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Depressive Symptoms and Cortisol Variability Prior to Surgery for Suspected Endometrial Cancer

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Summary

Endometrial cancer (EC) is the most common type of gynecologic cancer affecting women; however, very little research has examined relationships between psychological factors and hypothalamic-pituitary-adrenal (HPA) axis dysregulation in this population. The current study examined relations between depressive/anxious symptoms and salivary cortisol diurnal rhythm and variability in women undergoing surgery for suspected endometrial cancer. Depressive and anxious symptoms were measured prior to surgery using the Structured Interview Guide for the Hamilton Depression Inventory (SIGH-AD). Saliva was collected four times a day for the three days prior to surgery and then assayed by ELISA to obtain cortisol concentrations. Cortisol slopes and intraindividual variability were then calculated across subjects. Relations between depressive/anxious symptoms and cortisol indices were examined using multilevel modeling and linear regression analyses. Participants were 82 women with nonmetastatic endometrial cancer. Anxious symptoms were not associated with either cortisol slope or intraindividual variability, and depressive symptoms were unrelated to cortisol slope. However, after controlling for presence of poorer prognosis cancer subtypes, greater depressive symptoms (excluding symptoms possibly/definitely due to health/treatment factors) in the week preceding surgery were significantly related to greater cortisol intraindividual variability (β=.214; p<.05). These results suggest that depressive symptoms prior to surgery for suspected endometrial cancer are related to greater cortisol intraindividual variability, which is suggestive of more erratic HPA axis arousal. Future research should examine whether mood symptoms may be associated with compromised health outcomes via erratic HPA axis arousal in this population.

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Keywords

Endometrial Cancer; Cortisol; Intraindividual variability; Anxiety; Depression

1. Introduction

Cortisol is a glucocorticoid released by the hypothalamic-pituitary-adrenal (HPA) axis of the central nervous system during periods of stress or challenge. This glucocorticoid is also a potent anti-inflammatory agent with immunosuppressive properties and has also been implicated as playing a role in tumorigenesis (Antoni et al., 2006), particularly in cancers affecting women, who have been theorized to be differentially affected by the effects of stress hormones (Chrousos, 2010). In vitro models of ovarian cancer suggest that cortisol may potentiate catecholaminergic effects on tumor invasiveness (Nakane et al., 1990; Sood, et al., 2006) and upregulate pro-angiogenic factors in the tumor microenvironment, such as vascular endothelial growth factor (Lutgendorf, et al., 2003) and matrix metalloproteinase expression (Lutgendorf, Lamkin, et al., 2008). In the clinical literature, breast cancer patients with more advanced disease have greater average cortisol output compared to those with less advanced disease (Abercrombie, et al., 2004), and flatter cortisol slope is predictive of earlier mortality in breast cancer patients (Sephton, Sapolsky, Kraemer, & Spiegel, 2000). In sum, research in tumor biology and clinical models suggest that greater cortisol output and flatter cortisol rhythm (slope) may influence cancer progression in some cancers (Antoni, et al., 2006).

Relationships between psychological factors and cortisol in female cancer populations have also begun to emerge. For instance, breast cancer patients who suppress emotions display a flatter cortisol rhythm (slope) (Giese-Davis, Wilhelm, et al., 2006). Behavioral stress management techniques designed to modulate HPA-functioning in breast cancer patients have been shown to reduce serum cortisol, and this effect may be mediated by changes in appraisals, such as increased benefit finding and perceived ability to relax (Antoni, et al., 2009; Phillips, et al., 2008). In response to follow-up mammography, breast cancer survivors experience higher levels of cortisol preceding mammography and have a suppressed cortisol response (i.e., decreasing trend of cortisol following mammography, whereas the control group had an increased response) (Porter, et al., 2003), suggesting that breast cancer patients may experience higher overall levels of HPA-axis output (cortisol), but experience blunted physiological reactions to stressors (e.g., mammography). In ovarian cancer, greater cortisol output (i.e., area under the curve) is associated with greater pro-inflammatory cytokine (IL-6) release, and greater vegetative depressive symptoms are related to greater evening cortisol values (Lutgendorf, Weinrib, et al., 2008). Moreover, greater functional disability, fatigue, and vegetative depression are associated with high levels of nocturnal cortisol, as well as less diurnal cortisol change (i.e., lower ratio of nocturnal to morning cortisol values) in ovarian cancer (Weinrib, et al., 2010). In summary, psychological reactions to cancer may be related to HPA-axis functioning, both in responses to cancer diagnosis and treatment and in responses to psychological interventions.

