Original Article

Life Stress as a Risk Factor for Sustained Anxiety and Cortisol Dysregulation During the First Year of Survivorship in Ovarian Cancer

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BACKGROUND: Patients with ovarian cancer often report elevated anxiety at diagnosis that decreases posttreatment. However, a minority of patients experience sustained anxiety. Few studies have examined risk factors for persistent anxiety or its physiologic sequelae in ovarian cancer. Therefore, the authors investigated associations between prior life events, anxiety, inflammation (plasma levels of interleukin-6), and diurnal cortisol profiles in patients with ovarian cancer during the first year postdiagnosis. **METHODS:** Participants (n = 337) completed surveys and had blood and salivary sampling prediagnosis, postchemotherapy (6 months), and 12 months after diagnosis. The Life Events and Difficulties Schedule was administered to a patient subset (n = 127) within 1 month of diagnosis. Linear mixed-effects models were used to analyze relations between anxiety and biologic variables over time. Linear regression models assessed whether anxiety trajectories mediated associations between prior stress exposure and biologic variables. Age, chemotherapy at 1 year, and cancer stage were covariates. **RESULTS:** Decreased anxiety was associated with a more normalized cortisol slope over time (β = 0.092; *P* = .047). Early life adversity was related to flatter cortisol slopes over time (β = −0.763; *P* = .002); this relation was partially mediated by anxiety trajectory (*P* = .046). More danger-related events prediagnosis were associated with sustained anxiety (β = 0.537; *P* = .019) and flatter cortisol slopes over time (β = −0.243; *P* = .047); anxiety partially mediated the relation between danger and cortisol slope (*P* = .037). Neither anxiety nor prior stress exposure was related to levels of interleukin-6. **CONCLUSIONS:** Because dysregulated cortisol has been related to fatigue, poorer quality of life, and shorter survival in patients with ovarian cancer, those who have prior life events and chronic anxiety during the first year postdiagnosis may be at risk for more negative outcomes. *Cancer* 2018;124:3401-8. © *2018 American Cancer Society.*

KEYWORDS: anxiety, cortisol, early life stress, interleukin-6, ovarian cancer.

INTRODUCTION

Early life adversity (ELA) has been related to subsequent impairments in both physical and mental health outcomes, and it has been demonstrated that prior exposure to stress influences an individual's vulnerability to distress when confronted with stressors later in life.[1] One proposed explanation for this phenomenon is the *stress-sensitization hypothesis*,[2] which posits that adversity in childhood increases individuals' vulnerability to the effects of later stressful events. Among noncancer populations, it is reported that ELA sensitizes individuals to experience stressors as more threatening compared with individuals without such childhood experiences.[3] Associations also have been demonstrated between more recent life stress exposure and greater mood changes, particularly anxiety.[4]

The influence of prior stress exposure has been minimally examined in the context of patients receiving diagnosis and treatment for cancer; and, to our knowledge, no studies have used high-resolution assessments of stress exposure to understand the effects that stress has on psychological and biologic functioning in patients with ovarian cancer. Ovarian cancer is the most lethal of gynecologic cancers, with an overall 5-year survival rate of 45.6% and a 29% survival rate for the majority of women who are diagnosed with advanced-stage disease.[5] An estimated 29% to 38% of women who face a

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diagnosis of ovarian cancer report significant elevations in anxiety.[6,7] However, there has been minimal focus on the risk factors for anxiety and physiologic sequelae of anxiety among patients with ovarian cancer.

Prior stress exposure may compromise the functioning of stress-response systems.[8] Cortisol is a glucocorticoid hormone released by the adrenal cortex in response to inflammation[9] and stressful stimuli.[10] Cortisol has a well characterized diurnal rhythm, with a peak shortly after wakening and a nadir after midnight. Flatter cortisol slopes have been related to poorer survival in ovarian and other cancers.[11-14] In healthy adults, ELA has been associated with an elevated flattened cortisol trajectory, along with metabolic and immune changes.[15] In patients with ovarian cancer, we previously reported a relatively flat cortisol slope at the time of diagnosis,[16] which normalizes after primary treatment and tends to be maintained 1 year after diagnosis.[17] Although vegetative depression has been associated with flatter cortisol slopes and higher nocturnal cortisol levels over time in patients with ovarian cancer,[17] little is known about the association between prior stress exposure, current anxiety, and the recovery of diurnal cortisol rhythms after treatment for ovarian cancer.

