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Cortisol and inflammatory processes in ovarian cancer patients following primary treatment: Relationships with depression, fatigue, and disability ☆

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ABSTRACT

Elevations in the pro-inflammatory cytokine interleukin-6 (IL-6) and alterations in the anti-inflammatory hormone cortisol have been reported in a variety of cancers. IL-6 has prognostic significance in ovarian cancer and cortisol has been associated with fatigue, disability, and vegetative depression in ovarian cancer patients prior to surgery. Ovarian cancer patients undergoing primary treatment completed psychological self-report measures and collected salivary cortisol and plasma IL-6 prior to surgery, at 6 months, and at 1 year. Patients included in this study had completed chemotherapy and had no evidence of disease recurrence. At 6 months, patients showed significant reductions in nocturnal cortisol secretion, plasma IL-6, and a more normalized diurnal cortisol rhythm, changes that were maintained at 1 year. The reductions in IL-6 and nocturnal cortisol were associated with declines in self-reported fatigue, vegetative depression, and disability. These findings suggest that primary treatment for ovarian cancer reduces the inflammatory response. Moreover, patients who have not developed recurrent disease by 1 year appear to maintain more normalized levels of cortisol and IL-6. Improvement in fatigue and vegetative depression is associated with the normalization of IL-6 and cortisol, a pattern which may be relevant for improvements in overall quality of life for ovarian cancer patients.

1. Introduction

Inflammation has recently been described as the 7th hallmark of cancer (Colotta et al., 2009) and is widely considered a critical factor in the pathogenesis of ovarian cancer (Clendenen et al., 2011; Ness et al., 2000; Wu et al., 1992). Both tumor and stromal cells in the tumor microenvironment produce high levels of the inflammatory cytokine interleukin-6 (IL-6) (Watson et al., 1990; Nilsson et al., 2005; Offner et al., 1995; Obata et al., 1997) which serves to promote tumor growth and dissemination. In the tumor microenvironment, IL-6 promotes angiogenesis (Nilsson et al., 2005), invasion, and attachment (Obata et al., 1997), and the generation of tumor-associated macrophages (Jeannin et al., 2011) Plasma levels of IL-6 in ovarian cancer are quite elevated (Lutgendorf et al., 2008; Tempfer et al., 1997) and are thought to reflect levels of IL-6 in the tumor microenvironment (Edgell et al., 2010). Elevations of IL-6 are also associated with decreased time

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to recurrence and shorter survival time in ovarian cancer patients (Lane et al., 2011; Plante et al., 1994; Scambia et al., 1995).

In addition to direct effects of inflammatory cytokines such as IL-6 on tumor growth, elevated systemic levels of cytokines such as IL-6 have known effects on the central nervous system, eliciting the classical inflammatory repertoire described as "sickness behaviors" such as reduced food intake, fatigue, anhedonia, and lethargy (Dantzer et al., 2002; Dantzer, 2006; Musselman et al., 2001). In animal models of ovarian and breast cancer, plasma and/or central nervous system (CNS) IL-6 has been associated with reduced locomotion and depression-like behaviors (Lamkin et al., 2011; Pyter et al., 2009). We have previously reported an association between plasma IL-6 and vegetative depression, disability, and fatigue in ovarian cancer patients at the time of surgery (Lutgendorf et al., 2008). However, the effects of ovarian cancer treatment on this important cytokine, as well as the association of IL-6 with vegetative symptoms have not been characterized in a longitudinal analysis.

Cortisol is a glucocorticoid hormone released by the hypothalamic–pituitary–adrenal (HPA) axis in response to inflammation (Rhen and Cidlowski, 2005), stress and other stimuli (Chrousos and Gold, 1998), and serves as an important regulator of metabolic function. In healthy individuals, cortisol secretion follows a diurnal rhythm characterized by elevated levels in the morning which decline over the afternoon and evening, and reach a nadir during the first half of the night (Dallman et al., 2000; Tsigos and Chrousos, 2002) Dysregulated patterns of cortisol secretion, often characterized by elevated nocturnal cortisol, have been noted in diverse populations of cancer patients including breast, ovarian, and cervical cancers and lymphoma (Abercrombie et al., 2004; Jehn et al., 2010; Mormont and Lévi, 1997; Palesh et al., 2008)