No research to date has examined cortisol and psychological factors in endometrial cancer, which is the most common form of gynecological malignancy and the fourth most common cancer among women. The American Cancer Society estimates that 43,470 new cases will be diagnosed and 7,950 women will have died from the disease in 2010. While many cases of endometrial cancer are caught at an early stage, the 5-year survival-rate for stages III and IV cancer are 58% and 17% respectively (American Cancer Society, 2010). In fact, while the mortality rates of both breast cancer and ovarian cancer have decreased steadily over the past several decades, the mortality rate of endometrial cancer has remained stable since 1991

(American Cancer Society, 2010). These statistics highlight the fact that endometrial cancer remains a substantial public health burden. In spite of this, there remains a paucity of research examining relationships between psychological variables or physiological parameters of stress, associated with receiving a diagnosis of endometrial cancer and/or undergoing treatment for the disease. We have recently reported that a protein relevant to carcinogenesis and psychological stress (heat shock protein 70) is related to negative mood states in a small group of women undergoing treatment for suspected endometrial cancer (Pereira et al., 2010); however, no published research to our knowledge has examined the relationship between psychological factors and cortisol dysregulation in this clinical population specifically.

Although there are a number of approaches to modeling diurnal cortisol patterns (Adam & Kumari, 2009), there has been little consensus on the most appropriate method (Stewart & Seeman, 2000). Many use aggregate summations of cortisol slopes across days (Kraemer et al., 2006; Sephton et al., 2000), or characterize the total diurnal output via area under the curve analyses (Pruessner et al., 1997). In both approaches, greater cortisol output overall and less robust responses to endogenous cortisol production throughout the day are thought to represent dysregulation of the HPA-axis (Keller, et al., 2006). More recently, investigators have focused on capturing individual differences in the cortisol response through multilevel modeling techniques (Adam & Kumari, 2009; Hruschka, Kohrt, & Worthman, 2005), including hierarchical linear modeling (HLM) (Singer & Willet, 2003), which allow for the estimation of individual differences. Using these methods, one may calculate intraindividual cortisol variability or intraindividual standard deviation, a variable that represents the amount of variability in an individual's diurnal cortisol values when compared to that same individual's typical cortisol values.

Predictors of intraindividual cortisol variability (measured across days of cortisol collection to reliably estimate erratic cortisol output) are beginning to emerge in the literature, and include factors such as age (Tollenaar et al., 2010) and sex (Almeida, Piazza, & Stawski, 2009). Notably, relations have started to emerge between psychological factors, mood disorders in particular, and cortisol variability. For instance, applying multilevel modeling techniques to model intraindividual differences, greater intraindividual cortisol variability has been shown in individuals with major depressive disorder (Peeters et al. 2004) and remitted bipolar disorder (Havermans, Nicolson, Berkhof, & Devries, 2010) compared to controls. Furthermore, significant associations were demonstrated between greater depressive episode severity, more frequent depressive episode recurrence and greater intraindividual cortisol variability (Havermans et al., 2010). Taken together, these findings suggest that mood disturbances are associated with a more erratic pattern of cortisol production, which may be a novel index of cortisol dysregulation.

In summary, while recent work has examined intraindividual cortisol variability in healthy and psychiatric populations, it remains unclear how depressed mood may be associated with this construct, as a measure of cortisol dysregulation, in cancer. Therefore, the purpose of the present study was to examine the relationship between mood symptoms and cortisol dysregulation in women undergoing surgery for suspected endometrial cancer. In particular, diurnal cortisol slope and intraindividual cortisol variability were examined. Based on prior published research, it was hypothesized that greater depressive/anxious symptoms would be associated with a flatter cortisol slope and greater intraindividual cortisol variability.

2. Subjects and methods

2.1. Subjects

Participants were women undergoing total abdominal hysterectomy and bilateral salpingo oophorectomy (TAH–BSO) for suspected endometrial adenocarcinoma. Exclusion criteria included nonfluency in English, pre-menopausal status, recurrent endometrial cancer, neoadjuvant chemotherapy, pre-surgical radiation therapy, or primary cancer originating from a site other than the uterine corpus. Participants were also excluded if severe psychiatric illness was documented in the medical record.

2.2. Procedures

Recruitment for the study took place in a gynecologic oncology clinic at the University of Florida/Shands Health Science Center between June 2004 and August of 2009. Women were approached at their initial surgical consultation (following an abnormal endometrial biopsy) and, if interested, completed University of Florida Institutional Review Board approved informed consent procedures. Participants were scheduled to return to the clinic one week later for a pre-surgical medical evaluation and were provided the following materials to complete and return at this visit: (a) a packet of psychosocial questionnaires, and (b) a salivary cortisol collection kit. At this pre-surgical appointment, participants returned these materials, and study staff completed a psychosocial interview to assess depressive and anxious symptomatology. Participants received $20 compensation for study participation. Saliva samples were immediately transported to the laboratory for processing and storage. Following participants' surgeries, study staff reviewed participants' medical charts and abstracted history of comorbid medical conditions and tumor cellular classification, stage, and grade data.

