DISTRESS, NEUROIMMUNE DYSREGULATION, AND CLINICAL OUTCOMES IN WOMEN UNDERGOING TOTAL ABDOMINAL HYSTERECTOMY AND BILATERAL SALPINGO OOPHORECTOMY FOR SUSPECTED ENDOMETRIAL CANCER

By

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Dedicated to my family

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LIST OF ABBREVIATIONS

VEGF	Vascular Endothelial Growth Factor
AUCi	Area Under the Curve with respect to Increase
IL-6	Interleukin 6
ACS	American Cancer Society
BMI	Body Mass Index
TAH-BSO	Total Abdominal Hysterectomy & Bilateral Salpingo Oophorectomy
PNI	Psychoneuroimmunology
HPA	Hypothalamic-Pituitary-Adrenal
ANS	Autonomic Nervous System
Th	T Helper
SEM	Structural Equation Modeling
NCI	National Cancer Institute
IRB	Investigational Regulatory Board
EDTA	Ethylenediaminetetraacetic Acid
SIGH-AD	Structured Interview Guide for the Hamilton Anxiety & Depression Scales
PSQI	Pittsburgh Sleep Quality Index
MASQ	MacArthur Sociodemographic Questionnaire
PCOQ	Patient Centered Outcomes Questionnaire
ELISA	Enzyme-Linked Immunosorbent Assay
CTCAE	Common Terminology Criteria for Adverse Events
AMOS	Analysis of Moment Structures
FIML	Full Information Maximum Likelihood
CBT	Cognitive Behavioral Therapy
IFN	Interferon

TNF	Tumor Necrosis Factor
SAM	Sympatho-Adrenal-Medullary
Hct	Hematocrit
Hgb	Hemoglobin
WBC	White Blood Cells
RBC	Red Blood Cells
AIC	Akaike Information Criterion
df	Degrees of Freedom
CFI	Component Fit Index
TLI	Tucker Lewis Index
RMSEA	Root Mean Square Error of Approximation
CR	Critical Ratio
SE	Standard Error

Abstract of Dissertation Presented to the Graduate School
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Endometrial cancer is the most common gynecologic cancer in the United States (American Cancer Society, 2010). Psychoneuroimmunology literature has identified relationships between psychosocial factors, such as stress and depression, and clinical outcomes in various cancer populations (Antoni et al., 2006 and Rodrigue et al., 1999). Specific components of distress, including mood disturbance (Sephton et al., 2000), pain (Thornton et al., 2010), and sleep disturbance (Rich et al., 2005) have been associated with cortisol and cytokine production patterns that portend poorer clinical outcomes in cancer. However, no published research has examined relations among these psychosocial factors (mood disturbance, pain and sleep disturbance), cortisol dysregulation, vascular endothelial growth factor (VEGF), and clinical outcomes in women with endometrial cancer.

The current study included 113 women (*M*age= 61.38, *SD*=9.09) who completed psychosocial and biological assessments prior to undergoing surgery for suspected endometrial cancer. Structural equation modeling was utilized to examine the direct and indirect relationships of Distress and Neuroimmune Dysregulation on Negative Clinical

outcomes among this sample of women. All models demonstrated that sleep disturbance, pain and mood disturbance significantly contributed to Distress (Figures 3.1, 3.2 and 3.3). Additionally, abnormal cortisol production (lower AUCi) was significantly associated with advanced disease stage (path coefficient=-0.06, p= 0.03) and greater VEGF levels were significantly associated with greater post-operative complications (path coefficient=0.09, p=0.05) in this sample. Furthermore, an exploratory model evaluated the relationship between Distress and Neuroimmune function and included IL-6 as another neuroimmune factor. This model demonstrated the best overall fit ($\chi 2$=7.95, AIC=45.95), but did not find a significant relationship between Distress and Neuroimmune dysregulation (path coefficient=0.03, p=0.71).

Overall, these results support the development of interventions targeting sleep, pain and mood disturbance to improve quality of life in women undergoing surgery for suspected endometrial cancer. While the models could not fully evaluate mediation, model fit encouraged future studies to further evaluate the potential relationships among these factors. Additional research is necessary to determine if these symptoms of Distress are associated with clinical outcomes in women with endometrial cancer.

CHAPTER 1
INTRODUCTION

Epidemiology and Etiology of Endometrial Cancer

Endometrial cancer is defined as cancer of the uterine lining, or endometrium. Endometrial cancer is the most common gynecologic cancer and the second leading cause of gynecologic cancer death in the United States. Approximately 43,470 new cases of endometrial cancer and 7,950 deaths from the disease were expected to occur in 2010 (ACS, 2010). There are several categories of endometrial cancer, including epithelial carcinoma and stromal/mesenchymal tumors. The epithelial cancers include adenocarcinomas, of which the vast majority are endometrioid (80%; ACS, 2011). Less common types of endometrial adenocarcinomas include papillary serous and clear cell, which are histologically similar to those found in the ovary and fallopian tube and have a poorer prognosis than endometrioid cancers. Adenocarcinomas originate from abnormal glandular cells of the endometrium (ACS, 2011).

Risk factors for developing endometrial adenocarcinomas include older age, estrogen use without progesterone, early menarche and/or late menopause, obesity, diabetes, infertility or never having children, Lynch syndrome, tamoxifen use, and polycystic ovary syndrome (ACS, 2011). Specifically, these risk factors have been implicated in the pathophysiology of endometrial adenocarcinomas due to alterations in estrogen and progesterone levels in women, as well as promotion of inflammation (Wallace et al., 2010). Most endometrial cancer cells contain estrogen and progesterone receptors. Circulating hormones may bind to these receptors, leading to cellular proliferation of the endometrium (ACS, 2010). Although post-menopausal women no longer have monthly ovarian production of these two hormones, they still

experience production of estrogen from fatty tissue in the body. Post-menopausal women with obesity have particularly elevated estrogen levels, and these elevated estrogen levels may lead to proliferation of the endometrium and increased risk of endometrial cancer (ACS, 2011).

Obesity is also associated with chronic, systemic inflammation, and this has been suggested as a plausible biological mechanism for the association between obesity and endometrial cancer. A recent study found that elevations of specific cytokines, such as Interleukin (IL)-6, significantly mediated the relationship between higher body mass index (BMI) and epithelial endometrial cancer risk (Dossus et al., 2010). This builds upon other research that discovered higher levels of proinflammatory cytokines in women with endometrial cancer (Slater et al., 2006).

Prognosis and Treatment of Endometrial Cancer

Most cases of endometrial cancer (69%) are diagnosed at an early stage. Post-menopausal vaginal bleeding occurs in approximately 90% of women with endometrial cancer and is often the symptom that prompts early diagnostic evaluation (ACS, 2010). Survival rates in endometrial adenocarcinomas are higher if the initial diagnostic stage indicates local disease (current staging guidelines are provided in Appendix A). Five-year survival rates are relatively high in early stage disease (stage I: 75-88%, stage II: 69%), while more advanced stages (regional/distant disease) are associated with lower survival rates (stage III: 47-58%, stage IV: 15-17%). Myometrial invasion of disease in earlier stages may serve as an indicator of survival, with greater invasion associated with poorer prognosis (ACS, 2011). Research indicates that disease stage at the time of surgery is one of the most important prognostic factors of endometrial cancer (Sorosky, 2008).

National Comprehensive Cancer Network (NCCN) guidelines (2011) recommend women with suspected diagnosis of endometrial cancer undergo surgical staging, which then guides additional treatment decisions (ACS, 2011). Surgical staging for endometrial cancer usually includes total hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) and pelvic washings, as well as pelvic and para-aortic lymphadenectomy. Additional surgical procedures may include omentectomy, peritoneal washings and/or debulking/cytoreduction. Women with advanced stage disease and women who are poor surgical candidates are likely to receive radiation and/or chemotherapy, as well (Sorosky, 2008).

