Depressive Symptoms and Cortisol Variability Preceding Surgery for Suspected Endometrial Cancer

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Endometrial Cancer

• The most common form of gynecological malignancy and the 4th most common cancer among women

• 43,470 new cases will be diagnosed and 7,950 women will die from the disease in 2010

• Mortality rates of both breast cancer and ovarian cancer have ↓ over past several decades
  – Mortality rate of endometrial cancer has remained stable since 1991

Depression and Anxiety in Gynecologic Cancer

• Depression is estimated to occur in 12%-23% of patients diagnosed with gynecologic cancer\(^1\)

• Predictors for increased levels of anxiety and/or depression include\(^2\):
  – younger age
  – more advanced disease
  – more physical symptoms
  – shorter time since diagnosis

Cortisol and Cancer

- Cortisol is a hormone released by the hypothalamic-pituitary-adrenal (HPA) axis during periods of stress or challenge.
- Easily measured in saliva.
- Implicated as playing a systemic role in cancer.
Cortisol and Cancer

- Cortisol increases tumor invasiveness\(^1\)
- Cortisol upregulates tumor promoting factors in tumor microenvironment\(^2,^3\)
- Greater cortisol output observed in breast cancer patients with more advanced disease vs. those with less\(^4\)
- Flatter cortisol slope predicts earlier mortality in breast cancer patients\(^5\)

Cortisol Variability

• How variable or erratic is an individual’s cortisol output?

• Defined as “beep level” variance\(^1\)

• To what degree does an individual’s cortisol differ from their typical rhythm (slope)?

1. Peeters et al. 2004
Cortisol Variability

Outcome (e.g., cortisol)

Time (Day)

Subject X

1. Marsiske 2010
Mood Disorders and Cortisol Variability

Greater cortisol variability in individuals with:

– Major depressive disorder\(^1\)

– Remitted bipolar disorder\(^2\)
  • ↑ depressive episode severity and ↑ frequent episode recurrence and ↑ cortisol variability

…compared to controls.

Cortisol Variability in Cancer

- Cortisol variability lower in ovarian cancer patients compared to healthy controls

- Lower variability significantly related to:
  - ↑ fatigue
  - ↑ functional disability
  - ↑ vegetative symptoms of depression

1. Weinrib, et al., 2010.
Specific Aims

- **Specific Aim 1**: Examine relations between cortisol variability and depressive/anxious symptoms
  - *Hypothesis 1*: ↑ depressive/anxious symptoms would be associated with ↑ cortisol variability

- **Specific Aim 2**: Examine relations between cortisol slope and depressive/anxious symptoms
  - *Hypothesis 2*: ↑ depressive/anxious symptoms would be associated with a flatter cortisol slope
Participants

**Inclusion Criteria**
- Women seen for Gynecologic Oncology consult for suspected local/regional endometrial adenocarcinoma
- Scheduled to undergo total abdominal hysterectomy and bilateral salpingo oophorectomy (TAH–BSO) for diagnosis and staging

**Exclusion Criteria**
- Premenopausal
- Severe, uncontrolled psychiatric illness
- Recurrent endometrial cancer
- Primary site other than uterus
- Neoadjuvant chemotherapy or radiation therapy
Assessment

• Anxiety/Depression:
  – Structured Interview Guide for the Hamilton Anxiety and Depression scales (SIGH-AD) \(^1\)
  – Administered by advanced graduate students immediately prior to surgery
  – Ratings of depressive symptoms deemed to be due to the direct physiological effects of cancer, medications, etc. excluded

• Cortisol:
  – Saliva samples collected for 3 consecutive days immediately prior to surgery
  – Samples collected at 8:00, 12:00, 17:00 and 21:00 hours

Participants

Demographics

• 130 participants enrolled
  – Of these, 74 included more than one day of saliva sampling and were included in analyses

• Age: $M=61.99\,\text{yrs}; SD=8.95\,\text{yrs}$

• Race/ethnicity: Majority caucasian ($n=70; 95\%$)

Health Status

• Majority surgically staged with Stage I endometrial carcinoma ($n=64; 47\%$)

• 9% ($n=7$) tumors were deemed to be benign at surgical staging
Analyses

• Modeling cortisol variability
  – After controlling for diurnal cortisol rhythm using multi-level model, the standard deviation of each individual’s residual was saved as a separate variable, creating a variable of intraindividual standard deviation (ISD)\(^1\)

• Bivariate Pearson correlations applied to examine psychological variables of interest and cortisol variability estimate

• Multilevel modeling applied to examine psychological variables of interest and cortisol\(^2,3\)

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Control Variables

• The following control variables were examined:
  – medications known to affect HPA-axis
  – smoking status
  – cancer stage
  – tumor FIGO grade
  – Charlson comorbidity score*
Results
Specific Aim 1: Mood and Cortisol Variability