ELA has been associated with elevated levels of inflammation in healthy adults,[18] including continued vulnerability to inflammation later in life.[19] Ovarian tumor cells and other cells in the tumor microenvironment produce inflammatory cytokines, such as interleukin-6 (IL-6), which promotes angiogenesis and metastatic spread.[20] Plasma IL-6 is often elevated in patients with ovarian cancer[21] and has been associated with decreased time to recurrence and poorer survival in ovarian[22] and other cancers.[23] Investigation of the specificity of emotion-biology relations indicate anxiety-specific effects on both inflammatory activity and morning cortisol, independent of the effects of depression and neuroticism.[24] However, little is understood about the relation between prior stress exposure, anxiety symptoms, and IL-6 in patients with cancer.

This study examined associations between prior life stress exposure and trajectories of anxiety, cortisol, and inflammation over the first year after an ovarian cancer diagnosis. Early and recent precancer stress exposures were assessed as risk factors, and posttreatment cortisol and IL-6 levels were assessed as biologic sequelae. We hypothesized that higher levels of early and recent life stress exposure would be associated with persistent anxiety during the first year after diagnosis, with downstream effects on IL-6 and cortisol levels. We also hypothesized that symptoms of anxiety would decrease posttreatment and that this trajectory would be associated with decreased IL-6 and normalization of the diurnal cortisol slope over time.

MATERIALS AND METHODS

Participants

After Institutional Review Board approval at Washington University and the Universities of Iowa and Miami, patients with suspected ovarian cancer were prospectively recruited and consented during their presurgical clinic visit for a larger study focused on biobehavioral pathways and ovarian cancer progression. Eligibility was restricted to patients who had a primary diagnosis of epithelial ovarian, peritoneal, or fallopian tube carcinoma. Patients were excluded from the study if they were younger than 18 years; pregnant; diagnosed with benign disease, nonepithelial malignancies, or tumors of low malignant potential; had a previous cancer history; or had used systemic corticosteroids in the previous month. Patients who only had baseline data were excluded from the data analysis to avoid potential confounding influences of estimating longitudinal information from 1 time point.

Participants completed psychosocial questionnaires and home collection of salivary cortisol between study recruitment and diagnosis and before the 6-month and 1-year clinic follow-ups. Samples were stored at −80 °C until analysis. Blood draws were done the morning of surgery between approximately 5:30 AM and 12:00 PM and at the 2 follow-up appointments. The 6-month follow-up appointment was typically completed 1 month postchemotherapy completion, and the 1-year follow-up was completed at the routine 12-month clinic visit. The final sample included 337 patients who had complete data for at least 2 time points (Fig. 1).

Psychosocial Measures

Early and recent life stress exposure

Our primary measure of prior stress exposure, the Life Events and Difficulties Schedule (LEDS),[25] was administered to a subset of patients (N = 127) either in the hospital postsurgery or by telephone within approximately 1 month after diagnosis to assess their life stress exposure in early life and during the year before diagnosis. Interviewers trained and supervised by one of the authors (G.M.S.) conducted semistructured LEDS interviews with patients. Responses were organized and rated by an independent team of 2 or 3 expert raters who judged the specific type, timing, and severity of each life stressor according to the LEDS manual, which includes extensive

