



Short communication

Diurnal cortisol rhythms, fatigue and psychosocial factors in five-year survivors of ovarian cancer



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ABSTRACT

Fatigue is a challenge in ovarian cancer survivorship and greatly impacts quality of life. In other cancer populations, fatigue has been associated with abnormal diurnal cortisol patterns. However, little is known about biological and behavioral factors in 5+ -year ovarian cancer survivors and potential mechanisms underlying persistent fatigue have not been investigated in this population. Moreover, relationships between neuroendocrine and psychosocial factors in 5+ -year ovarian cancer survivors have not been studied. We addressed these issues by examining relationships between diurnal cortisol rhythms, fatigue, life stress, and social support in 30 survivors of ovarian cancer who were assessed at least 5 years (mean = 6.20 years) following their primary diagnosis. Flatter diurnal cortisol slopes were associated with higher levels of fatigue, suggesting a role for HPA-axis dysregulation in sustained fatigue experienced by survivors. Moreover, greater cumulative lifetime stressor exposure ($p = 0.023$) and stressor severity ($p = 0.004$) were associated with flatter diurnal cortisol slopes, while higher social attachment ($p = 0.001$) was associated with steeper diurnal cortisol slopes. These findings suggest that ovarian cancer survivors with greater lifetime stress exposure or lower social attachment may be at increased risk for circadian rhythm disruption, which in turn is associated with fatigue. Future research should examine relationships of clinical stage and inflammatory cytokines to cortisol rhythms and fatigue in long-term ovarian cancer survivors, as well as investigating the clinical significance of abnormal diurnal cortisol profiles in this population.

1. Introduction

Ovarian cancer has the highest mortality rate among gynecologic cancers, with an overall 5-year survival rate of 46%. This rate drops to 29% for patients with advanced stage disease, the stage at which most

women are diagnosed (American Cancer Society, 2017). Fatigue is a major threat to quality of life in cancer survivorship and 22% percent of ovarian cancer survivors report chronic fatigue and physical disability (Liavaag et al., 2007). In breast cancer survivors, flattened diurnal cortisol profiles have been associated with fatigue (Bower et al., 2005).

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However, neuroendocrine data on 5+ -year survivors of ovarian cancer is rare, and potential mechanisms underlying persistent fatigue have not been investigated in this population. The object of this study was to examine diurnal cortisol profiles and fatigue in women with ovarian cancer who had survived for at least 5 years.

Cortisol is a multifunctional glucocorticoid hormone released by the hypothalamic-pituitary-adrenal (HPA) axis. In healthy individuals, cortisol secretion follows a diurnal rhythm that peaks in the morning, declines throughout the day, and reaches a nadir at night. However, under conditions of chronic inflammation and/or stress, HPA feedback mechanisms can become compromised, resulting in a dysregulated (e.g., “flattened”) diurnal cortisol rhythm (Silverman and Sternberg, 2012).

At the time of ovarian cancer diagnosis, flatter diurnal cortisol rhythms are common and have been associated with higher levels of fatigue (Weinrib et al., 2010). Following 6 months of primary treatment/chemotherapy, improvements in fatigue are paralleled by a normalization in diurnal cortisol that is maintained at one year post-diagnosis (Schrepf et al., 2013). Among breast cancer survivors, flatter diurnal cortisol rhythms have been associated with fatigue severity, possibly due to sustained inflammatory activity (Bower et al., 2005).

Psychosocial factors like life stress and social support have been shown to influence diurnal cortisol in both healthy and cancer populations. For example, chronic stress is associated with flatter diurnal cortisol rhythms in healthy adults (Barker et al., 2012), while social support and social integration are associated with steeper diurnal cortisol profiles in healthy adults (Friedman et al., 2012) and in breast cancer patients (Abercrombie et al., 2004). The potential influence of psychosocial factors on the diurnal cortisol rhythms of ovarian cancer survivors has not been investigated.

To examine these relationships, we recruited a cohort of ovarian cancer survivors at 5+ years post-diagnosis and examined their levels of cumulative lifetime stress exposure, social attachment, and diurnal cortisol levels. We hypothesized that flatter diurnal cortisol rhythms would be associated with greater fatigue severity. We also hypothesized that greater lifetime stress exposure and lower levels of social attachment would be associated with flatter diurnal cortisol slopes.