Outcomes and Complications Following Endometrial Cancer Surgery

Although survival rates following TAH-BSO for endometrial cancer are quite high, morbidity during the acute postsurgical period is prevalent. As described above, TAH-BSO for endometrial cancer is invasive, and hospitalization following surgery can last from three to seven days even in the absence of any acute complications. Acute recovery (e.g., medical clearance to drive and lift > 10 lbs, etc.) can take four to six weeks (ACS, 2011), with full surgical recovery often requiring at least six months.

Rates of acute complications following TAH-BSO for endometrial cancer range from 15-23% for minor complications (e.g., urinary tract infection, anemia) and 12-19% for major, life-threatening complications (e.g., arrhythmias, pulmonary embolism) (Janda et al., 2010; Mourits et al., 2010). Factors associated with increased risk for acute postsurgical complications following TAH-BSO for endometrial cancer include the presence of medical comorbidity (Tozzi et al., 2005; Mourits et al. 2010; Vaknin et al., 2009) and stage III/IV disease (Lambrou et al., 2004). Although psychosocial factors have been implicated in the development of negative clinical outcomes in other common

cancers, such as breast cancer (Hjerl, et al. 2003 and Satin, et al. 2009), few psychosocial factors have been evaluated as risk factors for poor outcomes following surgery for endometrial cancer.

Biobehavioral (Psychoneuroimmunologic) Model of Tumorigenesis & Cancer Outcomes

Given the rates of acute medical morbidity following TAH-BSO for endometrial cancer, there is a need to identify modifiable presurgical risk factors associated with acute postoperative complications and cancer outcomes in this setting. Presurgical psychosocial factors may emerge as potentially modifiable risk factors. Specifically, according to the biobehavioral (psychoneuroimmunologic [PNI]) model of tumorigenesis (Antoni et al., 2006), psychosocial factors may influence the tumor microenvironment and cancer outcomes by activating the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS). Activation of these stress systems then results in a cascade of events, including the release of stress hormones (e.g., glucocorticoids and catecholamines), which in turn may promote inflammatory, immunosuppressive, and angiogenic immune responses that (a) favor tumorigenesis (Antoni et al., 2006), and (b) promote neuroimmune mediated postsurgical complications (Menger & Vollmar, 2004).

Presurgical psychosocial factors that may be particularly relevant to examine within this model include those that are highly prevalent, can be validly assessed, and are potentially modifiable within the perioperative setting. Mood disturbance, sleep disturbance, and pain are three psychosocial/behavioral factors that may be particularly important to target in the perioperative setting. Clinically significant anxiety (21%), depression (21-46%), sleep disturbance (37-60%), and pain (42-63%) are highly prevalent in women with gynecologic cancer (Thompson & Shear, 1998; Bradley et al.,

2006; Lutgendorf et al., 2001; Portenoy et al., 1994; Rummans et al., 1998). Although these psychosocial experiences are highly prevalent in women with gynecologic cancers, there is evidence that they are responsive to psychosocial interventions. Specifically, there is emerging evidence that cognitive behavioral interventions are effective at reducing pain, sleep disturbance, and mood disturbance, possibly in tandem, among cancer patients (Theobald, 2004; Dalton et al., 2004; Davidson et al., 2001; Antoni et al., 2009; Kwekkeboom et al., 2010).

Furthermore, there is emerging evidence that these cognitive behavioral interventions, which target psychosocial factors, also influence neuroimmunity by improving cortisol patterns (i.e., lowering evening serum cortisol levels) and cell-mediated immunity (i.e., increasing production of interferon (IFN)-gamma) in women with breast cancer (Antoni et al., 2009; Cruess, 2000; Savard et al., 2005), suggesting that cognitive behavioral approaches may buffer neuroimmune responses associated with tumorigenesis and poor clinical outcomes in cancer. However, research has yet to examine how these common psychosocial experiences are associated with neuroimmunity and clinical outcomes in women with gynecologic cancer. A comprehensive review of the literature linking these psychosocial factors (distress) with neuroimmunity and clinical outcomes is presented below.

Neuroimmunity and Clinical Outcomes in Cancer

Specific glucocorticoids (cortisol) and proinflammatory cytokines (VEGF) may be associated with clinical outcomes in women with cancer. For example, cortisol dysregulation (i.e. flattened diurnal slope) has been associated with increased mortality in women with breast cancer (Sephton et al., 2000). Additionally, cortisol may work synergistically with catecholamines to upregulate expression of VEGF (Antoni et al.,

2006). This is important, as VEGF is a proangiogenic and proinflammatory cytokine, promoting growth of tumor vasculature and cell-mediated inflammation in cancer (Reinders et al., 2003). Specifically in ovarian cancer, greater VEGF in serum and cytosol has been associated with tumor growth and angiogenesis, as well as the presence of metastatic disease and poorer survival (Lutgendorf et al., 2003; Thaker et al., 2007). Elevated VEGF in serum has also been found in women with endometrial cancer, as compared to women with non-malignant conditions (Shaarawy and El Sharkawy, 2001). This finding is significant due to the association between elevations of VEGF in cytosol (intracellular fluid) and shorter disease-free survival in this population (Chen et al., 2001). In addition, research on pro-inflammatory markers (cytokines) in patients with heart disease found that the presence of greater preoperative proinflammatory cytokines was associated with more severe postoperative complications in patients undergoing surgery for heart disease (Kaireviciute et al., 2010). Taken together, these findings suggest that both cortisol and VEGF may be important prognostic markers for disease progression and negative clinical outcomes in women with endometrial cancer.

Distress, Neuroimmunity, and Clinical Outcomes in Cancer

Distress can impact patient quality of life and is a notable clinical concern in cancer patients. The experience of distress in cancer often encompasses a range of physical, social and emotional factors (Vitek, Rosenzweig & Stollings, 2007). Common components of distress among cancer patients include depression, anxiety, pain and sleep disturbance. Of note, research suggests that mood disturbance (depression and anxiety), pain and sleep disturbance co-occur and maintain each other, thus impacting

the quality of life in cancer patients (Shapiro et al., 2003; Theobald 2004; Beck et al., 2005).

As alluded to previously, the biobehavioral model of tumorigenesis posits that distress may impact cancer outcomes, such as postoperative outcomes and disease progression, by influencing cortisol production, impairing cell-mediated immunity, and upregulating proinflammatory and proangiogenic cytokines (Antoni et al., 2006). However, research has yet to examine the aggregate effects of distress (mood disturbance, pain and sleep disturbance) and neuroimmune function on clinical outcomes during the perioperative period in women with suspected endometrial cancer.

Mood Disturbance

Depression can act as a chronic stressor, altering HPA function and immunity, subsequently leaving cancer patients susceptible to infection after surgery (Spiegel & Giese-Davis, 2003; Tjemsland et al., 1997). In patients undergoing hematopoietic stem cell transplant for hematologic cancers, mood disturbance (depression and anxiety) has been identified as a predictor of negative clinical outcomes, such as length of survival after transplantation (Rodrigue et al., 1999). The association between depression and elevated VEGF in women with ovarian cancer suggests that mood may contribute indirectly to micrometastatic spread of disease (Lutgendorf et al., 2008). While limited, methodologically-rigorous research has been conducted with the a priori aim of examining the impact of depression on clinical outcomes in gynecologic cancer, there is a relatively rich literature on depression and clinical outcomes in heart disease. Depression has been implicated in the progression and mortality of patients with heart disease (Blumenthal et al., 2003). Additionally, autonomic nervous system (ANS) dysregulation may be the mechanism by which depression is associated with negative

postoperative outcomes (i.e., extended hospitalizations) in patients undergoing major heart surgery (Dao et al., 2010).

Anxiety has also been associated with neuroendocrine and immune dysfunction, and this relationship may be particularly robust among women with cancer. Studies of women with breast cancer have demonstrated that higher stress and anxiety may modulate patterns of diurnal cortisol production that promote unfavorable clinical outcomes (Antoni et al., 2009; Vedhara et al., 2003). In addition, greater presurgical anxiety, pain and stress may lead to negative postsurgical outcomes, such as delayed wound healing and risk of infection (Broadbent et al., 2003; Ben-Eliyahu, 2003; Pearson et al., 2005).