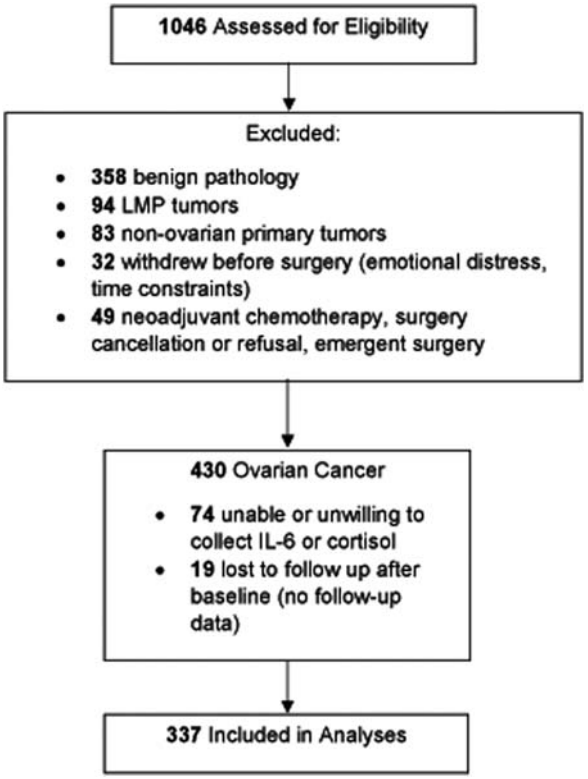

Figure 1. Patient flow diagram. IL-6 indicates interleukin 6; LMP, low malignant potential.

rating guidelines and more than 5000 prerated case vignettes. Final ratings were based on consensus judgments. Inter-rater agreement for stressor severity ratings in the current study were very good ($\kappa = 0.89$).

Acute stress events were rated on a 4-point scale from 1 (*little-to-no threat*) to 4 (*severe threat*). All events were categorized by their primary social-psychological characteristic (eg, loss, danger, entrapment). In addition, all events were coded as either cancer-related or noncancer-related, and only noncancer-related events were used in subsequent analyses.

The LEDS probes for early life stressors by asking standardized questions about biographic history and upbringing before age 18 years, followed by a detailed temporal and topical summary of early life events and chronic difficulties described and their impact. Using the original LEDS system threat rating values as a template, a novel rating system was developed to rate early life stressors using a 1-4 scale, ranging from 1 (*little-to-no threat*) to 4 (*marked threat*). Summary variables for these data included a dichotomous variable indicating the presence of any major life stressor before age 18 years and the total severity of all early life stressors experienced. Early life stress also was assessed secondarily using the Childhood Traumatic Events Scale (CTES),[26] a brief self-report scale assessing the occurrence and severity of specific categories of childhood trauma.

Anxiety

The Profile of Mood States-Short Form (POMS-SF), a 37-item inventory of mood adjectives,[27] is a well validated, self-report measure that is used widely with populations of patients who have cancer.[28] Anxiety symptoms were assessed using the anxiety/tension subscale, which measures perceptions of anxiety-related feelings over the past week endorsed on a scale from 0 (*not at all*) to 4 (*extremely*).

Depression

The Center for Epidemiological Studies Depression Scale[29] is a 20-item self-report scale measuring the frequency of depressive symptoms over the last week. Items are endorsed on a scale from 0 (*rarely*) to 3 (*most or all of the time*).

Biologic Measures

Cortisol

Salivary cortisol was collected upon awakening, between 1600 hours and 1830 hours, and at bedtime for the 3 days before surgery and before the 6-month and 1-year follow-up visits. Participants self-recorded collection times.[30] Assays were performed using a commercial chemiluminescence immunoassay (IBL, Hamburg, Germany) at the Technical University of Dresden. The lower detection limit is 0.41 nmol/L, and interassay and intraassay coefficients of variance are <10%.

Before statistical analyses, sampling time outliers for cortisol were removed. Ranges of sampling times were determined to fit the maximum number of participants while maintaining homogeneity. Acceptable ranges were from 0400 to 0900 hours for morning cortisol collection, from 1600 to 1830 hours for afternoon cortisol collection, and from 2000 to 2400 hours for nocturnal cortisol collection. Cortisol values greater than 4 standard deviations (SD) beyond the mean for a particular time point were excluded. Mean cortisol values at each time point were calculated, and values were transformed using the natural logarithm(ln) to normalize their distribution. The slope of diurnal change in the cortisol level was calculated in accordance with past research.[12,31] Regression of the 9 cortisol values on the hour of sample collection was calculated, with data pooled over the 3 days for each patient. Steeper slopes reflected by more negative slope values

indicate more rapid salivary cortisol declines over the course of the day and represent healthier values.

Interleukin-6

Quantification of plasma IL-6 levels was performed using an enzyme-linked immunosorbent assay (R&D Diagnostics, Minneapolis, MN) according to the manufacturer's instructions. The minimum detectable level is <0.7 pg/mL, and interassay variability ranges from 3.3% to 6.4%. Values below the minimum level detectable by the standard kit were assessed using an R&D high-sensitivity enzyme-linked immunosorbent assay. Values were $\log^{10}$ transformed to normalize their distribution.