2. Materials and methods

2.1. Participants

Women with primary invasive epithelial ovarian cancer who participated in a prospective study examining biobehavioral factors and tumor progression at a large Midwestern university hospital were re-contacted at least 5 years post-surgery. Exclusion criteria at the time of initial recruitment were: age under 18 years, history of previous cancer or comorbid condition with known immune system effects, current pregnancy, inability to accurately answer questions (dementia), and non-ovarian primary tumor site. From the original sample of 158 women recruited at the time of surgery, 54 were known to have survived for at least five years, were alive in 2013 when this follow-up began, and had known contact information. Eligible patients were re-contacted via phone; 12 were unreachable or declined due to lack of interest and 42 completed new informed consents and agreed to study procedures. Forty participants returned psychosocial packets, 33 returned salivettes, and 25 completed a structured lifetime stress interview via phone. Patients receiving chemotherapy at the 5+ -year time-point ($N = 2$) were excluded from analyses due to potentially confounding effects of chemotherapy on cortisol levels and symptoms. Participants possessing cortisol values ≥ 4 SD from the mean at any time-point were also excluded ($N = 1$). The final sample included all patients ($N = 30$) that completed the cortisol assessment at 5+ years and were not receiving chemotherapy. Laboratory salivary cortisol values obtained previously from 33 healthy women (mean age 51.9 ± 15.4 years) with no inflammatory conditions were used as a reference standard for normative cortisol levels (Weinrib et al., 2010). A subset of patients had psychosocial data on fatigue and

social attachment available at the time of surgery ($N = 27$ and 29 , respectively). We used data from these participants to examine the stability of fatigue and social attachment between the time of surgery to the 5+ -year time-point. The Institutional Review Board approved all procedures.

2.2. Assessments

2.2.1. Fatigue

The Profile of Mood States-Short Form (POMS-SF) is a 37-item self-report scale assessing mood over the past week, with subscales for fatigue, anxiety, dysphoria, anger, vigor and confusion (Shacham, 1983). The fatigue subscale was utilized in this study. This subscale asks participants to rate statements describing fatigue (e.g. “Exhausted,” “Fatigued”) on a five point Likert scale ranging from 0 (“not at all”) to 4 (“extremely”). The maximum score that could be achieved on this scale is 20. For the purposes of this study, participants who endorsed at least 10 out of 20 possible points on the POMS-SF fatigue subscale, indicating “moderate” to “extreme” fatigue on at least 4 out of 5 items, were qualitatively classified as experiencing moderate to extreme fatigue.

2.2.2. Cumulative lifetime stress exposure

The Stress and Adversity Inventory (STRAIN) is an assessment administered online or by an interviewer, and measures a person’s lifetime exposure to 96 different types of stressors (e.g., work, health, relationship, financial, legal/crime, accidents, deaths) that affect health. It has been validated in cancer populations (Bower et al., 2014). The outcomes of interest were summary variables representing the total count and severity of both acute and chronic stressors experienced across the lifetime.

2.2.3. Social attachment

The Social Provisions Scale (SPS) is a 24-item self-report scale measuring the extent to which social relationships are perceived as supportive (Cutrona and Russell, 1987). The SPS provides a measure of total social support in addition to six subscales. Here, we examined social attachment, a facet of social support encompassing emotional closeness and connectedness. We chose to examine social attachment, as opposed to other facets of social relationship support (e.g. instrumental social support), because social attachment has been most linked to biological processes in previous research (Lutgendorf et al., 2012).

2.2.4. Salivary cortisol

Patients collected cortisol with salivettes upon awakening, at 5 p.m., and at bedtime for three consecutive days. Samples were analyzed at the Technical University of Dresden using a commercial chemiluminescence immunoassay (IBL, Hamburg, Germany) with a lower detection limit of 0.41 n mol/L. Inter-assay and intra-assay coefficients of variance were less than 10%.

2.3. Statistical analyses

The Statistical Package for the Social Sciences (V.23, Armonk, NY) was used for data analysis. Distributions were examined for violations of normality and potential outliers. Cortisol values were natural log-transformed to normalize their distribution. Diurnal cortisol slope was calculated as previously described (Schrepf et al., 2013). Three participants missing afternoon cortisol values had slopes calculated from morning and bedtime samples, an approach consistent with recommendations from Kraemer et al. (2006) indicating slopes calculated from two daily values (morning and night) are as accurately representative of diurnal slope as those calculated from three daily values.¹ General linear models (GLM)s adjusting for age were used to

¹ In the entire sample, slopes calculated from morning and bedtime values were virtually identical to those calculated from three daily values ($r = 0.985$, $p < .0001$).

Table 1
Participant Characteristics.