Elevated nocturnal cortisol and blunted diurnal cortisol slopehave been observed in ovarian cancer patients prior to surgery, a pattern that has been hypothesized to be secondary to tumor-derived inflammation (Lutgendorf et al., 2008; Musselman et al., 2001; Weinrib et al., 2010) The specific effects of abnormal diurnal cortisol patterns on tumor physiology in humans are not known, although disruption of cortisol rhythms resulting in a flattened cortisol slope has been associated with shortened survival time in breast cancer patients (Sephton et al., 2000). In animal models, the disrupted release of cortisol in response to inflammation is of substantial importance, as altered glucocorticoid receptor expression secondary to elevated cortisol has been identified as a potential mechanism in the initiation of ovarian cancer (Rae and Hillier, 2005), the failure of cancer cells to undergo apoptosis (Melhem et al., 2009; Pan et al., 2011; Schlossmacher et al., 2011), the development of chemotherapy resistant ovarian cancer cells (Pang et al., 2006), and accelerated tumor growth (Filipski and Lévi, 2009). In addition to its association with tumor growth, cortisol dysregulation has been linked with quality of life of cancer patients. Abnormal cortisol rhythms have been associated with poor performance status (Touitou et al., 1996), fatigue (Bower et al., 2005), and depression (Jehn et al., 2010) in cancer patients. In addition, we have previously reported links between abnormal cortisol rhythms and vegetative symptoms of depression at the time of surgery in ovarian cancer patients (Lutgendorf et al., 2008; Weinrib et al., 2010).

Primary treatment for ovarian cancer typically involves surgical resection of the tumor, followed by six cycles of platinum-based chemotherapy, and lasts approximately 6 months (Bristow et al., 2002). Despite the prognostic and functional importance of cortisol and IL-6, little attention has been paid to how primary treatment affects these substances, their trajectory following primary treatment, and their relationship with patients' self-reported functional ability. One small study reported reductions in IL-6 and C-reactive protein in 38 patients with ovarian carcinoma immediately following chemotherapy (Zakrzewska and Poznanski, 2001) but did not examine psychological correlates or glucocorticoid levels. Another study reported reduced serum cortisol levels immediately after platinum-based chemotherapy (Morrow et al., 2002) as a correlate of nausea, but did not examine long term effects of primary treatment.

Using a prospective longitudinal design, we examined patterns of cortisol secretion, levels of IL-6, and self-reported measures of fatigue, disability and vegetative depression prior to surgery, at 6 months, and at 1 year among ovarian cancer patients who had completed primary treatment, had no evidence of disease recurrence, and were not receiving chemotherapy at 1 year. Our model was designed to examine the relationship between changes in inflammatory pathways following primary treatment and associated changes in clinically relevant measures of self-reported functioning. We hypothesized that levels of IL-6 would be reduced and diurnal patterns of cortisol normalized following primary treatment for ovarian cancer. Furthermore, we hypothesized that these changes would be maintained 1 year after surgery in patients whose disease had not recurred. We hypothesized that these reductions would be associated with decreases in self-reported fatigue, vegetative depression, and disability.

2. Methods

2.1. Participants

Consecutive gynecologic oncology patients with suspected ovarian cancer were prospectively recruited during their pre-surgical clinic appointment. Eligibility was restricted to patients with primary epithelial ovarian, peritoneal, or fallopian tube carcinomas. Histological diagnosis for inclusion in the study was confirmed by pathology. Patients with benign disease, non-epithelial malignancies, tumors of low malignant potential (LMP), history of previous cancer, use of systemic corticosteroids in the last month, receipt of neo-adjuvant chemotherapy and those below 18 years of age were excluded. Only patients who had been enrolled in the study long enough to have reached their 1 year follow-up were included in the present analyses. To avoid confounding influences of cancer recurrence and/or chemotherapy on inflammatory processes and diurnal cortisol, data was only used from patients who had no evidence of disease recurrence and were not receiving chemotherapy at the time of the 6 months or 1 year follow-up.

The final sample is described in Fig. 1. Of 510 potentially eligible patients, 180 had benign disease, 39 had tumors of low malignant potential, 41 had tumors of non-ovarian pathology, and 15 did not have surgery, received neo-adjuvant chemotherapy regimen, or did not meet another inclusion factor. Thirty-two patients withdrew from the study before surgery. Thus 202 ovarian cancer patients were eligible for inclusion. Of these patients, 31 did not have peripheral blood sampling before surgery. Four patients who died shortly after surgery were not included in the pre-surgical analyses as no longitudinal information could be collected. Of the 168 patients eligible for inclusion before surgery, 117 also collected salivary cortisol. The lower number of patients who collected cortisol is most likely due to the more burdensome and time consuming nature of the procedure (9 different collection times over 3 days) which exigent surgery sometimes rendered impossible. At the 6 months follow-up, peripheral blood samples were available for 114 patients without evidence of recurrence and who were not receiving chemotherapy at the time of follow-up; 58 collected salivary cortisol at this time-point. At 1 year, peripheral blood samples were available for 92 patients without evidence of recurrence and not receiving chemotherapy and 47 collected sali-