Clinical and Demographic Information

Demographic information on age, race, and ethnicity was collected by self-report. Information regarding tumor stage and grade and medications was extracted from medical records. A categorical variable was created describing patient use of antidepressants or anxiolytics, including 0 (no medication use), 1 (use of either antidepressants or anxiolytics), and 2 (simultaneous use of both antidepressants and anxiolytics).

Statistical Analysis

Analyses were conducted using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).[32] Distributions were examined for outliers and normality before analysis. To test for differences in anxiety, IL-6, and cortisol slope between patients with early stage (I and II) versus advanced stage (III and IV) disease, general linear models controlling for patient age were used, and Bonferroni corrections were applied to allow for pairwise comparisons between time points. Longitudinal analyses included all 3 time points in trajectory calculation and used linear mixed-effects models with fixed slopes and participant intercept terms in the lme4 package[33] for R. Mediation models, including life stress data, were analyzed using the PROCESS macro for SPSS (IBM Corporation, Armonk, NY).[34] Thresholds of prior life stress were tested by dichotomizing both anxiety and cortisol trajectories into no-change/increasing (persistent) versus decreasing trajectories and using ANOVA (analysis of variance) in SPSS to test the significance of differences between group means for prior stress exposure. All models controlled a priori for the use of antidepressants and anxiolytics, disease stage, and age, because aging has been associated with changes in the hypothalamic-pituitary-adrenal axis.[35] To reduce possible confounding effects of chemotherapy on inflammation and cortisol for patients who were still receiving treatment after 1 year, all models controlled for chemotherapy treatment at 1 year (present/absent).

TABLE 1. Patient Demographic and Clinical Characteristics, N = 337

Variable	No. of Patients (%)
Age: Mean ± SD, y	59.7 ± 11.68
Race	
American Indian/Alaskan Native	2 (0.6)
Asian	3 (0.9)
African American	7 (2.1)
Caucasian	325 (96.4)
Ethnicity	
Hispanic	22 (6.5)
Non-Hispanic	315 (93.5)
Stage	
I	66 (19.6)
II	23 (6.8)
III	208 (61.7)
IV	33 (9.8)
Unknown/missing	7 (2.1)
Grade	
Low	43 (12.8)
High	294 (87.2)
Tumor histology	
Serous	235 (69.7)
Endometrioid	30 (8.9)
Mucinous	11 (3.3)
Clear cell	19 (5.6)
Unknown/other	42 (12.5)
Severe early life stress [CTES]: Mean ± SD	0.97 ± 1.06
Noncancer danger events [LEDS]: Mean ± SD, n = 127	1.91 ± 1.19
Presence of early life adversity [LEDS], n = 127	
Yes	59 (46.5)
No	68 (53.5)

Abbreviations: CTES, Childhood Traumatic Events Scale; LEDS, Life Events and Difficulties Schedule; SD, standard deviation.

RESULTS

Participant Characteristics and Covariates

Table 1 indicates that the average (± SD) patient age at the time of diagnosis was 59.7 ± 11.68 years. Most participants had advanced disease (71.5%) and serous histology (69.7%). Levels of anxiety, IL-6, and cortisol slope did not differ significantly over time between patients who had early versus advanced stage disease (all $P > .156$). Age was not significantly associated with life stress or changes in anxiety, IL-6, or cortisol over time (all $P > .344$). Receipt of chemotherapy at 1 year (indicating disease relapse) was associated with a significant rise in IL-6 between 6 months and 1 year ($P = .042$), whereas patients who were not receiving chemotherapy had relatively constant IL-6 levels ($P = .86$).

Anxiety Trajectories Over the First Year Postdiagnosis

Anxiety levels decreased significantly over the course of the year after diagnosis ($F[1.843] = 102.043$; $P < .001$). Pairwise comparisons of anxiety as a function of follow-up time point revealed a significant decrease in anxiety scores between presurgery (mean ± SD, 9.51 ± 5.65) and 6 months (58 ± 4.70; $P < .001$) and relative stability between 6 months and 1 year ($P = .72$), with scores remaining below the reported norms for patients with cancer (mean score, 8.20).[28] Approximately 18% of patients reported sustained elevations in levels of anxiety both after the conclusion of primary treatment (6 months) and at 1 year.