<table>
<thead>
<tr>
<th></th>
<th>Depressive Symptomatology</th>
<th>Anxious Symptomatology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( M=6.57; SD=5.33; Min=0; Max=30 )</td>
<td>( M=5.17; SD=3.97; Min=0; Max=21 )</td>
</tr>
<tr>
<td>Depressive Symptomatology</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anxious Symptomatology</td>
<td>.78**</td>
<td>-</td>
</tr>
<tr>
<td>Cortisol Variability</td>
<td>.24*</td>
<td>.15</td>
</tr>
</tbody>
</table>

\*p<.05; \**p<.001
Results
Specific Aim 2: Mood and Cortisol Slope

• Depressive symptoms significantly predicted cortisol slope across the three days preceding surgery ($\beta = -0.00054$, $SE = 0.00025$, $p<.05$)
  – Participants with greater depressive symptomatology had steeper cortisol slopes

• Anxiety not significantly related to cortisol slope, although the trend approached significance ($\beta = -0.00059$, $SE = 0.00033$; $p=.09$)
Cortisol Across Three Groups of Depressive Symptom Scores

Depression without Organic Ratings
- Low Depression (1-3; N=40)
- Medium Depression (4-9; N=39)
- High Depression (10-30; N=29)

Error bars: 95% CI
Conclusions

• These results conflict with those uncovered between psychological factors/cortisol variability in other gynecologic cancers$^1$
  – ↓ Variability related to ↑ vegetative symptoms of depression
  – Medical factors were excluded in the current study

• Greater depressive symptoms predict steeper cortisol slope?
  – Subclinical depressive symptoms or the initial onset of depression may not be related to HPA-axis dysregulation in the same manner as clinical depression
  – Steeper cortisol slopes associated with depression in other samples$^2$

1. Weinrib et al., 2010; 2. Veen et al., 2011.
Limitations/Future Directions

Limitations

• Nonexperimental, study design
  – lacked a true benign-disease only comparison group
• Limited cortisol variance or fluctuation is captured across the 12 time points
• Study sample had a low percentage of racial and ethnic minority women

Future Directions

• Prospective, longitudinal, and/or experimental studies
  – Including a comparison group
• Oversample racial/ethnic minority women affected by gynecologic cancers
• Measuring health/surgical outcomes
• Interventions that address patient-centered outcomes, such as sleep, pain and affect
• Purpose:
  – Examine the effects of a 6-week, individual cognitive-behavioral intervention on patient-centered outcomes, proangiogenic/proinflammatory cytokines, and cortisol in women with newly diagnosed gynecologic adenocarcinomas treated with adjuvant chemotherapy
  – Control condition: 6-weeks of individually delivered psychoeducation

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Thank you!

Questions?
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Diurnal cortisol variability is shown among ovarian cancer patients, patients with benign pelvic disease, and healthy women. Ovarian cancer patients demonstrated significantly lower cortisol variability than the other groups. Values were Bonferroni corrected.

Table 3. Adjusted* Pearson Correlations Between Cortisol Values and Psychosocial Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Ovarian Cancer Patients</th>
<th>Benign Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nocturnal Cortisol</td>
<td>Cortisol Variability</td>
</tr>
<tr>
<td>FACT physical well-being</td>
<td>-0.17</td>
<td>0.29^b</td>
</tr>
<tr>
<td>Physician's rating of functioning</td>
<td>0.21^a</td>
<td>-0.28^b</td>
</tr>
<tr>
<td>Patient's rating of functioning</td>
<td>0.22^c</td>
<td>-0.31^b</td>
</tr>
<tr>
<td>POMS fatigue</td>
<td>0.29^b</td>
<td>-0.28^b</td>
</tr>
<tr>
<td>CES-D</td>
<td>0.20</td>
<td>-0.26^c</td>
</tr>
<tr>
<td>CES-D vegetative subscale</td>
<td>0.30^b</td>
<td>-0.30^b</td>
</tr>
<tr>
<td>CES-D depression subscale</td>
<td>0.11</td>
<td>-0.16</td>
</tr>
<tr>
<td>POMS distress</td>
<td>0.07</td>
<td>-0.14</td>
</tr>
<tr>
<td>Perceived Stress Scale</td>
<td>0.03</td>
<td>-0.16</td>
</tr>
<tr>
<td>No. of life events (LES)</td>
<td>-0.02</td>
<td>-0.15</td>
</tr>
<tr>
<td>Severity of life events (LES)</td>
<td>-0.04</td>
<td>-0.10</td>
</tr>
</tbody>
</table>

FACT indicates Functional Assessment of Cancer Therapy; POMS, Profile of Mood States; CES-D, Center for Epidemiological Studies Depression scale; LES, Life Experiences Survey.

* Ovarian cancer patient correlations are adjusted for stage and age; correlations for patients with benign disease are adjusted for age.

^a P ≤ .01.

^b P < .05.
Cortisol Variability

Outcome (e.g., cortisol)

Time (Day)

Subject X

1. Marsiske 2010
These findings are contrary to what has been found in other gynecologic cancer populations (Weinrib et al., 2010). May warrant head-to-head comparison.