Overall, these results suggest that mood states, such as depression and anxiety, may promote negative clinical outcomes among women with cancer via alterations of both cortisol production and VEGF. However, no published research to date has examined these plausible relations.

Pain

Pain has been identified as a critical, yet undertreated, symptom in cancer patients that may become chronic in more advanced stages. Severe, chronic pain may function as a stressor, leading to HPA axis dysregulation in the form of either overstimulation (greater cortisol output) (Tennant & Hermann, 2002) or understimulation (lower cortisol output) (Geiss et al., 2005), the latter of which may occur due to blunting or “wearing out” of the HPA axis. Geiss and colleagues (2005) further found that chronic pain was associated with greater proinflammatory cytokine production after surgery.

While limited data indicates that presurgical pain predicts greater incidence of postoperative complications in surgical populations, research has suggested that

presurgical pain may be associated with longer hospitalizations after TAH-BSO (Mourits et al., 2010). Women undergoing gastric bypass surgery also demonstrated relationships between presurgical pain and extended recovery times, as well as the presence of wound healing complications after surgery (McGuire et al., 2006).

Taken together, these data suggest that greater presurgical pain may be a predictor of more negative post-surgical outcomes in cancer. Given that chronic pain may operate as a significant stressor that is capable to modulating cancer-related neuroimmunity (Antoni et al., 2006), the possibility exists that more severe presurgical pain may be associated with poorer surgical outcomes among women with endometrial cancer.

Sleep Disturbance

Sleep is often evaluated as a subjective construct and factors of sleep disturbance can include quality, duration, latency, and disruption (Buysse et al., 1989). Various characteristics of poor sleep, such as greater number of awakenings, lack of restful sleep, and poor sleep quality, have been related to lower cortisol awakening response in saliva, which may reflect a blunting or "wearing out" of the HPA axis (Backhaus, Junghanns, & Hohagen, 2004). Specifically, experiencing a lack of sleep may lead to patterns of cortisol dysregulation that reflect impaired hippocampal regulation of negative feedback of the HPA axis (Spiegel et al., 1999; Irwin et al., 2003).

Furthermore, chronic insomnia has been associated with impaired neuroendocrine function and cancer progression (Vgontzas & Chrousos, 2002). Sephton and Spiegel (2003) suggested that frequent awakenings are a prominent behavioral disturbance in cancer patients, particularly those with advanced disease and those receiving treatment in the hospital. They further posit that poor sleep marked by irregular sleep-wake cycles

may be associated with circadian disruption that in turn may influence disease progression (Sephton and Spiegel, 2003). Specifically, one of the functions of nocturnal sleep is to promote cell-mediated immune responses (T helper cell type 1 [Th1] immunity), including anti-tumor immunity, and suppress humoral immune responses (T helper cell type 2 [Th2] immunity), which are less effective at fighting tumors and characteristic of advanced stage disease (Dimitrov et al., 2004). Cortisol dysregulation due to sleep disturbance may promote a Th2 dominant immune response, ineffective anti-tumor immunity, and disease progression. Also, sleep disturbance has been associated with higher levels of VEGF prior to treatments for cancer, indicating that patients with preoperative sleep difficulty may also be experiencing immunologic changes promoting angiogenesis and/or inflammation (Mills et al., 2005 and Guess et al., 2009).

Taken together, these findings suggest that it is plausible that sleep disturbance is related to patterns of neuroimmunity that are associated with poorer outcomes among individuals with cancer. Given (a) the comorbidity among sleep disturbance, mood disturbance, and pain in individuals with cancer, and (b) the associations between each of these factors and neuroimmunity/poorer clinical outcomes in cancer, a logical next step is to examine the aggregate effect of these components on neuroimmunity/clinical outcomes in cancer.

Significance of Present Study

The current study aimed to examine the direct and indirect relationships among presurgical distress, presurgical neuroimmune dysregulation and post-surgical clinical outcomes among women undergoing TAH-BSO for suspected endometrial cancer. Presurgical distress was comprised of mood disturbance (anxiety and depression), pain

levels, and sleep disturbance prior to surgery. Presurgical neuroimmune dysregulation was evaluated through measurements of salivary cortisol throughout the day and VEGF prior to surgery. Post-surgical clinical outcomes included surgically-staged disease (disease stage) and incidence/severity of postoperative complications. Structural equation modeling (SEM), specifically structural regression modeling, was utilized to examine a theoretical model of the shared variance explained by these factors.

Specific to the current study, comorbid pain, sleep and mood disturbance were expected to be present in women prior to surgery and associated with neuroimmune function. As previously described, these symptoms often occur simultaneously and may be modified through cognitive behavioral interventions. Examination of the relationships among distress, neuroimmune function and important clinical outcomes may encourage more holistic evaluation and treatment of women with suspected endometrial cancer.

Specific Aims

The overarching aims of the present study were two-fold: (1) to derive three underlying biopsychosocial constructs (Distress, Neuroimmune Dysregulation, and Negative Clinical Outcomes) from a specified set of observed variables (Distress → pain, sleep disturbance, and mood disturbance; Neuroimmune Dysregulation → vascular endothelial growth factor [VEGF] and diurnal cortisol area under the curve with respect to increase [AUCi]; and Negative Clinical Outcomes → disease stage and postoperative complications), and (2) to model the relationships among these resultant theoretical constructs (Distress, Neuroimmune Dysregulation, and Negative Clinical Outcomes) in a sample of women undergoing surgery for suspected endometrial cancer (Figure 1-1). Structural equation modeling (SEM) (i.e., structural regression modeling)

was used to assess the adequacy of the model depicted in Figure 1-1. Specifically, the use of structural regression modeling allowed the following specific aims to be pursued:

Aim 1. To examine the total effect of presurgical distress (pain, sleep disturbance, and mood disturbance) on clinical outcomes (surgically staged disease, number of postoperative complications) in women undergoing TAH-BSO for suspected endometrial cancer.

Hypothesis 1. Greater presurgical distress was associated with worse clinical outcomes.

Aim 2. To examine the direct effect of presurgical distress (pain, sleep disturbance, and mood disturbance) on presurgical neuroimmune dysregulation (vascular endothelial growth factor [VEGF], diurnal cortisol area under the curve with respect to increase [AUCi]).

Hypothesis 2. Greater presurgical distress was associated with greater presurgical neuroimmune dysregulation.

Aim 3. To examine the direct effect of presurgical neuroimmune dysregulation (VEGF, diurnal cortisol AUCi) on clinical outcomes (surgically staged disease, number of postoperative complications) in women undergoing TAH-BSO for suspected endometrial cancer.

Hypothesis 3. Greater presurgical neuroimmune dysregulation was associated with worse clinical outcomes.

Aim 4. To examine the indirect effect of presurgical distress (pain, sleep disturbance, and mood disturbance) on clinical outcomes (surgically staged disease, number of postoperative complications) in women undergoing TAH-BSO for suspected endometrial cancer.

Hypothesis 4. Greater presurgical neuroimmune dysregulation would mediate the relationship between greater presurgical distress and worse clinical outcomes.