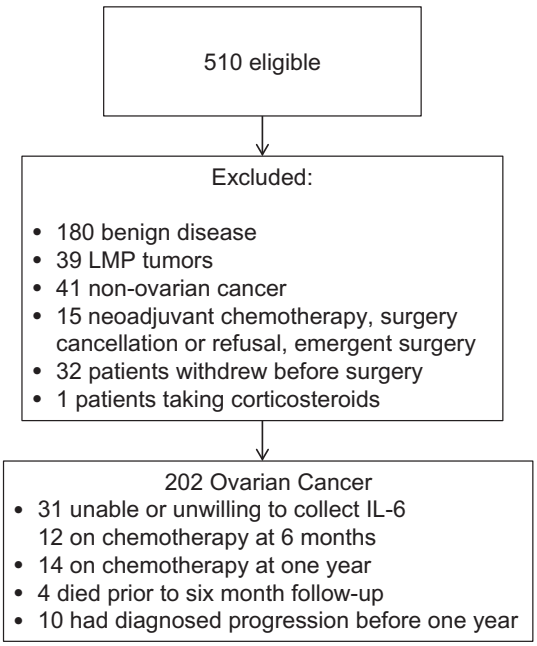

Fig. 1. Patient flow diagram.

vary cortisol. Because mixed models can estimate a missing time-point, patients were included if they had IL-6 collections at any two of these time-points.

2.2. Procedure

Informed consent was obtained during the pre-surgical visit, and participants received questionnaires and instructions for home collection of salivary cortisol. To ensure the best adherence to instructions, a research assistant contacted the participants prior to sampling to repeat instructions. Samples were refrigerated by patients until brought to the clinic at the time of surgery, where they were stored at −80 °C until analysis. If samples were not brought to follow-up visits, patients were requested to return them by mail and mailers were supplied. Peripheral blood was collected in the morning prior to surgery, and at the 6 months and 1 year follow-up clinic visits. Samples of pre-surgical blood were generally obtained before 12 p.m. (>85%); follow-up bloods were obtained at the time of the patient's appointment; more than 70% of these samples were obtained prior to 12 p.m. at each follow-up time-point. This level of homogeneity was desirable as IL-6 undergoes a slight degree of circadian variation (Vgontzas et al., 2005). All procedures were approved by the institutional review boards at participating institutions. At the time of surgery, participants had not yet received a definitive cancer diagnosis. The 6 months visit was usually performed 1 month following the completion of chemotherapy, and the 12-month assessment was performed at the routine 12 months follow-up visit.

2.3. Measures

2.3.1. Fatigue

The Profile of Mood States Short Form (POMS-SF; Curran et al., 1995) is a 37-item self-report scale assessing mood over the past week which has been used previously in cancer patient populations (Thornton et al., 2008). It is composed of 6 subscales: anxiety, dysphoria, anger, vigor, fatigue and confusion. The fatigue subscale consists of five words or phrases (i.e. "worn out," "exhausted," "weary") that are endorsed on a scale from 0 (not at all) to 4 (extremely). While fatigue is a heterogeneous concept, the POMS-fatigue subscale has been shown to correlate highly with other fatigue scales designed for cancer patients (Giacalone et al., 2010; Locke et al., 2007). In this study the fatigue subscale was used as an outcome measure in longitudinal analyses. The anxiety subscale was used as predictor of outcome variables in secondary longitudinal analyses.

2.3.2. Vegetative symptoms of depression

The Center for Epidemiological Studies Depression scale (CES-D; Radloff, 1977) is a 20 item self-report scale measuring frequency of depressive symptoms over the last week. Four subscales representing facets of depressive symptoms have been confirmed by factor analysis. These are depressed affect, vegetative depression, positive affect, and interpersonal relationships (Sheehan et al. 1995) Vegetative depression is characterized by reduced motivation and somatic complaints (i.e. "could not get 'going'", "had trouble keeping my mind on tasks," "sleep was restless"). Items were endorsed on a 0–3 point scale, with 0 representing symptoms occurred rarely, and 3 representing that symptoms occurred most or all of the time.

2.3.3. Performance status

Prior to surgery patients completed a measure of their Gynecologic Oncology Group performance status. Functional ability is rated from 0 (fully active) to 4 (completely disabled), with higher scores indicating less functional ability.