2.3. Assessment

2.3.1. Depression and anxiety—Depressive and anxious symptomatology during the week prior to surgery was measured using Structured Interview Guide for the Hamilton Anxiety and Depression scales (SIGH-AD; Williams, 1988). Doctoral students in clinical health psychology administered the interviews. All students were trained to administer the interview by D.P., who is also a licensed psychologist. The SIGH-AD has been used widely in medical populations and has adequate reliability and validity in these settings (Cruess, Antoni, Kumar, & Schneiderman, 2000). An abbreviated (24 item) version of the SIGH-AD (15 depression items and 9 anxiety items) was used in order to reduce patient burden and to remove items confounded with endometrial cancer symptomatology, such as genitourinary symptoms or weight loss. Symptom severity ratings were summed to yield scores for total depressive (possible range of 0-44) and anxious symptomatology (possible range of 0-29). Then, depressive symptoms severity ratings judged by the interviewer as possibly or definitely due to health/treatment factors were then subtracted from the total depressive symptomatology score to yield a score unconfounded by health/treatment factors. This latter score was used as a predictor in analyses.

2.3.2. Cortisol—Participants collected saliva samples at 8:00, 12:00, 17:00 and 21:00 hours for three consecutive days immediately prior to their surgery. These time points were chosen, as they have been used in studies linking cortisol slope to clinically meaningful outcomes, such as mortality, in cancers affecting women (Sephton et al., 2000). They were instructed not to brush their teeth, eat or drink, and smoke for a half hour prior to collecting saliva samples. Participants were asked to record the exact time of collection, in an effort to verify their adherence with instructions. Participants were asked to refrigerate the saliva samples until they were able to bring them to their pre-operative study visit, and they were provided with a small, insulated cooler to transport the samples back to the research team.

Once received by study personnel, saliva samples were frozen at −80 degrees Celsius until they were shipped to Salimetrics Inc. (State College, PA) for assaying. Samples were assayed for salivary cortisol in duplicate using a highly sensitive enzyme immunoassay (Salimetrics, State College, PA). The test used 25 μl of saliva per determination, has a lower limit of sensitivity of 0.003 μg/dl, standard curve range from 0.012 μg/dL to 3.0 μg/dL, an average intra-assay coefficient of variation of 3.5% and an average inter-assay coefficient of variation of 5.1%. Method accuracy determined by spike and recovery averaged 100% and linearity determined by serial dilution averaged 91.7%.

2.3.3. Control variables—Demographic variables (age, race/ethnicity, yearly income and education level) and relevant behavioral factors (tobacco, alcohol and other drug use) were collected via self-report measures and face-to-face interviews. Health factors possibly associated with cortisol were also obtained from medical chart review, including tumor stage/grade (Abercrombie et al., 2004) and a sum of the number of medications being taken that may affect HPA-axis functioning (Progesterone, NE-dopamine reuptake inhibitors, anti-hypertensives, adrenocortical steroids). Medical comorbidity was calculated using the Charlson Comorbidity index. This index tallies all pre-existing medical conditions (e.g., congestive heart failure, diabetes) and creates a sum score for each individual (Charlson, Pompei, Ales, & MacKenzie, 1987). In addition, adenocarcinoma subtype (Type I versus Type II) was covaried. Type I adenocarcinoma includes endometrioid adenocarcinoma, the most common subtype. Type I adenocarcinoma is considered to be a “low grade” variant carrying a favorable prognosis. Type II adenocarcinomas include uterine papillary serous and clear cell adenocarcinomas, both of which are considered aggressive “high grade” variants with poorer prognoses. To control for the potential relationship between tumor burden and cortisol rhythms (Abercrombie et al., 2004), a dichotomous variable was created: participants with preinvasive endometrial disease (complex hyperplasia with atypia) and Type I adenocarcinoma were coded as “0,” while those with Type II adenocarcinomas (clear cell, mucinous, or uterine papillary serous) were coded as “1.”

2.4. Statistical analyses

2.4.1. Data preparation—Descriptive statistics were examined for each variable of interest. Normal probability histograms were examined for all cortisol outcome variables. If deemed non-normal, outliers (values greater than 3 standard deviations from the mean) were removed and, if necessary, an appropriate statistical transformation was applied to ensure adequate characteristics of normality. All analyses were conducted with SPSS Version 17.0 (Chicago, IL).