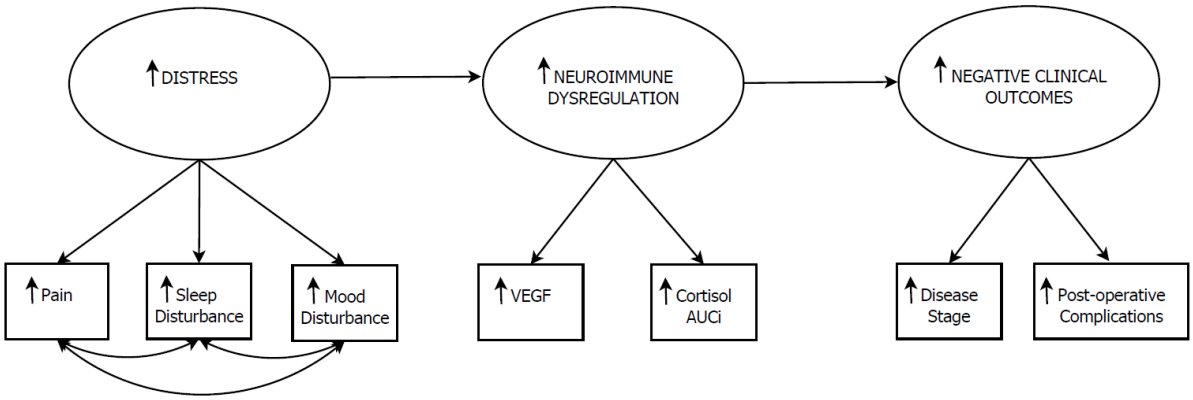


Figure 1-1. Structural regression model to be examined in the proposed study

CHAPTER 2
METHODS

Study Design

This study used data drawn from a larger, parent study examining psychoneurimmunologic relations in endometrial cancer immediately prior to surgery and four to six weeks following surgery (American Cancer Society [IRG-01-188-01] and National Cancer Institute [R03 CA 117480], PI: Deidre Pereira). The design of the parent study was observational/non-experimental and longitudinal, including biopsychosocial assessment at two timepoints (pre-surgery and post-surgery).

This observational/non-experimental study design is outlined in Figure 2-1. All participants were recruited from the Shands Gynecologic Oncology clinic in Gainesville, Florida as part of a study (PI: Deidre Pereira) funded by the American Cancer Society (IRG-01-188-01) and National Cancer Institute (R03 CA 117480). They were consented prior to surgery (TAH-BSO) for suspected endometrial cancer. They completed a psychosocial assessment and collected biological samples, including saliva, during the three days prior to surgery. These assessments were repeated at participants' postoperative visit. Following surgery, data were abstracted from participants' medical records. The study was conducted according to the regulations of the University of Florida Institutional Review Board (IRB).

This study utilized psychosocial and salivary cortisol data collected at the preoperative visit and negative clinical outcomes data obtained through medical record abstraction following the post-surgical visit. Variables that may confound true relationships among predictors, mediators, and outcomes were assessed through presurgical self report measures and post-surgical medical abstraction.

Participants

Participants from the parent study were recruited between 2003 and 2009. Inclusion criteria for the parent study were (a) women undergoing TAH-BSO for suspected endometrial cancer, (b) fluency in spoken English, and (c) at least 18 years old. Exclusion criteria were (a) recurrent endometrial cancer, (b) metastasis to the uterine corpus from another site, (c) presurgical chemotherapy or radiotherapy, (d) current psychotic disorder, and (e) current suicidal ideation/plan. Participants for the present study included those with at least partial psychosocial, cortisol, and VEGF data at presurgery for whom clinical outcome data could be abstracted from medical records during the immediate postsurgery period.

Procedures

During their initial consultation visits, preliminarily eligible women were identified by their physician and were approached by study personnel. Study personnel introduced the study and reviewed the IRB-approved informed consent with interested patients. After signing the consent form, patients completed a brief assessment screening for suicidality and psychosis. If a patient was still eligible, they received study materials, which included psychosocial questionnaires and a saliva kit. The study saliva kit included 12 Salivettes (Sarstedt, Inc., Newton, NC), a cryomarker, and soft-sided cooler for storage.

Participants completed questionnaires and collected saliva samples during the three days prior to their preoperative visit. Saliva samples were collected at four specific intervals (8am, 12pm, 5pm, and 9pm) across three consecutive days. When participants returned to the clinic for their preoperative visit, they returned questionnaires and saliva samples. Also, study personnel conducted a psychosocial interview, escorted patients

to their blood draw, and compensated them for participation in this portion of the study. Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes and were immediately taken to Dr. Edward Chan's laboratory in the Department of Oral Biology at the University of Florida for processing.

Assessment of Presurgical Psychosocial Factors

Study personnel administered the Structured Interview Guide for the Hamilton Anxiety and Depression Scale (SIGH-AD) (Williams, 1988) and the Pittsburgh Sleep Quality Inventory (PSQI) (Buysse et al., 1989) in interview format during the preoperative visit and participants completed a set of questionnaires prior to undergoing surgery. These questionnaires included the MacArthur Sociodemographic Questionnaire (MASQ) (Adler et al., 2000) and the Patient Centered Outcomes Questionnaire (PCOQ) (Robinson et al., 2005). All measures used in the current study were included as appendices (Appendix B).

Demographics

Demographic factors were assessed by the MASQ (Adler et al., 2000). This questionnaire was developed by the MacArthur foundation to assess both subjective and objective social status. The MASQ assessed subjective social status by asking participants to indicate their perceived position in society. Objective social status was assessed by family structure, education level, employment status, and financial status.

Mood Disturbance

Mood disturbance was operationalized as total anxious and depressive symptomatology. Anxiety and depressive symptoms were assessed using the Structured Interview Guide for the Hamilton Anxiety and Depression Scale (SIGH-AD) (Williams, 1988). The SIGH-AD was developed as a semi-structured interview, and in

the current study, trained study personnel conducted the interview and rated participants' responses in order to generate total depressive and anxious symptomatology scores. Ratings associated with symptoms judged by the interviewer to be possibly/definitely due to the direct physiological effects of a medical condition, medication, treatment, or substance, were then subtracted from the total scores in order to yield depressive and anxious symptomatology scores unconfounded by medical factors. The SIGH-AD has previously been modified and utilized in research with patients with HIV (Brown et al., 1992, Mitrani et al., 2011). The anxiety and depression scales have well-established reliability in a medical setting, Cronbach's alpha: SIGH-A= 0.83, SIGH-D: 0.83 (Mitrani et al., 2011).

In the parent study, the original SIGH-AD was modified to minimize participant burden and to exclude symptoms that can be reliably attributed to the direct physiological effects of endometrial cancer, such as abdominal pain/discomfort. The resulting abbreviated version was comprised of 24 items, including 15 depression items and 9 anxiety items. This modified score of the SIGH-AD demonstrated strong internal consistency (Cronbach's alpha=0.76). Total scores range from 0 to 74, with higher scores indicating greater mood disturbance. The current study used the sum of the depressive symptomatology score (excluding any ratings possibly/definitely associated with physiological factors) and anxious symptomatology score (excluding any ratings possibly/definitely associated with physiological factors) to operationalize total mood disturbance.

Sleep Disturbance

Sleep disturbance was assessed using the PSQI (Buysse et al., 1989). The PSQI generated seven subscale scores (subjective sleep quality, sleep latency, sleep

duration, sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction), as well as a total (global) score. The PSQI has been used to evaluate sleep disturbance in cancer patients, including patients with gynecologic cancer, and has demonstrated internal consistent reliability (Cronbach's alpha=0.77 to 0.81) and construct validity (Beck et al., 2004; Davidson et al., 2002). This measure was administered in interview format, but still demonstrated similar internal consistency (Cronbach's alpha=0.76). The PSQI total scores assessed preoperative sleep disturbance, with higher total PSQI scores indicating greater sleep disturbance.

Pain

Pain was assessed using items from a self-report measure, the Patient Centered Outcomes Questionnaire (PCOQ), which assessed (a) "usual" and "desired" levels of (i) pain, (ii) fatigue, (iii) emotional distress and (iv) interference with daily activities, (b) perceptions of successful and expected treatment outcomes across these four domains, and (c) importance of improvement across these four domains (Robinson, et al., 2005). The PCOQ has demonstrated reliability ($r(21)=0.84$ to 0.90, $p<0.001$) and validity ($r(21)=0.52$, $p<0.001$) compared to other standardized measures, and has been used in research with various chronic pain populations (Brown, et al., 2008). The PCOQ evaluated patients' usual levels of pain during the past week using a 0-100 numeric rating scale (0=none, 100=worst pain imaginable) with higher ratings indicating higher levels of pain. The PCOQ "usual pain" item was highly correlated with the Brief Pain Inventory ($r(42)=0.78$, $p<0.001$) in the current sample.