2.3.4. Sleep

A single item, "how many hours of sleep did you get on average in the last week?" was used in secondary analyses. Hours of sleep, rather than a measure of overall sleep quality, was used because most research linking sleep and glucocorticoid disruption has focused on hours of sleep deprivation rather than global sleep quality (Vgontzas et al., 1999; Weitzman et al., 1983).

2.3.5. Demographic, medical, and health information

Demographic data were obtained by patient self-report. Clinical information, including histology, stage, grade of tumor, and treatment history was abstracted from medical records.

2.3.6. Cortisol

Samples were collected upon awakening, in the afternoon between 16:00 and 18:30 p.m., and at bedtime for the 3 days before surgery, and 3 days following the 6- and 12-month clinic visit. Participants wrote the time of collection on the salivettes, a practice that has been shown to be reliable in previous studies (Kraemer et al., 2006). Salivary cortisol is stable at room temperature (Kirschbaum and Hellhammer, 1989). Assays were performed using a commercial chemiluminescence immunoassay (IBL, Hamburg, Germany) in the laboratory of Clemens Kirschbaum at the Technical University of Dresden. The lower detection limit is 0.41 nmol/L, and inter-assay and intra-assay coefficients of variance are <10%.

2.3.7. Interleukin-6

Detection of IL-6 in plasma was performed by enzyme-linked immunosorbent assay (R&D Diagnostics, Minneapolis, MN), with results interpolated from the standard curve provided with the kit. The minimum detectable level is less than 0.7 pg/mL and inter-assay variability for this assay ranges from 3.3% to 6.4%. IL-6 samples below the sensitivity of the regular assay were quantitated with the R&D High-Sensitivity ELISA. The obtained intra-assay coefficient of variance was less than 10%. Values were log (10) transformed to normalize their distribution.

2.4. Statistical analyses

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 19.0. All distributions were examined for outliers and normality before analysis.

2.4.1. Data reduction strategy

Before analyses, sampling time outliers for cortisol were removed. The first sample was collected in conjunction with personal awakening time, which is associated with a rise in cortisol (Kirschbaum and Hellhammer, 2000). Acceptable ranges of sampling times were determined to fit the maximum number of participants while maintaining a certain amount of homogeneity. Acceptable ranges were 0400 to 0900 h for morning cortisol, 1600 to 1830 h for afternoon cortisol, and 2000 to 2400 h for nocturnal cortisol. Samples which were more than four standard deviations above the mean of their particular time point were excluded (37 out of 1590 samples). Previous research has supported the use of aggregated cortisol measures to increase reliability of data (Kirschbaum and Hellhammer, 1989; Kraemer et al., 2006). Mean cortisol values at each time-point were calculated and values were transformed using the natural logarithm (ln) to normalize their distribution.

Because glucocorticoid dysregulation is characterized not only by elevations of salivary cortisol at particular times of day, but also by changes in diurnal slope, the slope of diurnal change in cortisol level was calculated in accordance with past research (Sephton et al., 2000, 2009). The 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 smaller (more negative) slope values, indicate more rapid salivary cortisol declines over the course of the day.

2.4.2. General linear model

To test for differences in interleukin-6 and cortisol levels between patients with low (stage 1 and 2) versus high stage disease (3 and 4), general linear models controlling for disease grade and patient age were used.

2.4.3. Mixed models

All longitudinal analyses used mixed effects models (SPSS MIXED procedure) with fixed slopes and intercept terms. This approach was used because such an analysis can handle unbalanced data and because it allowed us to control for correlated error where relevant (Laird and Ware, 1982). Since aging has been associated with alterations in the hypothalamic–pituitary–adrenal (HPA) axis (Deuschle et al., 1997) and with increased levels of IL-6 (Ershler et al., 1993), all analyses controlled for age. All analyses also controlled *a priori* for disease stage and grade as the best measures of disease severity which may be independently linked to inflammation (Macciò et al., 2009). Both IL-6 and nocturnal cortisol were included in all analyses to disaggregate their effects. As we have previously reported a strong relationship between nocturnal cortisol, fatigue, disability and vegetative depression at the time of surgery (Weinrib et al., 2010) we focused on nocturnal cortisol levels for longitudinal analyses involving the association of these quality of life measures with cortisol and IL-6.

Because associations have been reported between inflammatory processes and BMI (Fain, 2010; Illan-Gomez et al., 2012; Siervo et al., 2012), as well as with hours of sleep (Redwine et al., 2000; Vgontzas et al., 1999; Weitzman et al., 1983), in secondary analyses we tested models using BMI and hours of sleep, individually, as predictors of change in outcome variables. As improvements in inflammatory parameters and self-reported measures may be sensitive to anxiety (Campbell and Ehlert, 2012) change in anxiety was also tested independently as a predictor of change in all outcome variables. Finally, optimal vs. suboptimal surgical resection of tumor was examined to determine if reductions in inflammatory parameters were associated with better surgical outcome.

