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Diurnal cortisol and survival in epithelial ovarian cancer

Andrew Schrepf[a], Premal H. Thaker[b], Michael J. Goodheart[c,d], David Bender[c], George M. Slavich[e,f], Laila Dahmoush[g,h], Frank Penedo[i,j], Koen DeGeest[k], Luis Mendez[l], David M. Lubaroff[f,m,n], Steven W. Cole[e,f,o], Anil K. Sood[p,q], Susan K. Lutgendorf[a,c,g,n,*]

[a] *Department of Psychology, University of Iowa, E11 Seashore Hall, Iowa City, IA 52242, USA*
[b] *Division of Gynecologic Oncology, Washington University School of Medicine, Maternity Building-660 South Euclid, Campus Box 8064, St. Louis, MO 63110, USA*
[c] *Department of Obstetrics and Gynecology, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242, USA*
[d] *Department of Anatomy and Cell Biology, University of Iowa, USA*
[e] *Cousins Center for Psychoneuroimmunology, University of California, Los Angeles, 300 Medical Plaza Driveway, Los Angeles, CA 90095, USA*
[f] *Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, 760 Westwood Plaza, Los Angeles, CA 90095, USA*
[g] *Department of Urology, University of Iowa, 3 Roy Carver Pavilion, 200 Hawkins Dr, Iowa City, IA 52242, USA*
[h] *Department of Pathology, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242, USA*
[i] *Department of Medical Social Sciences, Northwestern University, 633 N. Saint Clair St., 19th Floor, Chicago, IL 60611, USA*
[j] *Department of Psychiatry and Behavioral Sciences, Northwestern University, 446 East Ontario, #7-200, Chicago, IL 60611, USA*
[k] *Division of Gynecologic Oncology, Oregon Health & Science University, Center for Women's Health, Kohler Pavilion, 7th Floor, 808 S.W. Campus Drive, Portland, OR 97239, USA*
[l] *Department of Obstetrics and Gynecology, Florida International University School of Medicine, 5000 University Dr, Coral Gables, FL 33146, USA*
[m] *Department of Microbiology, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242, USA*
[n] *Holden Comprehensive Cancer Center, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242, USA*

* Corresponding author at: Department of Psychology, University of Iowa, E11 Seashore Hall, Iowa City, IA 52242, USA. Tel.: +1 319 335 2432; fax: +1 319 335 0191.
E-mail addresses: Andrew-schrepf@uiowa.edu (A. Schrepf), thakerp@wudosis.wustl.edu (P.H. Thaker), michael-goodheart@uiowa.edu (M.J. Goodheart), david-bender@uiowa.edu (D. Bender), GSlavich@mednet.ucla.edu (G.M. Slavich), laila-dahmoush@uiowa.edu (L. Dahmoush), fpenedo@northwestern.edu (F. Penedo), lemendez@comcast.net (L. Mendez), David-lubaroff@uiowa.edu (D.M. Lubaroff), coles@ucla.edu (S.W. Cole), asood@mdanderson.org (A.K. Sood), susan-lutgendorf@uiowa.edu (S.K. Lutgendorf).

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[o] *Department of Medicine, UCLA School of Medicine, University of California, Los Angeles, 10833 Le Conte Ave, Los Angeles, CA 90095, USA*
[p] *Department of Gynecologic Oncology, UT MD Anderson Comprehensive Cancer Center, 1155 Herman Pressler, Unit Number: 1362, Houston, TX 77030, USA*
[q] *Department of Cancer Biology, UT MD Anderson Comprehensive Cancer Center, 1155 Herman Pressler, Unit Number: 1362, Houston, TX 77030, USA*

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Summary
Introduction: Hypothalamic-pituitary-adrenal (HPA) deregulation is commonly observed in cancer patients, but its clinical significance is not well understood. We prospectively examined the association between HPA activity, tumor-associated inflammation, and survival in ovarian cancer patients prior to treatment.
Materials and methods: Participants were 113 women with ovarian cancer who provided salivary cortisol for three days prior to treatment for calculation of cortisol slope, variability, and night cortisol. Cox proportional hazard regression analyses were used to examine associations between cortisol and survival in models adjusting for disease stage, tumor grade, cytoreduction and age. On a subsample of 41 patients with advanced disease ascites fluid was assayed for levels of interleukin-6 (IL-6) and correlated with cortisol variables.
Results: Each cortisol measure was associated with decreased survival time, adjusting for covariates (all $p < .041$). A one standard deviation increase in night cortisol was associated with a 46% greater likelihood of death. Patients in the high night cortisol group survived an estimated average of 3.3 years compared to 7.3 years for those in the low night cortisol group. Elevated ascites IL-6 was associated with each cortisol measure (all $r > 36$, all $p < .017$).
Discussion: Abnormal cortisol rhythms assessed prior to treatment are associated with decreased survival in ovarian cancer and increased inflammation in the vicinity of the tumor. HPA abnormalities may reflect poor endogenous control of inflammation, dysregulation caused by tumor-associated inflammation, broad circadian disruption, or some combination of these factors. Nocturnal cortisol may have utility as a non-invasive measure of HPA function and/or disease severity.

1. Introduction

Ovarian cancer is the second most commonly diagnosed gynecologic malignancy and the most deadly, with five year survival rates of 44% for all patients, and 27% for patients with metastatic disease (American Cancer Society, 2014). Recent research has demonstrated effects of neuroendocrine signaling on a variety of pathways implicated in ovarian tumor growth including angiogenesis, invasion, anoikis, and promotion of inflammation in the tumor microenvironment (Cole and Sood, 2012). To date, mechanisms that have been characterized predominantly involve beta-adrenergic signaling. Neuroendocrine signals from the hypothalamic-pituitary-adrenal (HPA) axis regulate endogenous inflammation and metabolic activity, via the release of glucocorticoids (Tsigos and Chrousos, 2002). Although glucocorticoids are known to play a regulatory role in other cancers, little is known about the role of the HPA axis in the context of ovarian cancer.

Cortisol, a glucocorticoid, is released into circulation by the adrenal cortex following upstream signaling from the pituitary and hypothalamus (Rhen and Cidlowski, 2005). Cortisol follows a diurnal cycle; levels typically peak in the morning and reach a nadir during the second half of the night, though significant inter-individual differences are common even in apparently healthy people (Chrousos, 1995; Stone et al., 2001; Clow et al., 2010). Excess circulating cortisol provides negative feedback to the hippocampus and hypothalamus, however, under conditions of chronic inflammation the feedback system can become unresponsive, resulting in abnormal diurnal cortisol rhythms (Silverman and Sternberg, 2012).

Glucocorticoids have a variety of effects in cancer; they have been shown to inhibit apoptosis in breast, cervical and ovarian cancer cell lines and in animal models of breast cancer (Volden and Conzen, 2013). Incubation of ovarian cancer cells with cortisol has been shown to reduce expression of tumor-suppressor genes SLIT2 and ROBO1 (Dickinson et al., 2011), as well as to suppress the cytotoxic effects of paclitaxel, a drug commonly used in ovarian cancer chemotherapy (Flint et al., 2009). Moreover, flattened diurnal cortisol rhythms have been linked to decreased survival in breast, lung, and renal cell carcinoma patients, adjusting for clinical and demographic characteristics (Sephton et al., 2000, 2013; Cohen et al., 2012). For example, in a recent study of renal cell carcinoma patients, flatter cortisol slope