2.4.2 Modeling and predicting diurnal cortisol slope—Multilevel modeling (MLM) was applied to examine potential relationships between psychological variables of interest and cortisol. MLM has been increasingly used to model the diurnal time trends observed in cortisol (Adam & Gunnar, 2001; Almeida et al., 2009; Hruschka et al., 2005). Following Singer and Willett (2003), only the k-2 polynomial trends are identified; therefore, we tested linear and quadratic time trends. The quadratic time trend was included in the final model after removing the collinear effects of the linear time trend. To make estimates of cortisol more interpretable, saliva collection times were rescaled to have the starting value equal zero while keeping the original scale between points of time to preserve the original distance between points of collection. In addition, given that participants recorded the actual time at which saliva was collected, the average sample time at which each of the four cortisol measurements were taken (over the three days) was used as the time-of-day predictor. Data were represented by three levels of data collection: time of cortisol collection within day of collection (Level 1), day of collection (Level 2) and between-persons differences (Level 3). Analyses revealed that the Level 2 “Day” effect was not significant and contributed to

model convergence problems; it was therefore eliminated from all analyses that followed. The final analyses included two levels of analysis: time within day and between-person differences in cortisol. To examine between-person predictors of interest, two separate models were run: one including SIGH-AD Depression as a continuous predictor and one including SIGH-AD Anxiety as a continuous predictor. These were entered as Level 2 predictors to explain individual differences in initial value of cortisol (SIGH-AD Depression and Anxiety main effects as two separate models) and cortisol slope (SIGH-AD Depression*time interaction and SIGH-AD Anxiety*time interaction as two separate models). Both depression and anxiety scores from the SIGH-AD were centered to ensure that parameter estimates were more interpretable (Blackwell, de Leon, & Miller, 2006). The following control variables were examined and included in the analyses if they significantly predicted the cortisol time trend or if they significantly improved the model fit based on comparing −2 log likelihood ratios in maximum likelihood estimation: sum of the number of relevant medications prescribed and used (listed above), current smoking status (recoded as a dichotomous variable; 0=current non-smoker, 1=current smoker), cancer stage, tumor grade, Type I vs. Type II subtypes, and Charlson Comorbidity score.

2.4.3. Modeling and predicting intraindividual cortisol variability—MLM was also used to examine intraindividual variability in cortisol output. In order to examine variability in the context of data with significant time trends, the data were first “detrended,” in order to eliminate the time trend as a potential confound (Hultsch & MacDonald, 2004). To this end, MLM was applied to accurately model the anticipated diurnal time trend of cortisol of cortisol production throughout the day, and the residuals of each individual’s regression were saved. This approach is similar to what has been called “beep-level variance” (Peeters, Nicolson, & Berkhof, 2004) cortisol pulsatility (Young, Abelson, & Lightman, 2004) and approximate entropy in cortisol production (Posener, et al., 2004), which refer to what level individuals vary from their typical cortisol output, after controlling for the anticipated diurnal time trend.. In the present study, the standard deviation of each individual’s residual was then saved as a separate variable, creating a variable of cortisol intraindividual variability (Stuart, Macdonald, Hultsch & Bunce, 2006). Bivariate Pearson correlation analyses were conducted to examine the relationship between cortisol variability and the psychological variables of interest (depression/anxiety). Any significant psychological variable-cortisol variability correlations were then explored further using hierarchical regression analyses (ordinary least squares) while controlling for variables associated with cortisol. Modeling of the cortisol trend used the MIXED feature within the SPSS program.

3. Results

3.1. Subject characteristics

One hundred thirty-four women were enrolled into the study. Three of these participants were excluded for having adenomyosis (a benign endometrial condition) and/or complex hyperplasia without atypia (a hyperplastic condition with very little likelihood of progressing to invasive cancer) following surgery. Of the remaining 131 participants, 26 were excluded, as they did not contribute any psychosocial or cortisol data due to systematic data collection problems (e.g., participant was discharged from clinic without the knowledge of the study researchers and before any data could be collected). Of the 105 remaining participants, 82 contributed complete psychosocial data and more than 1 saliva sample. Analyses were conducted on these 82 participants. Comparison of these 82 participants to the 23 who provided only partial psychosocial and/or cortisol data revealed that there were no statistically significant differences on major demographic, psychosocial, or cancer-related variables between the final sample of 82 and the 23 providing only partial data (see Table 1).

