Short communication

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

Michaela G. Cuneo[a], Andrew Schrepf[b], George M. Slavich[c], Premal H. Thaker[d], Michael Goodheart[e], David Bender[f], Steve W. Cole[g], Anil K. Sood[h], Susan K. Lutgendorf[i,*]

[a] Department of Psychological & Brain Sciences, University of Iowa, W322 Seashore Hall Iowa City, IA, 52242, United States
[b] Chronic Pain and Fatigue Research Center and Department of Anesthesiology, University of Michigan, 24 Frank Lloyd Wright Dr., Ann Arbor, MI, 48105, United States
[c] Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, UCLA Medical Plaza 300, Room 3156, Los Angeles, CA, 90095-7076, USA
[d] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University St. Louis School of Medicine, 660 S Euclid Ave, St. Louis, MO, 63110, United States
[e] Holden Comprehensive Cancer Center, University of Iowa, Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, University of Iowa, 200 Hawkins Drive, Iowa City, IA, 52242, United States
[f] Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, University of Iowa, 200 Hawkins Drive, Iowa City, IA, 52242, United States
[g] Department of Medicine Division of Hematology/Oncology and Molecular Biology Institute, David Geffen School of Medicine, University of California, Los Angeles, 10833 Le Conte Ave, Los Angeles, CA, 90095, United States
[h] Departments of Gynecologic Oncology, Cancer Biology and Center for RNA Interference and Noncoding RNA, University of Texas, M.D. Anderson Cancer Center. 1515 Holcombe Blvd, Houston, TX 77030, United States
[i] Holden Comprehensive Cancer Center, University of Iowa, Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, University of Iowa, W322 Seashore Hall, Iowa City, IA, 52242, United States and Department of Urology, University of Iowa, University of Iowa, W322 Seashore Hall, Iowa City, IA, 52242, United States

ARTICLE INFO

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).

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).