All models were first evaluated with an auto-regressive covariance structure. If residual correlations were non-significant, a diagonal covariance structure was employed. A diagonal covariance structure implies that there is no further relationship between variables beyond those specified in the model and that observations made on the same individual may be independent (Littell et al., 2000). Because of the significant time lag between measurements, approximately 6 months, this covariance structure was considered. An autoregressive covariance structure specifies that residual errors of observations on the same individual are correlated (Littell et al., 2000). Model fit was evaluated by Wald *Z* tests of rho covariance parameters and by comparison of Schwarz's Bayesian Criterion (BIC) to models with other covariance structures. Pairwise comparisons of estimated marginal means, using a Sidak adjustment, were conducted to examine changes from baseline to 6 months and from 6 months to 1 year.

2.4.4. Change in cortisol and IL-6 over time

Residual correlations in models of afternoon and nocturnal cortisol changes over time were not significantly different from zero according to Wald tests (both p values >0.089), suggesting a diagonal correlational structure is more appropriate. The use of a diagonal covariance structure for these models was further supported by a lower BIC value and highly significant diagonal variances (all p values <.0001), suggesting better model fit. In contrast, residual correlations in the model of change in morning cortisol concentrations and IL-6 were significantly different from zero according to Wald tests (p values <.0001); thus, an auto-regressive covariance structure was employed. This approach was justified by lower BIC values compared to the diagonal covariance structure

2.4.5. Change in self-reported measures with change in cortisol and IL-6

The models of the association of changes in vegetative depression, disability and fatigue with changes in IL-6 and cortisol had significant *rho* values according to the Wald test (all p<.036) so we employed an auto-regressive covariance structure. This approach was supported by lower (BIC) suggesting better model fit. Compared to models using auto-regressive heterogeneous covariance structures, Schwarz's Bayesian Criterion (BIC) was lower for our models, suggesting better fit.

3. Results

3.1. Patient characteristics

As seen in Table 1, the average age of participants at the time of surgery was 58 years (SD = 12.2). Most had advanced stage disease (72%), high grade neoplasms (85%) and serous histology (74%).

3.2. Covariates and potential confounding factors

Levels of IL-6 and nocturnal cortisol did not vary significantly between patients with early versus advanced stage disease (IL-6: $p = 0.176$; cortisol: $p = 0.741$) at baseline. Neither stage nor grade showed a significant association with changes in cortisol or IL-6 over time (all p values >0.174). Older patients showing significantly less pronounced changes in cortisol at each time-point between surgery and one-year (all p values <0.026); however, age did not have a significant association with changes in IL-6 over time ($p = 0.944$). In contrast, older patients reported significantly greater reductions in vegetative depression over time ($p = 0.006$). In secondary analyses, BMI, change in hours of sleep, change in

Table 1
Patients' demographic and clinical characteristics.

Measure	Cancer patients $N = 163$
Age in years	
Mean (SD)	57.5 (12.2)
Marital status	
Single	11.3%
Divorced/separated	12%
Widowed	12.7%
Married/living with partner	64%
Race	
American Indian/Alaskan native	1.2%
Asian	0.6%
African American	1.9%
Caucasian	96.3%
Ethnicity	
Hispanic	6.9%
Non-hispanic	93.1%
Cancer stage	
Stage I	20.3%
Stage II	7.6%
Stage III	63.3%
Stage IV	8.9%
Cancer grade	
Low	14.2%
High	85.8%
Tumor histology	
Serous	73.5%
Endometrioid	11.7%
Mucinous	4.9%
Clear cell	3.7%
Unknown/other	6.2%
Cytoreduction	
Optimal	75.9%
Suboptimal	24.1%

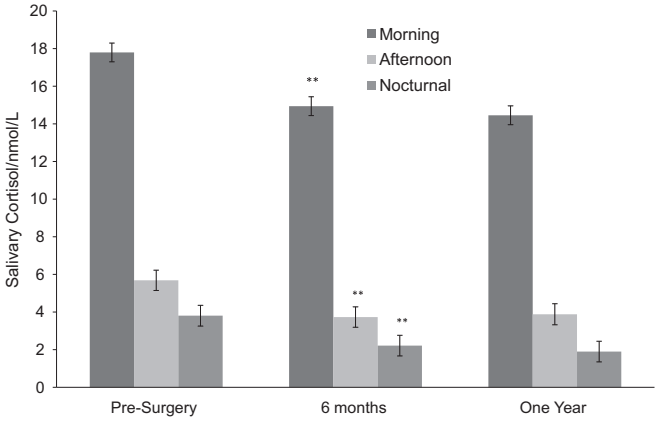

Fig. 2. Estimated marginal means of salivary cortisol concentrations pre-surgery, at 6 months and 1 year controlling for disease stage, grade, and age of patients. **Indicates a significant change ($p < .01$) from previous time point. Log transformed values are back-transformed.

anxiety and presence/absence of residual tumor, all had non-significant relationships with the outcome variables (all p values >0.17).