3.2. Cortisol values

Participants' raw cortisol values were examined for normality, and two cortisol values were determined to be 3 standard deviations from the mean and were eliminated from further data analyses. After the removal of these outliers, cortisol data displayed adequate characteristics of normality. Mean raw cortisol values for each time of collection are presented in Figure 1.

3.3. Depressive/anxious symptomatology and diurnal cortisol slope

Depressive symptomatology scores ranged from 0 to 30 (M=6.66; SD=5.66), while anxious symptomatology scores ranged from 0 to 21 (M=5.17; SD=4.01). Depressive symptomatology scores were non-normally distributed, and therefore a square root transformation was applied to ensure adequate characteristics of normality. As previously stated, multilevel modeling was applied to model the cortisol data and account for the diurnal time trend typically observed in cortisol rhythms. As expected, a significant negative linear time trend was observed in cortisol (β = −0.015, SE = .0012, p<.001) as well as a significant positive quadratic trend at the end of the day (β = .0016, SE = .0003, p<.001). There was not a significant trend of cortisol across days (β = .0015, SE = .0065, p=.82). Also as expected, there was significant variance, or significant random effects, in both the first measurement of cortisol at 8AM (p<.001), linear time trend within the day (p<.001).

Out of the possible control variables investigated (current smoking status, cancer stage, tumor grade, adenocarcinoma subtype, medication use[1]), only the Charlson comorbidity score was significantly related (p<.05) to cortisol slope in the multilevel model; therefore, only comorbidity score was retained as a control variable in the depression and anxiety conditional growth model[2].

After controlling for comorbidity, neither depressive nor anxious symptoms predicted the initial value of cortisol (β = 0.015, SE = 0.014, p=.29; and β = 0.0014, SE = 0.0038, p=.72; respectively). Similarly and contrary to hypotheses, neither depressive nor anxious symptoms predicted linear cortisol slope across the three days preceding surgery (β = −0.00044, SE = 0.00033, p = .19; and β = −0.00025, SE = 0.00029, p = .41; respectively). Furthermore, neither depressive nor anxious symptoms were related to the positive quadratic trend observed in the cortisol rhythm within day (data not shown).

3.4. Depressive/anxious symptomatology and intraindividual cortisol variability

Intraindividual cortisol variability data were examined for normality. Cortisol variability data was non-normal and therefore a square root transformation was applied. After applying this transformation, the data displayed adequate characteristics of normality. Of the control variables examined, only adenocarcinoma subtype was associated with intraindividual cortisol variability; specifically, participants with Type II adenocarcinomas had significantly lower cortisol variability than those with Type I adenocarcinomas, t(81)=2.33, p=.023.

Using Pearson correlations, intraindividual cortisol variability was not related to anxiety symptoms, r (82) = .110; p=*ns*. However, intraindividual cortisol variability was marginally significantly associated with depressive symptomatology, r(82) = .197; p=.07. Given the significant group difference in intraindividual cortisol variability between Type I and Type II adenocarcinomas, a hierarchical regression (ordinary least squares regression in which predictors are entered in theoretically ordered blocks) was conducted controlling for

[1]Only 8 patients were taking corticosteroids (primarily inhalers) at the time of data collection. The models presented were re-run excluding these participants and the results were not affected (data not shown).

[2]Both MLM models with comorbidity index as a control and without controls were estimated. The inclusion of Charlson comorbidity index scores did not significantly improve model fit (-2 log likelihood chi square comparison); however, it was retained as a control variable given that comorbidity significantly predicted cortisol slope.

presence of Type II adenocarcinomas. After controlling for the presence of aggressive, high-grade adenocarcinoma variants, greater depressive symptomatology was significantly associated with greater intraindividual cortisol variability (β=.214; p<.05) (Figure 2).

To further illustrate the relationship between depressive symptomatology and intraindividual cortisol variability, raw cortisol values were plotted for the five participants reporting the lowest depressive symptoms (i.e., no depressive symptoms) prior to surgery (Figure 3a) and the five participants with the greatest depressive symptoms prior to surgery (Figure 3b). As suggested by these Figures, compared to participants with no depressive symptoms, participants reporting the greatest depressive symptoms demonstrated greater dispersion of raw cortisol values from their individual regression slopes.

4. Discussion

Recently, Garssen, Boomsma, and Beelen (2010) identified research examining relations between psychological factors and biological stress systems during the perioperative period in cancer as a high priority area (Garssen, Boomsma, & Beelen, 2010). In spite of the fact that (a) endometrial cancer is one of the most common cancers among women and (b) major abdominal surgery is the primary treatment for most early stage, endometrioid adenocarcinomas, very few published studies have examined psychosocial – biological stress system relationships in endometrial cancer. As such, the purpose of the present study was to examine the relationship between depressive/anxious symptomatology and intraindividual cortisol variability and cortisol slope in women proceeding to TAH-BSO for suspected endometrial cancer.