Assessment of Neuroimmunity

Cortisol

Cortisol was measured in saliva, which has been considered a reliable measure of free circulating cortisol in the body (Kirschbaum & Hellhammer, 1994). Participants collected saliva samples at four specific times (8am, 12pm, 5pm, and 9pm) across three consecutive days prior to their preoperative clinic visit. Participants were asked to record the accurate time of their sampling if it differed from the expected times. Saliva samples were stored at -80°C until they could be shipped to Salimetrics (State College, PA) for analysis using Enzyme-Linked Immunosorbent Assay (ELISA).

As described by Salimetrics (State College, PA), ELISA procedures for cortisol require adding an unknown amount of antigen (test sample) to a surface covered by cortisol antibodies. The antigen bound to the antibodies that were present and the magnitude of fluorescence emitted was assessed to determine cortisol concentration. All samples was assayed in duplicate and the test requires 25 µL of saliva per determination. The test had a lower limit of sensitivity of 0.0003 µg/dL, standard curve range of 0.012 µg/dL to 3.0 µg/dL, average intra-assay coefficient of variation of 3.5%, and average inter-assay coefficient of 5.1%. The accuracy (100.8%) of this method was determined by spike and recovery and linearity (91.7%) was determined by serial dilution. Values were assessed from matched serum and saliva samples and demonstrated a strong linear relationship (r (47) = 0.91, $p < 0.0001$).

Various methods have been used to quantify cortisol output in psychoneuroimmunology literature and each method demonstrates a unique characteristic of cortisol production. Specifically, cortisol has commonly been evaluated using cortisol awakening response, diurnal cortisol slope, area under the curve with

respect to ground and area under the curve with respect to increase (Vedhara et al., 2006). In the current study, cortisol area under the curve with respect to increase (AUCi) was chosen as a measure of cortisol production. Pruessner and colleagues (2003) provided a trapezoidal formula (below) for computation of cortisol AUCi, which were used in the current study.

$$AUC_I = \left(\sum_{i=1}^{n-1} \frac{(m_{(i+1)} + m_i) \cdot t_i}{2} \right) - \left(m_1 \cdot \sum_{i=1}^{n-1} t_i \right)$$

AUCi was chosen because this measure represents systemic reactivity and dysregulation of cortisol production. Cortisol AUCi was calculated for each day of saliva collection, and the study utilized an average value for each participant.

VEGF

Concentration of plasma VEGF was assessed in blood samples collected during the preoperative assessment visit. The blood samples were processed and plasma samples were stored for future assaying of immune factors, such as VEGF, by Dr. Chan's lab. Commercially available ELISA kits were used to assay VEGF concentrations (pg/mL) in samples (VEGF Quantikine Kit, R&D Diagnostics, Minneapolis, MN). Briefly, each plate contains fluorescent beads linked with cytokine-specific antibodies, and application of the samples to this plate allows cytokines to bind with these antibodies. The liquid sample is then assessed for VEGF concentration.

Assessment of Postsurgical Clinical Outcomes

FIGO Disease Stage

Disease stage was determined surgically and was abstracted via medical record review and classified according to International Federation of Gynecology and

Obstetrics anatomic/prognostic group (Appendix A) (FIGO, 2008). Disease stage was assigned a numerical value based on the following scale: 0= benign/no evidence of cancer, 1=Stage I, 2=Stage II, 3 = Stage III, and 4 = Stage IV.

Postoperative Complications

Incidence and severity of postoperative complications was abstracted via medical record review. All medical events documented in participants' inpatient, postsurgical medical records were cross-referenced with adverse events listed in the Common Terminology Criteria for Adverse Events 4.03 (CTCAE; National Cancer Institute, 2009). The guide (included in Appendix B) was intended to foster reporting of adverse events associated with cancer interventions. An adverse event was defined as an unfavorable and unexpected sign, symptom or disease that is temporally associated with a medical procedure, like TAH-BSO, that may be directly related to the procedure. All adverse events, or postoperative complications, were categorized by anatomical system, etiology, or purpose within an organ system. Each adverse event is also assigned a grade (1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=death), and the criteria for assigning each grade are described in detail. For the present study, the entirety of the participant's medical records from the date of surgery until the date of discharge was reviewed by two independent raters to assess for the occurrence of any events listed within the CTCAE. The two raters demonstrated consistent post-operative complication ratings (α=0.98). Typical events included events such as pneumonia, urinary tract infection, and anemia. For each event recorded in the medical record, the severity of the event was graded using the criteria listed in the CTCAE. The two raters achieved consensus regarding any methodological questions or any post-operative complications that required additional clarification according to the CTCAE (Table 2-2). For example,

blood loss is a notable category in the CTCAE, but the medical record of each participant has various ways to record the amount of blood loss. Therefore, clear numerical rating guidelines were determined based on what would be an expected amount of blood loss and what should be rated according to the CTCAE guidelines for blood loss (including hematocrit, hemoglobin and red blood cell counts). The outcome variable of interest was the sum of the severity scores for each postoperative complication (adverse event) documented in the patient's medical record. Although no published PNI research has used the CTCAE to assess the incidence and severity of adverse events, the CTCAE has been utilized to assess long-term follow-up of postoperative complications in women undergoing TAH for endometrial cancer (Janda et al., 2010 and Mourits et al., 2010).

Assessment of Potential Control Variables

Control variables were collected from the patient's medical record and via self-report measures. The MASQ was utilized to evaluate potential objective and subjective control variables, such as age, marital status, and race/ethnicity. Additionally, medical record abstraction provided data on comorbid conditions and BMI, as these factors have been linked to worse disease outcome in cancer (Reeves et al., 2007, Satariano and Ragland, 1994, and Everett et al., 2003). Medical comorbidity was assessed using the Charlson Comorbidity index, with higher scores indicating a larger number of pre-existing medical conditions (Charlson et al., 1987).

Statistical Analyses of Study Aims

The present study sought to examine the direct and indirect relationships among distress, neuroimmune dysregulation and negative clinical outcomes through structural regression modeling, a subtype of structural equation modeling (SEM) (Figure 1-1). A

structural regression model is the combination of a path analysis model and measurement model (Kline, 2005). Simply stated, this approach allowed evaluation of relationships among observed variables and latent variables within a model. SEM methods better accounted for measurement error variance than other common statistical approaches. Analysis of Moment Structures (AMOS) software (Arbuckle, 2008) used full information maximum likelihood (FIML) estimates to account for missing data (Carter, 2006). FIML was suggested when using SEM in small to medium sample sizes. Since the assumption of normally distributed continuous data plays a significant role in SEM, the measured data were evaluated for normality prior to running statistical analyses. Measured variables were statistically transformed, as needed, to attain normal distributions. Specific latent variables, with multiple indicators (at least 2), were examined in the current model (Table 2-1).

The model fit was evaluated recursively, and measured variables were expected to load onto their respective latent factors. Modifications to this model were guided by theoretical and statistical assumptions of SEM. However, if an appropriate model could not be fit to the data, a simpler path analysis model was utilized to examine the primary aims. Given that this was the case, Aims 1, 2, and 3 were examined by using linear regression analyses. A total of 3 equations (1 per aim) were tested. If the null hypotheses were rejected for each Aim, then Aim 4 (mediation) was tested using the methods of Preacher and Hayes (2004).

Sample Size and Model Specification

Power Analysis

Few studies have evaluated psychosocial predictors of cortisol and VEGF and clinical outcomes among cancer populations. As such, there are few studies from which

to draw effect sizes for adequate sample size estimation. However, a primary study by Vedhara and colleagues (2006) examining the effects of psychosocial predictors of cortisol and clinical outcomes among cancer populations demonstrated a moderate effect size (r=0.28) according to Cohen's effect size conventions (Cohen, 1977). Another study conducted by Lutgendorf and colleagues (2002) investigated psychosocial predictors of VEGF and clinical outcomes in women with ovarian cancer and found large effect sizes (f^2=0.53). A recent study using an SEM model to evaluate relationships among psychosocial factors and neuroimmune factors found a moderate effect size for the relationship between psychosocial factors (pain, depression and fatigue) and cortisol (r=0.35; Thornton et al., 2010). Therefore, the effect sizes among psychosocial factors, neuroimmunity, and clinical outcomes were expected to be in the moderate effect size range.