3.3. Changes in cortisol and IL-6 over time

Morning, afternoon and nocturnal cortisol levels dropped significantly over the course of the year following surgery (morning cortisol: $F_{2,93} = 5.75$, $p = .004$; afternoon cortisol: $F_{2,98} = 10.30$, $p < .0001$; nocturnal cortisol: $F_{2,95} = 17.21$, $p < .0001$). IL-6 decreased significantly over the year following surgery as well ($F_{2,201} = 66.21$, $p < .0001$). Pairwise comparisons of cortisol levels as a function of follow-up time-point revealed highly significant decreases for morning, afternoon and evening cortisol levels between surgery and 6 months (all p values <0.007), but no significant differences between 6 months and 1 year (both p values >0.633), suggesting relative stability during months 6–12. Diurnal slope became significantly steeper between surgery and 1 year ($F_{2,109} = 8.91$, $p < .001$) indicating that following primary treatment, a more normalized pattern of diurnal cortisol concentrations was observed. Similarly, IL-6 decreased between surgery and 6 months ($p < .0001$) but levels were relatively consistent between 6 months and 1 year ($p = .989$). Estimated marginal means are presented in Figs. 2 and 3. (Estimated marginal means provide a more accurate estimate of values than raw means when covariates are included in the model).

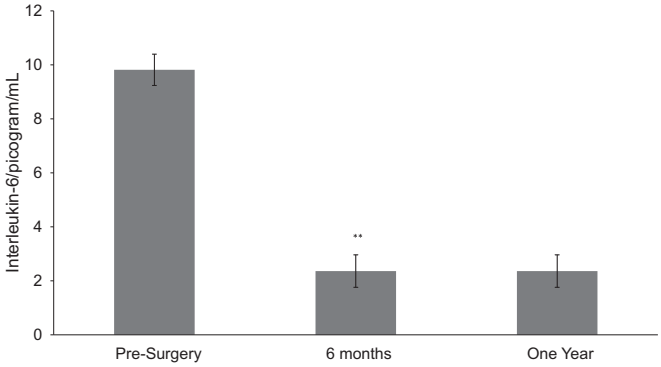

Fig. 3. Estimated marginal means of IL-6 in peripheral blood pre-surgery, at 6 months, and at 1 year controlling for disease stage, grade, and age of patients. **Indicates a significant change ($p < .01$) from previous time point. Log transformed values are back-transformed.

Table 2
Self report measures (estimated marginal means).

Measure	Pre-surgery $N = 168$	6-month $N = 114$	One-year $N = 92$
Self-Reported Measures Mean (standard error)			
POMS[a] fatigue subscale	7.93(.68)	6.76(.68)*	6.82(.74)
CES-D[b] vegetative subscale	6.79(.43)	4.51(.45)*	4.54(.48)
GOG[c] performance status	.86(.09)	.60(.10)*	.46(.10)

*Represents a significant change from previous time-point ($p < .05$), pair-wise comparisons with Sidak adjustment.
[a] Profile of mood states.
[b] Center for epidemiological studies-depression.
[c] Gynecological oncology group.

3.4. Relationships of changes in cortisol and IL-6 over time with fatigue and vegetative depression

During the period from surgery to 1 year, decreased IL-6 was significantly associated with decreased fatigue ($F_{1,120} = 5.24$, $p = 0.024$) and vegetative depression ($F_{1,188} = 12.20$, $p < 0.001$) and was marginally associated with decreased self-reported disability ($F_{1,180} = 2.91$, $p = 0.090$). Decreased nocturnal cortisol was significantly associated with decreased self-reported disability ($F_{1,172} = 7.41$, $p = 0.007$) and fatigue ($F_{1,116} = 3.96$, $p = 0.049$) and was marginally associated with decreased vegetative depression ($F_{1,180} = 3.30$, $p = 0.071$). Estimated marginal means are presented in Table 2. Parameter Estimates are presented in Tables 3–5.

4. Discussion

The key finding of this study is that following primary treatment of patients diagnosed with epithelial ovarian cancer, diurnal

Table 3
Parameter estimates, change in profile of mood states fatigue subscale.