Associations Between Life Stress and Anxiety Levels

To identify patients who were at risk for negative emotional and biologic outcomes, we assessed the extent to which ELA and recent life stress exposure predicted different anxiety trajectories over the year after diagnosis. Patients with ELA reported relatively sustained elevations in anxiety levels over time (LEDS: $\beta = 0.062$; $P = .037$; CTES: $\beta = 0.191$; $P = .033$). Patients who reported more danger-related events in the year before diagnosis also had relatively sustained elevations in anxiety over time ($\beta = 0.397$; $P = .019$), whereas entrapment-related and loss-related events were not associated with anxiety trajectories. The severity of events was not significantly associated with the anxiety trajectory.

In addition, the role of anxiety trajectory in the relation between the number of severe early life stressors and the cortisol slope trajectory was consistent with mediation. The relation between ELA and the cortisol slope trajectory was significant (LEDS: $\beta = -0.328$; $P = .013$; CTES: $\beta = -0.763$; $P = .002$), as was the relation between the anxiety trajectory and the cortisol slope trajectory (LEDS: $\beta = -0.454$; $P = .044$; CTES: $\beta = -0.471$; $P = .046$). The bootstrap estimate of the indirect (mediational) effect was significant (LEDS: $\beta = -0.065$; $P = .044$; CTES; $\beta = -0.078$; $P = .048$). Similarly, the relation between the number of danger-related life events (LEDS) and the cortisol slope trajectory was influenced by the anxiety trajectory in a manner consistent with mediation ($\beta = -0.118$; $P = .043$). These mediation models are presented in Figure 2.

We conducted exploratory analyses to examine the threshold of prior stress exposure linked with persistent anxiety and cortisol dysregulation. The mean ± SD number of severe early life stressors (CTES) in the persistent anxiety group was 1.82 ± 1.61, whereas that in the decreasing anxiety group was 0.44 ± 1.13 ($P = .038$). The mean ± SD number of severe early life stressors in the dysregulated cortisol group was 0.79 ± 1.18 versus 0.39 ± 0.91 in the normalized cortisol group ($P = .048$). The mean ± SD number of danger events in the persistent anxiety group was 2.28 ± 1.94 versus 0.72 ± 1.19 danger events in the decreasing anxiety group ($P = .029$). Similarly, the mean ± SD number of danger events in the dysregulated cortisol group was 1.55 ± 1.07 versus 0.69 ± 1.01 in the normalized cortisol group ($P = .044$).

Parallel Trajectories of Anxiety and Cortisol Over 1 Year

During the period from diagnosis to 1 year, decreases in anxiety were significantly associated with decreases in the cortisol slope ($\beta = 0.092$; $P = .047$), indicating a more normalized pattern of diurnal cortisol as anxiety decreased over time (Table 2). Decreased anxiety levels were not significantly associated with decreased IL-6 over time ($\beta = 0.027$; $P = .091$). In secondary analyses to examine whether these effects were specific to anxiety independent of depression, the trajectory of depressed mood (ie, the Center for Epidemiological Studies Depression Scale) was included. The relation between depressed mood and changes in the cortisol slope was not significant ($\beta = -0.019$; $P = .14$). Depressed mood also was not significantly associated with IL-6 over time ($\beta = 0.011$; $P = .737$). However, the relation between changes in anxiety and changes in the cortisol slope became nonsignificant when controlling for the trajectory of depressed mood over 1 year ($\beta = 0.035$; $P = .086$), suggesting that general distress may be contributing to this relation. The relation between changes in anxiety and changes in IL-6 remained nonsignificant when controlling for depressed mood.

DISCUSSION

The key finding of the current study is that patients with ovarian cancer who had a history of ELA and/or greater danger-related events in the year before diagnosis were more likely to have persistent anxiety and dysregulation of the cortisol slope during the first year after diagnosis. Anxiety was associated with a flatter cortisol slope over the first year postdiagnosis, suggesting greater dysregulation of a neuroendocrine hormone previously associated with cancer survival.[12,13,17] Although anxiety decreased over the first year postdiagnosis for most patients, those who reported relatively persistent anxiety demonstrated sustained flattened cortisol slopes. Neither anxiety nor prior stress exposure was related to IL-6.