Kline (2005) reviews power analysis approaches for SEM and suggested evaluation of power for multiple linear regressions as an estimation of power for SEM approaches. With seven indicators, a power of 0.8 and α=0.05, a sample size of 50 was deemed sufficient to attain moderate effect sizes (f^2=0.3). The sample size for the present study was estimated a priori to include data from 100 participants, as use of SEM and FIML approaches will allow inclusion of participants with some missing data. Thus, the a priori sample size estimate was deemed to be adequate to detect these effect sizes.

Model Specifications

Additionally, few studies have utilized SEM approaches in psycho-oncology, in part due to small sample sizes and high attrition (or death) in oncology samples (Schnoll et al., 2004). However, for the current study, a sample size of 100 participants was

deemed to be sufficient a prior for accurate parameter estimates and appropriate error estimates. A similar sample size was utilized to evaluate an SEM model of similar complexity in a recent psycho-oncology study of breast cancer patients (Thornton et al., 2010). In order to support a robust model with this sample size, data were examined for normality and efforts were made to transform all non-normally distributed data (Lei & Lomax, 2005). Another method to determine adequate sample size was the ratio of participants to observed (measured) variables. The current study utilized 7 observable variables (refer to Figure 1-1), so the suggested ratio of 10 cases per observed variable, was exceeded, signifying a robust model (Kline, 2005).

Strong SEM models were “over-identified,” which occurs when the number of measured variables is greater than the number of estimated parameters (Thompson, 2000). Keeping a positive value of degrees of freedom was a primary assumption in creating an “over-identified” model, as the degrees of freedom are equal to the maximum number of parameters that can be estimated in a specific model. Degrees of freedom were determined by the following formula {df= [p*(p+1)]/2}, where p= the number of observed variables (Thompson, 2000). Using this formula {df=28=[7*(8)]/2}, the current model could not estimate more than 27 parameters. Parameters in this model included the error associated with each measured variable (7), the associations between the indicators and respective latent variables (7), the correlations among measured variables (3) and the correlations among latent variables (3); a total of only 20 parameters. Additional parameters were estimated in recursive versions of this model, to fully examine all theoretical parameters. As previously mentioned, if the data were significantly non-normal or sample size limited power of subsequent models, a

simpler path analysis model was planned for examination of the study aims among the observed variables.

Table 2-1. Latent and measured variables

Latent Variable	Measured Variables
Distress	Pain (PCOQ), Sleep Disturbance (PSQI), and Mood Disturbance (SIGH-AD: depression and anxiety)
Neuroimmune Dysregulation	VEGF and Cortisol AUCi
Negative Clinical Outcomes	Disease Stage and Postoperative Complications

Table 2-2. CTCAE Consensus Items

Discrepancy:	Details Regarding Coding Decisions:
Coding Blood Loss	Hemoglobin values are the best indicator of anemia (used in the CTCAE) but the medical record often reports a variety lab values (red blood cells, hematocrit, or specific anemia subtype values). If hemoglobin was unavailable, a combination lab values was required to attain a severity rating for blood loss. Detailed values determined for each level of severity: 0= Nothing noted or only reported hematocrit (>26) 1= Mild: Asymptomatic – Hgb 10-12, Hct 25-35, RBC 3-4 2= Moderate: Symptomatic – Hgb 8-10, Hct 20-25, RBC 2-3 3= Severe: Transfusion indicated – Hgb <8, Hct <25, RBC 2
Pain Ratings	Normal postoperative pain includes routine medication: Abnormal pain levels were identified by a plan to monitor pain ratings (1), patient report of uncontrolled pain (1) and/or changes in pain medication (2)
Prophylactic Antibiotics	Did not code as a complication unless infection was present.
Ileus vs. obstruction	Different treatment modalities (TPN vs. elective interventions) led to different categorization of complications.
Abnormal Lab Values	Any other irregular lab value being monitored is rated here if it does not fit a CTCAE category: White Blood Cells: High values: 1= Mild: Asymptomatic-WBC 10-17 2= Moderate: Symptomatic- 17-100 3= Severe: Intervention->100 =leukocytosis (corresponds with CTCAE) Low values: 1= Mild: WBC<1000 2= Moderate: WBC<500 3=Severe: WBC not registered Platelet abnormalities: When monitoring minor changes, coded as 1
Respiratory Concerns	Identification of complications and differentiation of categories: 1) When only treatment methods are recorded – code as a 2 ex. incentive spirometer – used for treatment of atelectasis 2) Atelectasis and pleural effusion should be coded separately. While they are likely to co-occur, they are separate CTCAE categories which can result from different pathophysiology and have varying consequences. 3) Hypoxia is coded separately from other complications.

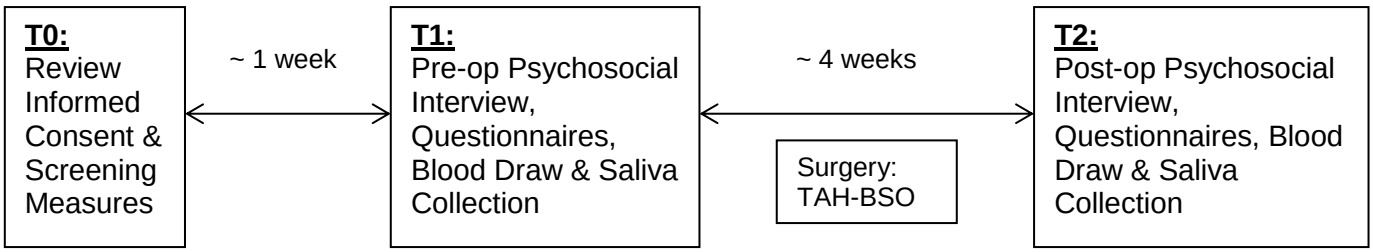


Figure 2-1. Study design

CHAPTER 3
RESULTS

Sample Characteristics

A total of 134 women who underwent surgery for suspected endometrial cancer were enrolled in the original study. From this sample, 21 women withdrew prior to surgery, did not complete preoperative measures, and did not have clinical outcome data available. Their data was a source of systematic missing data, which should not be included in SEM analyses. Therefore, the final sample was comprised of 113 women, who may have incomplete data at random. Since the women who withdrew from the study did not complete assessments prior to surgery, no comparative analyses could be conducted between the included and excluded participants. Descriptive statistics were utilized to evaluate normality of the data all biological variables, non-normal psychosocial data and outcome data were natural-log transformed prior to running statistical analyses.

The final sample of women (N=113) were primarily Caucasian (91.10%), ranging in age from 35-84 (*M*=61.38, *SD*= 9.09), and 79.2% of the sample had at least a high-school education. Regarding their current marital status, 57%.10% of women were currently married, 19.10% were divorced/separated, 17.10% were widowed, and 76.70% were never married. Overall, these women (N=80) reported an average family income of $25,000-$34,999, although a number of women did not complete this item of the MASQ.