Parameter	β	p
Disease stage		
1	−.44	.825
2	3.75	.136
3	1.73	.302
4	0	
Grade		
Low	−.046	.978
High	0	
Age	−.064	.132
Nocturnal cortisol[a]	1.05	.049
Interleukin-6[b]	1.75	.024

[a] Natural log-transformed.
[b] Log_{10}-transformed.

Table 4
Parameter estimates, change in gynecologic oncology group patient performance status.

Parameter	β	p
Disease Stage		
1	−.58	.035
2	−.51	.126
3	−.26	.260
4	0	
Grade		
Low	.24	.280
High	0	
Age	−.01	.223
Nocturnal cortisol[a]	.26	.007
Interleukin-6[b]	.20	.090

[a] Natural log-transformed.
[b] Log_{10}-transformed.

Table 5
Parameter estimates, change in self-reported center for epidemiologic studies – depression vegetative depression subscale.

Parameter	β	p
Disease Stage		
1	−.97	.419
2	−.67	.643
3	−1.37	.180
4	0	
Grade		
Low	−.68	.507
High	0	
Age	−.07	.005
Nocturnal cortisol[a]	.66	.071
Interleukin-6[b]	1.75	.001

[a] Natural log-transformed.
[b] Log_{10}-transformed.

cortisol rhythms become more normalized, and IL-6, a key indicator of inflammation, markedly decreases. Morning, afternoon and nocturnal cortisol levels decreased significantly between the time of surgery and 6 months follow-up; peripheral blood IL-6 followed the same pattern. The diurnal cortisol slope became steeper between surgery and 6 months follow-up; this more normalized slope was also maintained at 1 year. Prior to surgery afternoon salivary cortisol concentrations in ovarian cancer patients were 33% higher than those of a group of healthy women previously studied in our lab, and nocturnal concentrations were 51% higher (Weinrib et al., 2010). In contrast, at the six-month clinic visit, afternoon and nocturnal levels were comparable to the healthy community sample (Weinrib et al., 2010). Pre-surgical IL-6 levels of ovarian cancer patients were almost four times higher than ranges previously reported for healthy adults (Ferrucci et al., 1999; Sergi et al., 2011); IL-6 levels dropped to approximate the range for healthy older adults by 6 months post-surgery. Both IL-6 and cortisol levels were fairly constant between 6 months and 1 year, suggesting that the normalization of peripheral blood IL-6 and cortisol rhythms seen at 6 months was maintained at 1 year in patients who did not experience disease recurrence. These longitudinal findings extend previous cross-sectional findings reporting higher levels of IL-6 and disrupted cortisol rhythms in women with ovarian cancer (Lutgendorf et al., 2008; Tempfer et al., 1997; Zakrzewska and Poznanski, 2001; Weinrib et al., 2010) and demonstrate for the first time that successful primary treatment is associated with persistent decreases in inflammation-linked substances in ovarian cancer patients.

The most likely explanation for the reduction in markers of systemic inflammation and normalization of cortisol is reduction or elimination of the cytokine-secreting tumor mass via primary chemotherapy and surgery. Solid neoplasms such as epithelial ovarian tumors secrete IL-6 (Nilsson et al., 2005; Obata et al., 1997; Offner et al., 1995; Watson et al., 1990). IL-6 facilitates the action of interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) on the hypothalamus (Perlstein et al., 1991; Sparkman et al., 2006; Zhou et al., 1996) thus ultimately increasing cortisol secretion (Alesci et al., 2005; Mastorakos et al., 1993). The majority (76.3%) of the patients in this study experienced optimal cytoreduction, indicating the presence of less than 1 cm of residual disease following surgery. Further reduction/elimination is thought to have been achieved through chemotherapy, and participating patients were considered disease-free at the time of 6 months and/or 1 year follow-ups.

In previous work we found no differences in pre-surgical anxiety or distress between women whose pelvic mass was subsequently determined to be benign and those with ovarian cancer. Despite this, the ovarian cancer group had higher levels of evening cortisol and a flatter diurnal slope (Weinrib et al., 2010). We have also previously reported that levels of plasma IL-6 are much higher in ovarian cancer patients than in those with tumors of low malignant potential (LMP) prior to surgery (Lutgendorf et al., 2008), despite equivalent pre-surgical anxiety. In the current data, change in anxiety did not predict change in any of the outcome variables. Taken together, these findings support our contention that the normalization of inflammatory parameters and improved quality of life are not due to reductions in cancer-related anxiety but to primary treatment for ovarian cancer. This lends support to the hypothesis that glucocorticoid disruption and elevated IL-6 in ovarian cancer patients is due, at least in part, to tumor-derived inflammation.