Results revealed that, in contrast to hypotheses and related prior research (Bhattacharyya, Molloy, & Steptoe, 2008), depressive symptomatology was not related to cortisol slope. There are several possible explanations for this result. First, the SIGH-AD queried only about the incidence and severity of mood symptoms in the week prior to participants' scheduled surgeries, and as such, it did not allow for a diagnosis of depression or an assessment of the chronicity of mood symptoms. It is possible that the physiological resistance to glucorticoid secretion that would yield a flattened cortisol slope may only be observed among those with major depressive disorder or prolonged, moderate to severe depressive symptomatology (Miller, Cohen, & Ritchey, 2002). As such, the nonsignificant results of the present study may not be comparable to those obtained among patients with severe or long-standing mood symptoms. Second, participants in the present sample reported relatively low levels of depressive symptomatology, and the nonsignificant relationship between depression and cortisol slope may be due to the low amount of variance in depressive symptomatology. Third, our study may have been underpowered to detect an effect in the multilevel model tested in our study.

However, consistent with hypotheses, greater depressive symptomatology in the week prior to surgery was significantly associated with greater intraindividual cortisol variability. These findings are in accord with prior work demonstrating higher cortisol variability in major depressive disorder (Peeters, et al., 2004) and episode severity in remitted bipolar disorder (Havermans, et al., 2010). However, the clinical implications of these results are unclear at the present time, partly because no published research has examined the relationship between intraindividual cortisol variability and clinical outcomes in cancer. It is possible that greater intraindividual cortisol variability may be indicative of greater circadian rhythm disruption. For instance, it is well established that individuals with chronic and severe disruptions in the sleep-wake cycle (i.e., a circadian rhythm) demonstrate greater variability in subjective and objectives measures of sleep efficiency than nonimpaired controls (Buysse, et al., 2010). Extrapolating from this research, it is possible that high levels of

intraindividual cortisol variability are indicative of HPA axis functioning that is erratic, unpredictable, and inappropriately under- and over-responsive to the actual demands of the host and his/her environment. While it is presently unknown whether high intraindividual cortisol variability has negative long-term health implications in cancer, it is noteworthy that there is some research suggesting that circadian rhythm disruption may be associated with carcinogenesis (Sephton & Spiegel, 2003; Touitou, Bogdan, Levi, Benavides, & Auzeby, 1996). Future research should examine intraindividual cortisol variability, as well as other indicators of circadian disruption such as sleep disturbances, longitudinally to establish whether they are associated with cancer outcomes, such as disease free survival.

Contrary to hypotheses, anxiety was not significantly associated with cortisol slope or intraindividual cortisol variability in the present study. Prior published research has suggested a relationship between anxiety and cortisol (AUC) in breast cancer patients (Giese-Davis, DiMiceli, Sephton, & Spiegel, 2006; Vedhara, et al., 2003). However, substantial methodological differences exist between these studies and the present study. For example, Giese-Davis and colleagues (2004) found that those who repressed emotions and high-anxious groups had significantly flatter diurnal slopes when compared to cortisol profiles of those classified as self-assured in this sample. This finding suggests that there may be important moderators of the relationship between anxiety and cortisol slope in women with cancer, a hypothesis that warrants future examination. Antoni and colleagues (2009) recently found that Cognitive Behavioral Stress Management (CBSM) improved mood symptoms, lowered cortisol levels, and promoted adaptive cytokine regulation in women with breast cancer. However, this investigation did not uncover a significant mediating effect of anxiety on the relationship between reductions in cortisol and participating in CBSM, suggesting that reductions in cortisol may not always be driven by reductions in anxiety. Future investigations should remain mindful to include potential mediators/moderators of anxiety-cortisol relationships.