Characteristic	Ovarian Cancer Survivors (N = 30)
Age, Mean (SD)	63.17 years (13.0)
Survival time, Mean (range)	6.2 years (4.9–9.2)
Ethnicity/Race	N (Percent)
Caucasian, Non-Hispanic	30 (100%)
Cancer Stage	
Early	18 (60.0%)
Advanced	12 (40.0%)
Cancer Grade	
Low	10 (33.3%)
High	20 (66.7%)
Cancer Recurrence	
Yes	7 (23.3%)
No	23 (76.7%)
Histology	
Serous	15 (50.0%)
Endometrioid	8 (26.7%)
Mucinous	4 (13.3%)
Clear Cell	3 (10.0%)
Psychosocial Measures, Mean (SD; range)	
POMS: Fatigue Subscale	7.23 (5.4; 0.0–19.0)
SPS: Attachment Subscale	14.23 (2.4; 7.0–16.0)
Stress and Adversity Inventory	
Total Stressors Count	22.5 (10.5; 10.0–50.0)
Total Stressors Severity	55.17 (25.1; 27.0–119.0)

compare cortisol values of 5+ -year survivors (morning, afternoon, night, and slope) to previously obtained reference values.

GLMs controlling *a priori* for disease stage and age were used to examine relationships between fatigue, psychosocial variables, and diurnal cortisol slope. Diurnal cortisol slope was used as the dependent measure in these analyses, as it is thought to indicate overall HPA-axis function (Bower et al., 2005; Silverman and Sternberg, 2012).

3. Results

3.1. Participant characteristics

Ovarian cancer survivors (12 advanced stage, 18 early stage) had a mean age of 63.2 years (range 38.9–93.0). Mean survival time since diagnosis was 6.2 years (range 4.9–9.2). Seven survivors (23.3%) had a disease recurrence (see Table 1). Participants did not differ significantly from those who were unable to be reached or declined to participate (N = 24) on age, stage, ethnicity, race, or tumor histology; however, a significantly larger proportion of those who were unable to be reached or declined to participate had high grade tumors (see Supplemental Table 1). Neither cancer stage nor patient age was significantly related to diurnal cortisol slope or to cortisol at any time-point (all *p*-values > 0.062) but as a conservative measure analyses adjusted for these covariates. Diurnal cortisol slopes of 5+ -year ovarian cancer survivors did not significantly differ from healthy female reference values (Weinrib et al., 2010), adjusting for age, $F(1,60) = 1.57$, $p = 0.22$. The values of both fatigue and social attachment were highly correlated between the time of surgery and 5+ years ($r = 0.515$, $p = 0.006$, $r = 0.732$, $p < 0.001$; respectively), indicating stability of these measures over time.

3.2. Diurnal cortisol rhythms and fatigue in 5+ -year survivors

Nine out of 30 participants (30%) endorsed at least 10 out of 20 possible points on the POMS-SF fatigue subscale, indicating “moderate” to “extreme” fatigue on at least 4 out of 5 items (means and SDs are in Table 1). Ovarian cancer survivors with flatter diurnal cortisol slopes

had significantly higher levels of fatigue in a model controlling for age and stage ($\beta = 0.57$, $p = 0.002$). For illustrative purposes, diurnal cortisol levels for survivors with low versus moderate to extreme fatigue ratings are shown in Fig. 1.

3.3. Psychosocial predictors of diurnal cortisol in 5+ -year survivors

Greater cumulative lifetime stress exposure and severity were both associated with significantly flatter diurnal cortisol slopes ($\beta = 0.48$, $p = 0.023$ and $\beta = 0.60$, $p = 0.004$, respectively). In contrast, survivors reporting higher levels of social attachment had significantly steeper cortisol slopes ($\beta = -0.56$, $p = 0.001$; means and SDs for psychosocial variables located in Table 1).

4. Discussion

This is the first study to investigate diurnal cortisol levels in 5+ -year ovarian cancer survivors. A key finding of this study was that although ovarian cancer survivors tended to have relatively normal diurnal cortisol slopes, those with flatter slopes were more likely to experience fatigue at 5+ years after diagnosis than survivors with steeper slopes. Thirty percent of the survivors in this study qualitatively reported moderate to extreme levels of fatigue. This is consistent with previous reports of persistent fatigue in approximately 20–30% of ovarian and breast cancer survivors (Bower et al., 2005; Liavaag et al., 2007). Our findings extend prior research demonstrating relationships between diurnal cortisol rhythms and fatigue in newly diagnosed ovarian cancer patients (Weinrib et al., 2010), and are consistent with research demonstrating relationships between flatter diurnal cortisol rhythms and persistent fatigue in breast cancer survivors (Bower et al., 2005). Taken together, these findings suggest that HPA-axis dysregulation may be a contributing factor to fatigue in ovarian cancer survivors as well, even 5+ years following diagnosis. Of note, the source of flatter cortisol slopes among fatigued survivors was due to elevations in afternoon and evening cortisol levels, rather than lower morning levels (Fig. 1), suggesting that the flatter slopes observed in more fatigued survivors may have been due to a higher sensitivity to stressors during the day or evening, rather than a failure to suppress cortisol when levels are already high (Spiegel et al., 2006).