Descriptive Statistics for Measured Variables

Mood, Pain, and Sleep

The mean composite SIGH-AD score was 12.89 (*SD*=9.02, range 0-51). PCOQ ratings indicated that while 36.4% of women were experiencing no pain, over 50% of women indicated a usual pain level of 10 or greater; usual pain ratings ranged from 0-98 (*M*=21.25, *SD*=27.15). Furthermore, most women acknowledged some difficulty sleeping. PSQI global scores ranging from 1-18 (*M*=6.94, *SD*=4.30). Using a modified cut-off score of 8, as recommended by Carpenter & Andrykowski (1998), in the current study approximately 30% of women in this sample had poor sleep quality, which corresponded to the percent of women who described their sleep quality as "poor" (*M*=1.01, *SD*=0.79) on a scale from 1 (very poor) to 5 (excellent). Additionally, about 50% of women reported sleep efficiencies lower than 85%, which has been considered the upper limit for sleep efficiency in someone described as a poor sleeper (Espie et al., 2003). Additionally, within this sample of women 665.7% reported getting less than or equal to 7 hours of sleep each night, 96.2% experienced sleep disturbances (subscale score>0) and 65.4% reported sleep onset latency greater than 15 minutes (subscale score>0). Despite the overall sleep difficulty these women were experiencing prior to surgery, only 310.8% of women reported use of sleep medications and 15.4% acknowledged frequent daytime dysfunction (subscale score>1).

VEGF and Cortisol AUCi

The sample's corresponding presurgical biological data included VEGF levels and cortisol AUCi levels. Mean VEGF concentration was 265.91 (*SD*=340.09), while mean natural log transformed cortisol AUCi level was 1.05 (*SD*=0.74). These values were transformed for parametric analyses.

FIGO Disease Stage

While 9 women (8%.0%) were found to have benign disease (Stage 0), most women were found to have a diagnosis of cancer (*N*=105, 92.0%). Surgical staging commonly revealed Stage Ia (*N*=210, 197.7%) and Ib (*N*=46, 410.7%) endometrial cancer, and no women in this sample had metastasis at the time of surgery (stage IV, Table 3-1). Of the women who received a diagnosis of cancer, 88 (78%) had a diagnosis of endometrial adenocarcinoma, endometrioid type.

Post-operative Complications

Thirty-six women (321.86%) experienced no postoperative complications. Of the remaining 77 women who experienced postoperative complications, the mean overall sum score (accounting for severity of each complication) was 3.77 (*SD*=5.60, range =1-35) The most common complications included respiratory, thoracic and mediastinal disorders (*N*=43) or blood and lymphatic system disorders (*N*=52). There were a total of 210 different complications identified, which were categorized as mild (37%), moderate (30%), and severe (33%) complications according to the CTCAE.

Biobehavioral Control Variables

This sample of women had characteristically high BMI's, (*M*=36.45 kg/m2- obesity class II, *SD*=11.06) and medical comorbidity at the time of surgery (Charlson comorbidity score: *M*=2.50, *SD*=1.04). Specifically, this sample of women included women with 0-5 comorbid conditions, with 61 women having one documented comorbid condition and 67 women having two or more documented comorbid conditions. Comorbid conditions included diabetes (*N*=38), coronary artery disease (*N*=10), connective tissue disorder (*N*=8), chronic pulmonary disease (*N*=7), cerebrovascular

disease (*N*=5), congestive heart failure (*N*=2), peripheral vascular disease (*N*=2), and moderate to severe renal disease (*N*=1).

Analyses of Primary Aims

Associations Among Control Variables and Clinical Outcomes

Correlations were computed to examine the relationship between potential control variables and dependent variables/clinical outcomes (Table 3-3). Age, Body Mass Index (BMI), and Charlson Comorbidity Score were all significantly related to neuroimmune markers and/or clinical outcomes in the study. Older age was significantly associated with greater cortisol AUCi levels, (r(81)=0.24, p<0.05). With regard to clinical outcomes, lower BMI, (r(109)=-0.24, p<0.05,) and higher Charlson comorbidity scores, (r(110)=0.24, p<0.05) were significantly associated with more advanced disease stage.

Age, BMI, and Charlson Comorbidity scores were controlled for in the correlation analyses reported below; however, as explained under "Proposed Model and Subsequent Model Adjustments," the proposed SEM models were unidentified when the control variables were added to the models. As such, these control variables were removed from the SEM models.

Associations Among Measured Variables

Zero-order correlations were calculated among the measured variables (Table 3-4). PSQI global sleep ratings and SIGH-AD ratings were highly correlated, suggesting that participants who experience greater sleep disturbance may also experience greater psychological distress, (r(94)=0.66, p<0.001). PCOQ pain ratings were significantly correlated with PSQI global ratings, indicating that participants with higher levels of usual pain may also experience greater sleep disturbance (r(69)=0.34, p<0.001). PCOQ ratings were highly, positively correlated with SIGH-AD ratings, (r(73)=0.30, p<0.001).

Correlation analysis did not reveal relationships among Distress factors were not significantly associated with any neuroimmune markers or clinical outcomes (Table 3-3).

There was a marginal, positive correlation between VEGF and Cortisol AUCi, ($r(64)=0.21$, $p=0.09$). However, post-operative complications and disease stage were not associated, ($r(109)=0.07$, $p=0.49$). Cortisol AUCi was negatively correlated with FIGO disease stage, ($r(81)=-0.22$, $p<0.05$), but not postoperative complication scores, ($r(80)=-0.05$, $p=0.67$. VEGF values were not associated with disease stage, ($r(81)=0.05$, $p=0.64$,) or postoperative complication scores, ($r(79)=0.10$, $p=0.37$).

Correlation analyses among measured variables while controlling for BMI, Age and Charlson Comorbidity Scores revealed that PSQI global sleep ratings and PCOQ pain ratings were still significantly associated with SIGH-AD ratings (PSQI: $r(43)=0.52$, $p<0.001$; PCOQ: $r(43)=0.39$, $p<0.015$) (Table 3-5). However, the relationship between higher levels of pain and greater sleep difficulty became only marginally significant, ($r(43)=0.25$, $p=0.08$). VEGF and cortisol AUCi were not significantly associated, ($r(43)=0.19$, $p=0.22$). Higher VEGF levels were marginally no longer significantly associated with greater post-operative complications, ($r(43)=0.13$, $p=0.4206$), or disease stage, $r(43)=0.18$, $p=0.25$., Additionally, while lower cortisol AUCi was not significantly associated with more advanced disease stage, ($r(43)=-0.23$, $p<0.05=0.13$), or postoperative complications, $r(43)=-0.05$, $p=0.72$. The symptoms of distress were not related to the neuroimmune markers or negative clinical outcomes (Table 3-4).

Proposed Model and Subsequent Model Adjustments

The proposed model intended to examine a mediational relationship among three underlying biopsychosocial constructs (Distress, Neuroimmune Dysregulation, and Negative Clinical Outcomes) from a specified set of observed variables (Distress

→pain, sleep disturbance, and mood disturbance; Neuroimmune Dysregulation →vascular endothelial growth factor [VEGF] and diurnal cortisol area under the curve with respect to increase [AUCi]; and Negative Clinical Outcomes →disease stage and postoperative complications). However, versions of this mediation model were unidentified and could not be evaluated with the proposed structure.

Consequently, the initial model structure was adjusted to theoretically evaluate the primary aims of the study utilizing only the latent construct of Distress. This construct was composed of respective measured variables that were interrelated. Given that (a) latent factors constructed with less than three measured variables may not be as structurally sound and (b) both the latent factors of Neuroimmune Dysfunction and Negative Clinical Outcomes contained only two measured variables, these latent factors were dismantled. The latent factor of Neuroimmune Dysregulation was separated into two individual measured variables (multiple mediators), while the latent factor of Negative Clinical Outcomes was separated into two individual outcomes of interest (Figures 3-1 and 3-2). Then, SEM was used to assess the adequacy of these adjusted models allowing examination of the specific aims of the study.

Model 1: Distress, Neuroimmune Markers and Postoperative Complications

The first model (Figure 3-1) examined the indirect effect of presurgical distress (pain, sleep disturbance, and mood disturbance) on postoperative complications in women undergoing TAH-BSO for suspected endometrial cancer. Greater levels of presurgical neuroimmune markers (VEGF and cortisol AUCi), were expected to mediate the relationship between greater presurgical distress and postoperative complications.