The findings of the present study should be interpreted in light of several limitations. First, the study design was nonexperimental, and as such, causal interpretations cannot be made. Future research should employ experimental designs to assess causality. Second, although the study design captures three days worth of data, only limited cortisol variance or fluctuation is captured across the 12 time points. A larger sample with more cortisol measurements may yield more robust findings, or possibly, different results. Third, the mixed model analysis was only able to accurately model a portion of the cortisol trend. Therefore, the residuals used to calculate the intraindividual cortisol variability may not accurately control for the entire time trend seen in the diurnal cortisol variation within the day. Applying the residuals to additional mixed model approaches may be warranted, as others have suggested (Almeida, Piazza, & Stawski, 2009). In future investigations, including different error structures and autocorrelations between timepoints of cortisol collection in calculating cortisol variability may also be informative (Peeters et al., 2004). Fourth, the study design lacked a benign-disease only comparison group. Inclusion of a comparison group would allow for the examination of differences in mood/cortisol relationships between women with surgically-staged gynecologic cancer and those with surgically-confirmed benign disease in addition to being able to tease out the contribution of cancer-related biological factors to psychological factors-cortisol relationships. Finally, the study sample had a low percentage of racial and ethnic minority women. Given that African-American women with endometrial cancer have poorer survival rates than Caucasian women (Yap & Matthews, 2006), the present sample's lack of racial/ethnic diversity may limit the ability to generalize the study's findings to women who carry the highest disease burden. Future research should oversample racial/ethnic minority women affected by gynecologic cancers in order to maximize generalizability.

In summary, this study found that greater depressive symptoms were significantly related to greater intraindividual cortisol variability but unrelated to linear cortisol slope in a group of women undergoing surgery for suspected endometrial cancer. Anxious symptoms were not significantly related to either outcome variable of HPA-axis dysregulation. Future research should examine whether depressive symptoms may be associated with meaningful negative clinical outcomes in women undergoing surgery for suspected endometrial cancer through its effects on intraindividual cortisol variability, which may represent a novel index of HPA axis-dysregulation.

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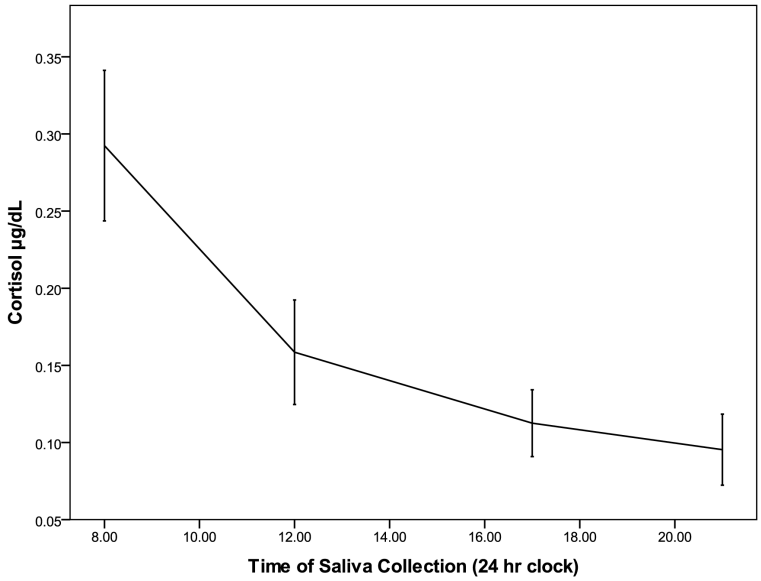

Figure 1.
Average cortisol values for the four time points of saliva collection.

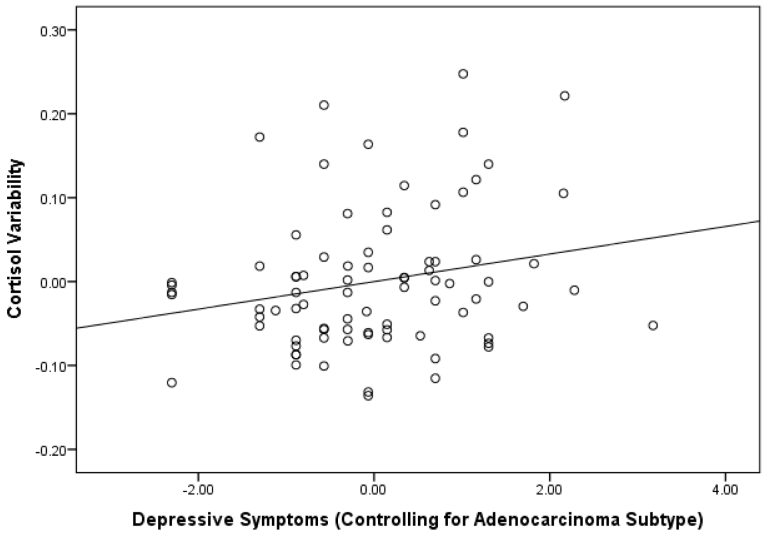

Figure 2.

Regression of depressive symptoms predicting cortisol variability. The x and y axes represent z-scores, demonstrating a positive relationship between depressive symptoms and cortisol variability, after controlling for adenocarcinoma subtype.