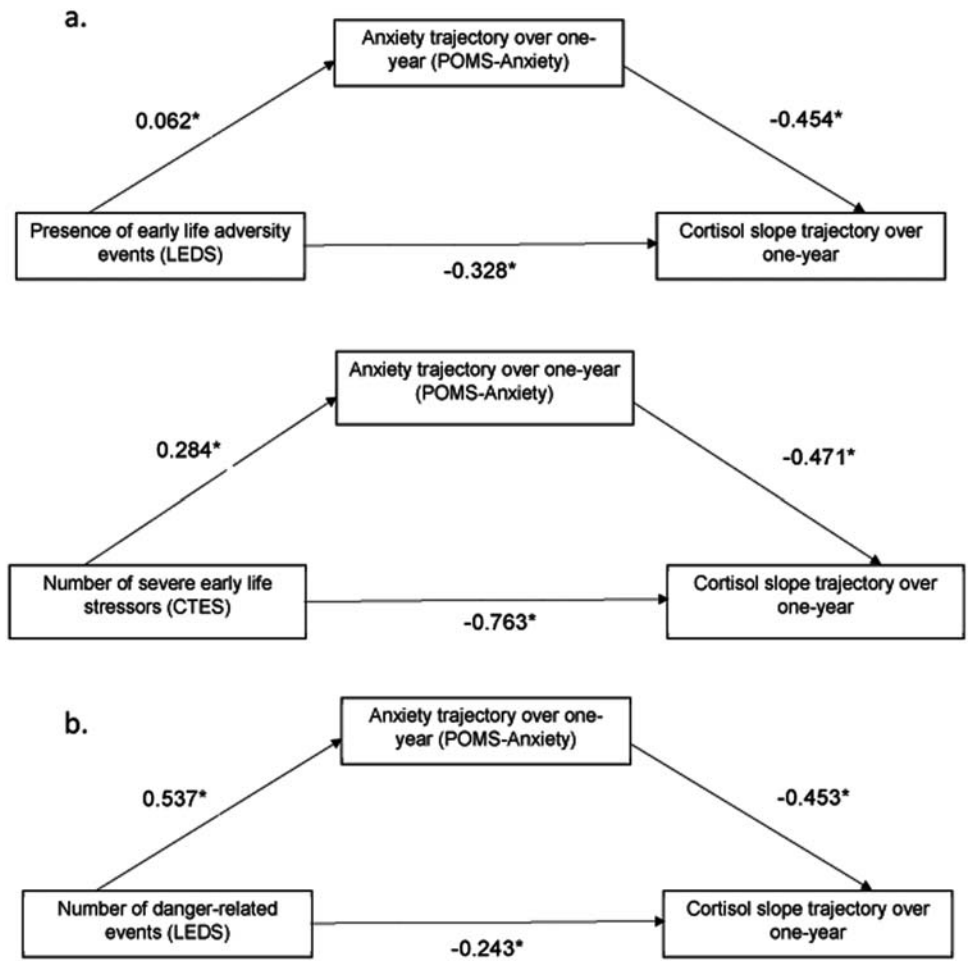

Figure 2. Unstandardized regression coefficients are illustrated for the (a) correlation between early life stress and the cortisol slope trajectory, and (b) danger stress events and the cortisol slope trajectory, as mediated by anxiety trajectory. Asterisks indicate $P < .05$. CTES indicates the Childhood Traumatic Events Scale; LEDS, the Life Events and Difficulties Schedule; POMS, the Profile of Mood States.

Our finding of a general decrease in anxiety over time is consistent with prior research in this population[36] and makes the persistence of anxiety in specific individuals all the more salient. Although a recent meta-analysis reported gradual increases in anxiety disorders during treatment in patients with ovarian cancer,[37] 75% of the included studies had cross-sectional designs and thus did not longitudinally assess posttreatment anxiety, which we did assess in the current study. The relation between danger-related events (ie, physical, interpersonal, or financial threat) in the year before diagnosis and persistent anxiety symptoms parallels previous research in the general population demonstrating associations between events involving danger and mood changes (particularly anxiety).[4] Although the comorbidity between depressive and anxious symptoms tends to be relatively high, the influence of acute stress event type on the development of symptoms is often specific to depression or anxiety alone.[38] Consistent with our findings, in the recent life stress literature, danger has been associated more closely with subsequent anxiety symptoms than with depression.[4] It is noteworthy that the inclusion of depression as a