Decreases over time in nocturnal cortisol and IL-6 were associated with decreases in self-reported fatigue and vegetative depression over the same time period. These findings extend our previous cross-sectional observations of relationships between these factors at the time of surgery (Weinrib et al., 2010) and are consistent with reports of associations of glucocorticoid dysregulation with conditions characterized by fatigue and vegetative depression (Marques et al., 2009; Neeck and Crofford, 2000; Vegiopoulos and Herzig, 2007). Moreover, our findings indicate that reductions in self-reported impairments are maintained at 1 year in patients who remain disease-free. Previous research has demonstrated improvement in QOL measures in ovarian cancer patients following chemotherapy (Von Gruenigen et al., 2006; Wenzel et al., 2007). Vegetative depression and fatigue have been found to greatly influence overall QOL in this population (Fox and Lyon, 2007). Our findings suggest that part of this improvement may be linked to the reduction of tumor-associated inflammation and

normalization of cortisol patterns, which appear to be related to primary treatment.

It is likely that several processes contribute simultaneously to changes in vegetative depression in ovarian cancer patients. The interactions of pro-inflammatory cytokines such as IL-6 with the central nervous system have been well characterized. (Conti et al., 2004; Terreni and De Simoni, 1998) and IL-6 has been linked to depressive spectrum behaviors characterized as "sickness behaviors" (Dantzer et al., 2002; Dantzer, 2006). Both IL-6 and hypercortisolemia have been linked to depression (Dowlati et al., 2010; Howren et al., 2009; Liu et al., 2011; Lopez-Duran et al., 2009; Stetler and Miller, 2011) and disruption of cortisol rhythms has been linked to depression in breast and ovarian cancer populations (Abercrombie et al., 2004; Jehn et al., 2006); Lutgendorf et al., 2008; Weinrib et al., 2010) It is possible that the residual tumor mass may have affected both inflammatory pathways and self-reported functional outcomes. However, extent of surgical resection was not significantly associated with reduction of inflammation. It is also possible that physical discomfort and or pain associated with the tumor mass and/or ascites may have affected inflammatory pathways and functional outcome measures independently (De Jongh et al., 2003; de Oliveira et al., 2011). Because the current study does not include substantive measures of pain we were unable to examine the relationship of pain with variables of interest. Future research should consider the role of pain in inflammation reduction.

4.1. Limitations

These findings are correlational, and even though longitudinal analyses have several advantages over cross-sectional designs, no causal relationships can be inferred. Our findings are limited to a subset of patients who were without diagnosed disease progression at 6 months and 1 year. Levels of inflammation and their associations with vegetative depression, disability and fatigue in patients with disease progression cannot be inferred from these results. Imminent surgery precluded quite a few patients from collecting cortisol at the pre-surgical time-point, and participation at 6 months and 1 year follow-ups was diminished by the burden of sample collection; thus the reduced sample of patients who collected cortisol may not be fully representative of the whole spectrum of ovarian cancer patients. As patients included in this study did not require supplemental treatments (i.e. additional chemotherapy) they may represent a healthier subset of all ovarian cancer patients with more normalized levels of biomarkers. Additionally, a larger patient sample may have allowed comparisons of biomarkers in the present sample to levels in patients with disease recurrence. Associations with disability should be interpreted with caution; we do not propose any specific mechanisms by which cortisol or IL-6 might induce physical limitations. It is possible that disability reported at the time of surgery was secondary to the physical burden of tumor and ascites and associated discomfort and that decreases of self-reported disability are not necessarily the consequence of reductions in IL-6 and cortisol normalization. Our model did not allow for discrimination of within-person changes from between-person, static effects. It is therefore not possible to distinguish which effects drove the significant coefficients.

5. Conclusions

These findings extend previous cross-sectional observations by demonstrating normalized levels of IL-6 and cortisol in epithelial ovarian cancer patients following primary treatment. Normalization of inflammation and diurnal cortisol patterns was paralleled by improvements in functional abilities of patients. Inflammatory cytokines and cortisol may contribute to patterns of vegetative symptoms. Further research may focus on the trajectory of other angiogenic and inflammatory molecules following primary treatment and the relationship of IL-6 reduction and cortisol normalization to disease course in ovarian cancer patients. As alterations in glucocorticoid secretion are associated with changes in expression of the glucocorticoid receptor these findings may have important implications for disease mechanisms. Characterizing the trajectory of mediators of inflammation may lead to innovative therapies in the treatment of epithelial ovarian cancer.

Conflict of Interest

The authors of this manuscript have nothing to declare.

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