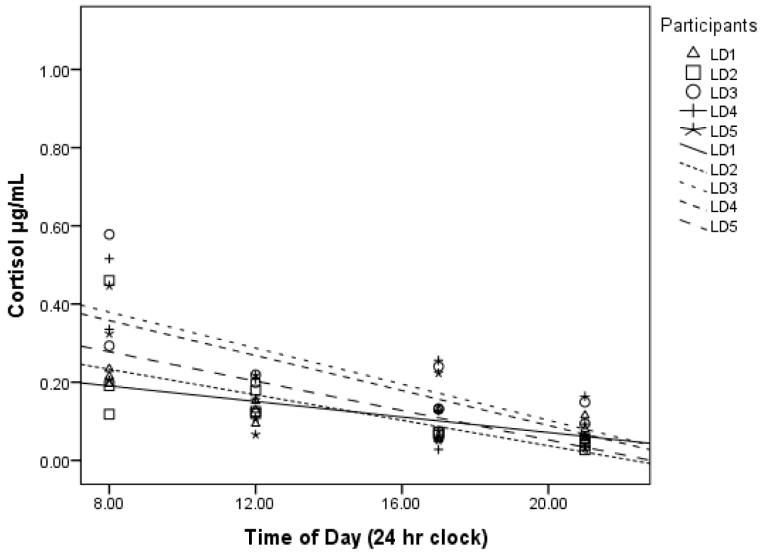

Figure 3a.

Cortisol variability: participants with the lowest depressive (LD) symptom scores. Cortisol values and corresponding regression lines are displayed. These 5 participants reported no depressive symptoms prior to surgery. Each line represent the individual's cortisol slope, with characters representing actual cortisol values. These select participants demonstrate low cortisol variability, as their actual cortisol values are in close proximity to their average pattern of cortisol output.

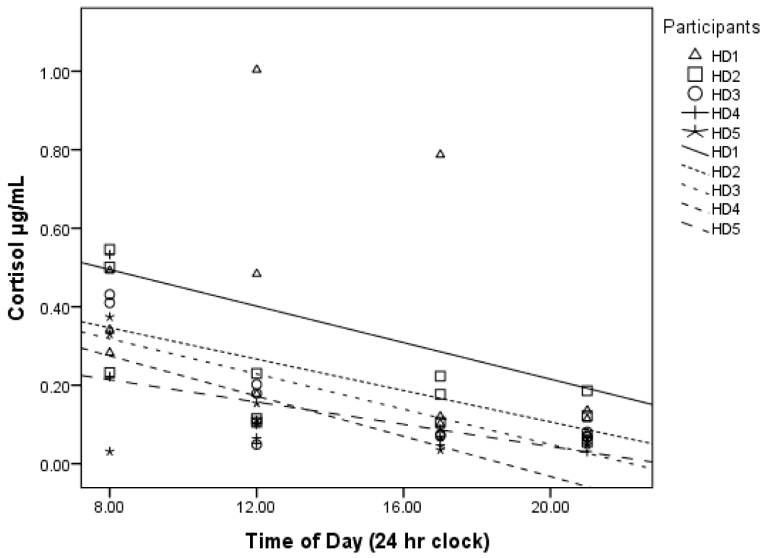

Figure 3b.

Cortisol variability: participants with the highest depressive (HD) symptom scores. These 5 participants reported the highest depressive (HD) symptom scores of the study sample. High cortisol variability is represented by the plotted cortisol values (represented here by the individual's average patterr of cortisol output).

Table 1

Comparison of Participants Included and Excluded in Data Analyses.

Variable	Included in Analyses (*N*=82)		Excluded from Analyses (*N*=23)		Test Statistic			Effect Size	
	M (SD)	n	M (SD)	n	t-value	X^2	p-value	d	Cramer's Phi
SIGH-AD Depression	6.66 (5.66)		5.91 (4.02)		.59		.56	.08	
SIGH-AD Anxiety	5.17 (4.01)		4.78 (3.55)		.42		.68	.05	
Age	61.76 (8.88)		59.39 (9.56)		1.11		.27	.13	
BMI	36.15 (11.04)		38.09 (12.12)		.73		.47	.08	
Cancer Grade[a]						.24			.21
						4.22			
Well-differentiated		45		14					
Moderately differentiated		24		2					
Poorly differentiated		8		2					
Cancer Stage[a]						2.05	.56		.14
Stage I		55		17					
Stage II		13		2					
Stage III		11		2					

[a]Three participants included in analyses are not represented here. These three participants had complex hyperplasia with atypia, which is precancerous endometrial lesion; therefore, cancer grade and stage do not apply.