue, diurnal cortisol rhythms, proinflammatory cytokines, rest/activity patterns, and sleep in breast cancer survivors and will provide a more comprehensive picture of the complex inter-relationships among these variables.

Other factors that may influence cortisol slope in breast cancer survivors include cancer-related stressors, such as persistent fear of recurrence (Spencer et al., 1999; Vickberg, 2003); previous studies have shown a flattening of cortisol rhythm and elevated evening cortisol levels among individuals undergoing chronic stress (Grossi et al., 2001; Powell et al., 2002). Disturbances in cortisol

rhythms have also been observed in cancer patients with advanced disease (Touitou et al., 1995, 1996). However, given that the women in this sample were initially diagnosed with early-stage cancer and showed no evidence of recurrence or progression, it seems unlikely that diurnal rhythm changes were associated with disease activity. Instead, alterations in cortisol slope may have predated the cancer diagnosis, as a substantial proportion of healthy individuals show flattened cortisol rhythms (Smyth et al., 1997; Stone et al., 2001). Differences in cortisol slope may also be related to waking time; if fatigued women woke up later than controls, the evening decrease in cortisol level may have been delayed.

The primary limitation of this study is the small sample size, as we choose to restrict participation to a small, well-characterized sample of breast cancer survivors. Findings require replication in a larger group of patients. Another potential limitation is the reliance on self-report for timing of sample collection, as a recent study suggests that participants may not be compliant with saliva collection procedures and that off-time assessments may bias slope calculations (Kudielka et al., 2003). However, this effect appears to be most pronounced for samples collected 30 min post-awakening, which were not included in the current study. In addition, watches were provided to cue sample times and compliance with the collection schedule was strongly emphasized.

The findings presented here suggest a subtle dysregulation in HPA axis function among breast cancer survivors with persistent fatigue. Whether these changes are a cause or consequence of behavioral and immunological alterations in fatigued survivors is an important topic for future research. Currently, cancer survivors who experience fatigue and their physicians have little understanding of this symptom and thus, limited options for treatment. Insight into physiological mechanisms underlying fatigue is critical for developing appropriate interventions to improve energy and overall quality of life in the growing population of cancer survivors.

Acknowledgements

References

Andrykowski, M.A., Curran, S.L., Lightner, R., 1998. Off-treatment fatigue in breast cancer survivors: a controlled comparison. J. Behav. Med. 21, 1–18.

Berglund, G., Bolund, C., Fornander, T., Rutqvist, L.E., Sjoden, P.O., 1991. Late effects of adjuvant chemotherapy and postoperative radiotherapy on quality of life among breast cancer patients. Eur. J. Cancer 27, 1075–1081.

Bower, J.E., Ganz, P.A., Desmond, K.A., Rowland, J.H., Meyerowitz, B.E., Belin, T.R., 2000. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J. Clin. Oncol. 18, 743–753.

Bower, J.E., Ganz, P.A., Aziz, N., Fahey, J.L., 2002. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom. Med. 64, 604–611.

Bower, J.E., Ganz, P.A., Aziz, N., Fahey, J.L., Cole, S.W., 2003. T-cell homeostasis in breast cancer survivors with persistent fatigue. J. Natl. Cancer Inst. 95, 1165–1168.

Broeckel, J.A., Jacobsen, P.B., Horton, J., Balducci, L., Lyman, G.H., 1998. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J. Clin. Oncol. 16, 1689–1696.

Catley, D., Kaell, A.T., Kirschbaum, C., Stone, A.A., 2000. A naturalistic evaluation of cortisol secretion in persons with fibromyalgia and rheumatoid arthritis. Arthritis Care Res. 13, 51–61.

Crofford, L.J., Pillemer, S.R., Kalogeras, K.T., Cash, J.M., Michelson, D., Kling, M.A., Sternberg, E.M., Gold, P.W., Chrousos, G.P., Wilder, R.L., 1994. Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. Arthritis Rheum. 37, 1583–1592.

Dantzer, R., 2001. Cytokine-induced sickness behavior: mechanisms and implications. Ann. N.Y. Acad. Sci. 933, 222–234.

Deuschle, M., Schweiger, U., Weber, B., Gotthardt, U., Korner, A., Schmider, J., Standhardt, H., Lammers, C.H., Heuser, I., 1997. Diurnal activity and pulsatility of the hypothalamus-pituitary-adrenal system in male depressed patients and healthy controls. J. Clin. Endocrinol. Metab. 82, 234–238.