Consistent with this hypothesis, ovarian cancer survivors with higher cumulative lifetime stress exposure and/or higher lifetime stress severity were more likely to have flatter diurnal cortisol rhythms, whereas survivors with high social attachment were more likely to have steeper diurnal cortisol rhythms. High cumulative lifetime stress exposure and low social attachment may reflect recurrently stressful environments that contribute to HPA-axis dysregulation and flatter diurnal cortisol rhythms (Friedman et al., 2012). Conversely, high social attachment may buffer against stress and/or release of cortisol from the HPA-axis (Heinrichs et al., 2003). Notably, both social attachment and fatigue were relatively stable between diagnosis and 5+ years, suggesting that the biological effects of social attachment may have been influencing the relevant pathways over a considerable length of time. However, in the absence of repeated assessments over time, this cannot be fully investigated.

Given the relationships observed in our study, it is possible that lifetime stress and low social attachment represent risk factors for fatigue in cancer survivors via modulation of diurnal cortisol rhythms, a hypothesis that can be evaluated in future work with a larger sample. Future research should also investigate how other psychosocial factors might moderate the relationship between stress and diurnal cortisol rhythms in ovarian cancer survivors. For example, in patients with metastatic breast cancer, repression and high anxiety are associated with flatter diurnal cortisol rhythms (Giese-Davis et al., 2004), whereas post-traumatic growth, which may reflect more effective coping strategies, has been associated with steeper diurnal cortisol rhythms (Diaz et al., 2014).

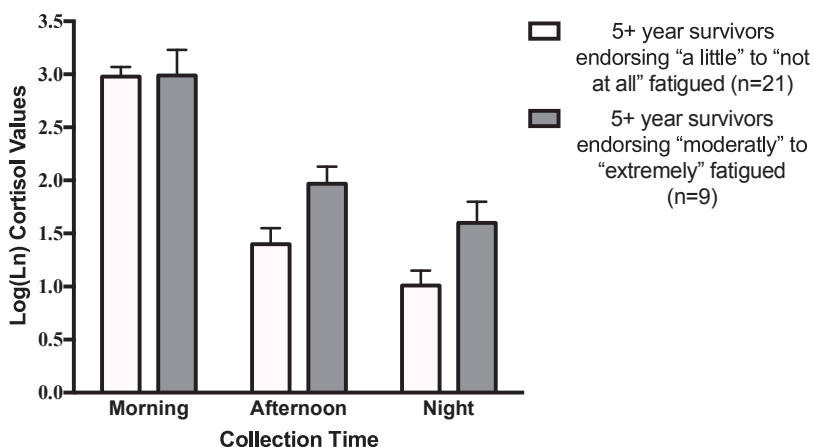


Fig. 1. Morning, afternoon, and night cortisol values of ovarian cancer survivors reporting low versus moderate/extreme fatigue at 5+ years post-diagnosis.

Several limitations of this study should be noted. First, although this sample of 5+ year ovarian cancer survivors is unique, our ability to perform sub-analyses by cancer stage or past cancer recurrence and to create a comprehensive model of all psychosocial variables (e.g., examining mediation) was limited by sample size. Furthermore, analyses in this study were correlational and causality cannot be confirmed. Because sleep was not systematically assessed, results do not reflect the role of dysregulated sleep in fatigue. Although the POMS-SF fatigue subscale is well validated in cancer populations (Shacham, 1983), it does not provide cutoff scores, and use of a more comprehensive fatigue measure could have enabled more granular analysis of components of fatigue. Individuals with co-morbid conditions with known immune effects at the time of surgery were excluded from the study. However, as co-morbid conditions were not re-assessed at the 5+ year follow-up we cannot eliminate the possibility that findings may have been influenced by these factors. As follow-ups were conducted by phone or mail, we were unable to collect blood samples to examine the potential role of inflammatory cytokines in the relationships observed in this study.

4.1. Conclusions

This is the first study to examine diurnal cortisol, fatigue and psychosocial factors in ovarian cancer survivors who have survived at least 5 years post-diagnosis. Fatigue continues to impact a subset of ovarian cancer patients into long-term survival (Liavaag et al., 2007) and the present findings suggest a role for HPA-axis dysregulation in this sustained fatigue. Furthermore, cancer survivors with a history of greater lifetime stress exposure and/or low social attachment may be vulnerable to dysregulation of circadian processes. Future research should examine the relationship of clinical stage and inflammatory cytokines to cortisol rhythms and fatigue in ovarian cancer survivors, as well as investigating the clinical significance of abnormal diurnal cortisol profiles in this population.

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Conflicts of interest

All authors reported no conflict of interest except Dr. Thaker who is a consultant for Celsion and has a Merck-institutional grant.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the

online version, at <http://dx.doi.org/10.1016/j.psyneuen.2017.06.019>.

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