TABLE 2. Descriptive Statistics for Cortisol and Interleukin-6

	Mean ± SD		
Variable	Baseline	6 Months	1 Year
Cortisol slope	−0.089 ± 0.063	−0.121 ± 0.063	−0.131 ± 0.154
IL-6, pg/mL	25.204 ± 36.911	4.365 ± 8.971	3.621 ± 3.772

Abbreviations: IL-6, interleukin 6; SD, standard deviation.

covariate reduced the magnitude of the relation between anxiety change and change in the cortisol slope, suggesting that general distress may be a component of the relation to changes in cortisol.

The relation observed between the anxiety trajectory and the cortisol slope extends previous reports of a cross-sectional association between high anxiety and flatter diurnal cortisol rhythms in patients with metastatic breast cancer[39] to ovarian cancer survivors. The association observed between ELA and a flatter cortisol slopes is consistent with the extant literature, which has primarily focused on noncancer populations, such as healthy adults with a history of childhood maltreatment[40] and postpartum women.[41]

The absence of a relation between anxiety and IL-6 contrasts with reports of elevated IL-6 in healthy adults with clinically significant anxiety, independent of depressed mood,[24] and in patients with posttraumatic stress disorder.[42] These discrepancies may reflect differences in the severity of symptoms present in anxiety disorders versus those assessed here. In addition, the dramatic decrease in IL-6 levels that we previously observed in patients with ovarian cancer after surgery and chemotherapy may have obscured relations with psychosocial variables at the follow-up time points. For example, the variability of raw IL-6 levels prediagnosis (SD, 36.91 pg/mL) was extremely high compared with variability at 1 year (SD, 3.7 pg/mL). Although prior research has demonstrated an enhanced IL-6 response to laboratory stressors for individuals who have experienced ELA,[18] the lack of association we observed between ELA and the IL-6 trajectory may arise from differences in sample characteristics, because much of the prior research has been done on noncancer populations with severe ELA.

Limitations

Despite the longitudinal design of this study, the findings are correlational, and causal effects cannot be assumed. The emergent timing of surgery prevented several patients from collecting cortisol at baseline, and participation at follow-up time points was diminished by patient burden, debility, and death. The remaining patients who had cortisol data at 1 year may have been more robust and not fully representative of the cohort. Although it is well validated in cancer populations, the POMS tension/anxiety subscale is a measure of anxiety symptoms only, with no clinical cutoff score. The CTES has been used in cancer populations but is not well validated. Although the LEDS is well validated, a novel rating system was developed for assessing ELA.

Conclusion

In conclusion, ELA and prior danger events emerged as risk factors for sustained anxiety and cortisol dysregulation in patients with ovarian cancer over the first year after diagnosis. Because flatter cortisol slopes have been related to poorer survival in ovarian[11] and other cancers,[12-14] the clinical implications of these findings include a renewed focus on interventions targeting anxiety among ovarian cancer survivors.

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CONFLICT OF INTEREST DISCLOSURES

Premal H. Thaker reports personal fees from Celsion outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Jessica S. Armer: Conceptualization, formal analysis, methodology, writing–original draft, and writing–review and editing. **Lauren Clevenger**: Investigation, formal analysis, and writing–review and editing. **Lauren Z. Davis**: Investigation, formal analysis, and writing–review and editing. **Michaela Cuneo**: Investigation, formal analysis, and writing–review and editing. **Premal H. Thaker**: Resources, conceptualization, and writing–review and editing. **Michael J. Goodheart**: Resources, conceptualization, and writing–review and editing. **David P. Bender**: Resources and writing–review and editing. **Laila Dahmoush**: Pathology confirmation and writing–review and editing. **Anil K. Sood**: Conceptualization and writing–review and editing. **Steve W. Cole**: Conceptualization and writing–review and editing. **George M. Slavich**: Conceptualization, life stress assessment, and writing–review and editing. **Susan K. Lutgendorf**: Supervision, conceptualization, funding acquisition, project administration, formal analysis, and writing–review and editing.

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