Gaab, J., Huster, D., Peisen, R., Engert, V., Schad, T., Schurmeyer, T.H., Ehlert, U., 2002. Low-dose dexamethasone suppression test in chronic fatigue syndrome and health. Psychosom. Med. 64, 311–318.

Ganz, P.A., Rowland, J.H., Desmond, K., Meyerowitz, B.E., Wyatt, G.E., 1998a. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J. Clin. Oncol. 16, 501–514.

Ganz, P.A., Rowland, J.H., Meyerowitz, B.E., Desmond, K.A., 1998b. Impact of different adjuvant therapy strategies on quality of life in breast cancer survivors. Recent Results Cancer Res. 152, 396–411.

Grossi, G., Perski, A., Lundberg, U., Soares, J., 2001. Associations between financial strain and the diurnal salivary cortisol secretion of long-term unemployed individuals. Integr. Physiol. Behav. Sci. 36, 205–219.

Hays, R.D., Sherbourne, C.D., Mazel, R.M., 1993. The RAND 36-Item Health Survey 1.0. Health Econ. 2, 217–227.

Holzner, B., Kemmler, G., Greil, R., Kopp, M., Zeimet, A., Raderer, M., Hejna, M., Zochbauer, S., Krajnik, G., Huber, H., Fleischhacker, W.W., Sperner-Unterweger, B., 2002. The impact of hemoglobin levels on fatigue and quality of life in cancer patients. Ann. Oncol. 13, 965-973.

Irvine, D., Vincent, L., Graydon, J.E., Bubela, N., Thompson, L., 1994. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. A comparison with the fatigue experienced by healthy individuals. Cancer Nurs. 17, 367-378.

Irwin, M., 2002. Effects of sleep and sleep loss on immunity and cytokines. Brain Behav. Immun. 16, 503-512.

Kirschbaum, C., Hellhammer, D.H., 1989. Salivary cortisol in psychobiological research: an overview. Neuropsychobiology 22, 150-169.

Knobel, H., Havard, L.J., Brit, L.M., Forfang, K., Nome, O., Kaasa, S., 2001. Late medical complications and fatigue in Hodgkin's disease survivors. J. Clin. Oncol. 19, 3226-3233.

Kronfol, Z., Nair, M., Zhang, Q., Hill, E.E., Brown, M.B., 1997. Circadian immune measures in healthy volunteers: relationship to hypothalamic–pituitary–adrenal axis hormones and sympathetic neurotransmitters. Psychosom. Med. 59, 42-50.

Kudielka, B.M., Broderick, J.E., Kirschbaum, C., 2003. Compliance with saliva sampling protocols: electronic monitoring reveals invalid cortisol daytime profiles in noncompliant subjects. Psychosom. Med. 65, 313-319.

Lindley, C., Vasa, S., Sawyer, W.T., Winer, E.P., 1998. Quality of life and preferences for treatment following systemic adjuvant therapy for early-stage breast cancer. J. Clin. Oncol. 16, 1380-1387.

MacHale, S.M., Cavanagh, J.T., Bennie, J., Carroll, S., Goodwin, G.M., Lawrie, S.M., 1998. Diurnal variation of adrenocortical activity in chronic fatigue syndrome. Neuropsychobiology 38, 213-217.

Maier, S.F., Watkins, L.R., 1998. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol. Rev. 105, 83-107.

McCain, G.A., Tilbe, K.S., 1989. Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis. J. Rheumatol. Suppl. 19, 154-157.

McEwen, B.S., Biron, C.A., Brunson, K.W., Bulloch, K., Chambers, W.H., Dhabhar, F.S., Goldfarb, R.H., Kitson, R.P., Miller, A.H., Spencer, R.L., Weiss, J.M., 1997. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. Brain Res. Brain Res. Rev. 23, 79-133.

Neeck, G., Federlin, K., Graef, V., Rusch, D., Schmidt, K.L., 1990. Adrenal secretion of cortisol in patients with rheumatoid arthritis. J. Rheumatol. 17, 24-29.

Nicolson, N.A., van Diest, R., 2000. Salivary cortisol patterns in vital exhaustion. J. Psychosom. Res. 49, 335-342.

Petrovsky, N., McNair, P., Harrison, L.C., 1998. Diurnal rhythms of pro-inflammatory cytokines: regulation by plasma cortisol and therapeutic implications. Cytokine 10, 307-312.

Posener, J.A., Schildkraut, J.J., Samson, J.A., Schatzberg, A.F., 1996. Diurnal variation of plasma cortisol and homovanillic acid in healthy subjects. Psychoneuroendocrinology 21, 33-38.

Powell, L.H., Lovallo, W.R., Matthews, K.A., Meyer, P., Midgley, A.R., Baum, A., Stone, A.A., Underwood, L.,

McCann, J.J., Janikula, H.K., Ory, M.G., 2002. Physiologic markers of chronic stress in premenopausal, middle-aged women. Psychosom. Med. 64, 502-509.

Raudenbush, S.W., Byrk, A.S., Congdon, R.T., 2000. HLM Version 5.02. Scientific Software, Chicago.

Ries, L.A.G, Eisner, M.P., Kosary, C.L., Hankey, B.F., Miller, B.A., Clegg, L., Mariotto, A., Fay, M.P., Feuer, E.J., Edwards, B.K. (Eds.), 2003. SEER Cancer Statistics Review, 1975-2000. National Cancer Institute, Bethesda, MD.

Roscoe, J.A., Morrow, G.R., Hickok, J.T., Bushunow, P., Matteson, S., Rakita, D., Andrews, P.L., 2002. Temporal interrelationships among fatigue, circadian rhythm and depression in breast cancer patients undergoing chemotherapy treatment. Support. Care Cancer 10, 329-336.

Schwartz, J.E., Stone, A.A., 1998. Strategies for analyzing ecological momentary assessment data. Health Psychol. 17, 6-16.

Sephton, S., Spiegel, D., 2003. Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease?. Brain Behav. Immun. 17, 321-328.

Sephton, S.E., Sapolsky, R.M., Kraemer, H.C., Spiegel, D., 2000. Diurnal cortisol rhythm as a predictor of breast cancer survival. J. Natl. Cancer Inst. 92, 994-1000.

Servaes, P., Verhagen, S., Bleijenberg, G., 2002. Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. Ann. Oncol. 13, 589-598.

Smyth, J.M., Ockenfels, M.C., Gorin, A.A., Catley, D., Porter, L.S., Kirschbaum, C., Hellhammer, D.H., Stone, A.A., 1997. Individual differences in the diurnal cycle of cortisol. Psychoneuroendocrinology 22, 89-105.

Spencer, S.M., Lehman, J.M., Wynings, C., Arena, P., Carver, C.S., Antoni, M.H., Derhagopian, R.P., Ironson, G., Love, N., 1999. Concerns about breast cancer and relations to psychosocial well-being in a multiethnic sample of early-stage patients. Health Psychol. 18, 159-168.

Stone, A.A., Schwartz, J.E., Smyth, J., Kirschbaum, C., Cohen, S., Hellhammer, D., Grossman, S., 2001. Individual differences in the diurnal cycle of salivary free cortisol: a replication of flattened cycles for some individuals. Psychoneuroendocrinology 26, 295-306.

Touitou, Y., Levi, F., Bogdan, A., Benavides, M., Bailleul, F., Misset, J.L., 1995. Rhythm alteration in patients with metastatic breast cancer and poor prognostic factors. J. Cancer Res. Clin. Oncol. 121, 181-188.

Touitou, Y., Bogdan, A., Levi, F., Benavides, M., Auzeby, A., 1996. Disruption of the circadian patterns of serum cortisol in breast and ovarian cancer patients: relationships with tumour marker antigens. Br. J. Cancer 74, 1248-1252.

Vgontzas, A.N., Chrousos, G.P., 2002. Sleep, the hypothalamic–pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. Endocrinol. Metab. Clin. North Am. 31, 15-36.

Vgontzas, A.N., Papanicolaou, D.A., Bixler, E.O., Lotsikas, A., Zachman, K., Kales, A., Prolo, P., Wong, M.L., Licinio, J., Gold, P.W., Hermida, R.C., Mastorakos, G., Chrousos, G.P., 1999. Circadian interleukin-6 secretion and quantity and depth of sleep. J. Clin. Endocrinol. Metab. 84, 2603-2607.

Vgontzas, A.N., Zoumakis, M., Papanicolaou, D.A., Bixler, E.O., Prolo, P., Lin, H.M., Vela-Bueno, A., Kales, A., Chrousos, G.P., 2002. Chronic insomnia is

associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. Metabolism 51, 887–892.

Vickberg, S.M., 2003. The concerns about recurrence scale (CARS): a systematic measure of women's fears about the possibility of breast cancer recurrence. Ann. Behav. Med. 25, 16–24.

Visser, M.R., Smets, E.M., 1998. Fatigue, depression and quality of life in cancer patients: how are they related?. Support. Care Cancer 6, 101–108.

Ware Jr., J.E., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care 30, 473–483.