This model demonstrated that greater Distress was significantly predicted by associated with higher PCOQ pain ratings (path coefficient= 1.50, p<0.001), higher

PSQI scores (path coefficient=0.67, p<0.001), and higher SIGH-AD ratings of anxiety and depression (path coefficient=0.75, p<0.001;Table 3-8). The model also found a significant relationship between higher VEGF levels and greater postoperative complications (path coefficient=0.09, p=0.05), but not cortisol AUCi and postoperative complications (path coefficient=-0.01, p=0.55) However, a relationship did not emerge between Distress and VEGF (path coefficient=0.14, p=0.72) or Cortisol AUCi (path coefficient=0.57, p=0.65). While the model was considered to be a good overall fit to the data (x^2=10.65, P=0.22, CFI=0.95), mediation could not be further evaluated (Tables 3-5 and 3-6).

Model 2: Distress, Neuroimmune Markers and Disease Stage

The second model (Figure 3-2) examined the indirect effect of presurgical distress (pain, sleep disturbance, and mood disturbance) on surgically staged disease in women undergoing TAH-BSO for suspected endometrial cancer. Greater levels of presurgical neuroimmune markers (VEGF and cortisol AUCi) were expected to mediate the relationship between greater presurgical distress and disease stage.

Contrary to hypotheses, a significant relationship between lower cortisol AUCi (indicating HPA axis understimulation, rather than overstimulation) and advanced disease stage was found in this model (path coefficient=-0.06, p<0.05); however, no relationship was found between VEGF and disease stage (path coefficient=0.09, p=0.37). Consistent with Model 1, greater Distress was significantly predicted associated with higher PCOQ pain ratings (path coefficient=1.48, p<0.001), higher PSQI scores (path coefficient=0.68, p<0.001), and higher SIGH-AD ratings of anxiety and depression (path coefficient=0.75, p<0.001; Table 3-8). There were no significant relationships found between VEGF and Distress (path coefficient=0.18, p=0.63) or

Cortisol AUCi and Distress (path coefficient=0.57, *p*=0.64). While the fit statistics support the theoretical model fit (χ^2=10.81, P=0.21, CFI=0.95), the model was comparable to the previous model evaluating postoperative complications, since it did not elucidate a relationship among Distress and neuroimmune markers and did not demonstrate an improvement in fit (Table 3-6, AIC-model 1=48.65, AIC-model 2= 48.81).

Exploratory Analyses

Model 3: Distress and Neuroimmune Dysregulation

One of the primary aims was to evaluate the relationship among the latent factors of Distress and Neuroimmune Dysregulation. In order to evaluate this initial aim, IL-6, another critical inflammatory marker in endometrial cancer, was added to the original model. The mean level of IL-6 in this sample was 4.20 µg/mL (SD=14.92). The exploratory model (Figure 3-3) was identified after the addition of IL-6 utilizing three measured variables for each latent factor.

This model demonstrated some improvement in overall fit (χ^2=7.95, P=0.44, CFI=1.00, AIC=45.95, (Tables 3-5 and 3-6), but still did not reveal a significant relationship among Distress and Neuroimmune Dysregulation (path coefficient=0.03, *p*=0.71; Table 3-8). Higher PCOQ pain ratings (path coefficient=1.53, *p*<0.001), higher PSQI scores (path coefficient=0.65, *p*<0.001), and higher SIGH-AD ratings of anxiety and depression (path coefficient=0.76, *p*<0.001) were all consistently associated with the Distress factor. Additionally, VEGF, IL-6 and cortisol (AUCi) did not significantly contribute to the Neuroimmune Dysregulation (VEGF: path coefficient=3.66, *p*=0.34, IL-6: path coefficient=0.99, *p*=0.27 and AUCi: path coefficient=10.05, *p*=0.27), but no significant relationships were found with this latent factor. When the Negative Clinical

Outcomes latent factor was added to this model, the model was unidentified suggesting a structural and theoretical problem when this latent factor was added to the SEM models presented in this study.

Table 3-1. FIGO disease stage

	f	%	Valid %	Cumulative %
Stage 0	9	8.0	8.0	8.0
Stage IA	21	18.6	18.6	26.5
Stage IB	46	40.7	40.7	67.3
Stage IC	9	8.0	8.0	75.2
Stage IIA	4	3.5	3.5	78.8
Stage IIB	11	9.7	9.7	88.5
Stage IIIA	8	7.1	7.1	95.6
Stage IIIB	1	0.9	0.9	96.5
Stage IIIC	4	3.5	3.5	100.0

Table 3-2. Postoperative complication categories

Postoperative Complication Categories	**Frequency**
General Disorders and Administration Site Conditions	14
Cardiac Disorders	10
Vascular Disorders	11
Gastrointestinal Disorders	18
Respiratory, Thoracic, and Mediastinal Disorders	43
Blood and Lymphatic System Disorders	52
Metabolism and Nutrition Disorders	8
Renal and Urinary Disorders	6
Infections and Infestations	11
Nervous System Disorders	1
Injury, Poisoning and Procedural Complications	5
Investigations	28
Musculoskeletal and Connective Tissue Disorders	2
Endocrine Disorders	1

Table 3-3. Zero-order correlations among measured variables and controls

	Age	BMI	Comorbidity	SIGH-AD	PCOQ	PSQI	Cortisol AUCi	VEGF	FIGO Cancer Stage
Age (N=113)									
BMI (N=111)	-0.19*								
Comorbidity (N=112)	0.01	-0.04							
SIGH-AD (N=106)	-0.30***	0.06	0.04						
PCOQ (N=77)	-0.09	0.21	-0.06	0.30***					
PSQI(N=96)	-0.32***	0.04	0.07	0.66***	0.34***				
Cortisol AUCi (N=83)	0.24*	-0.02	-0.02	0.04	0.03	0.05			
VEGF (N=83)	0.08	0.04	0.08	0.06	-0.04	0.07	0.21		
FIGO Cancer Stage (N=113)	-0.03	-0.24*	0.24*	0.11	-0.02	0.14	-0.22*	0.05	
Postoperative Complications (N=111)	0.05	-0.17	0.13	-0.02	-0.13	-0.09	-0.05	0.10	0.07

*Indicates $p<0.05$, **Indicates $p<0.01$, ***Indicates $p<0.001$

Table 3-4. Partial correlations (Controls: Age, BMI, Comorbidity)

N=43	SIGH-AD	PSQI	PCOQ	Cortisol AUCi	VEGF	FIGO Cancer Stage
SIGH-AD						
PSQI	0.52***					
PCOQ	0.25	0.39**				
AUCi	0.13	0.11	0.12			
VEGF	0.16	0.08	-0.07	0.19		
FIGO Cancer Stage	0.11	0.14	0.08	-0.23*	0.18	
Postoperative Complications	0.08	-0.15	-0.16	-0.05	0.13	-0.01

*Indicates $p<0.05$, **Indicates $p<0.01$, ***Indicates $p<0.001$

Table 3-5. Model summary

Model	NPAR	CMIN	DF	*P*	CMIN/DF
1. Post-operative Complications Model	19	10.65	8	0.22	1.33
2. Disease Stage Model (FIGO)	19	10.81	8	0.21	1.35
3. Distress and Neuroimmune Dysregulation	19	7.95	8	0.44	0.99

Table 3-6. Fit statistics

Model	χ^2	RMSEA	TLI	CFI	Hoelter	AIC
1. Postoperative Complications Model	10.65	0.05 (0.41)	0.87	0.95	164	48.65
2. Disease Stage Model (FIGO)	10.81	0.06 (0.39)	0.86	0.95	161	48.81
3. Distress and Neuroimmune Dysregulation	7.95	0.00 (0.63)	1.00	1.00	219	45.95

Table 3-7. Standardized regression weights

	1	**2**	**3**
Pain and Distress	0.43	0.42	0.43
PSQI Global and Distress	0.85	0.85	0.84
Total SIGH-AD and Distress	0.74	0.73	0.74
VEGF and Distress	0.05	0.06	
Cortisol AUCi and Distress	0.06	0.06	
Postoperative Complications and AUCi	-0.07		
Postoperative Complications and VEGF	0.21		
Disease Stage and AUCi		-0.23	
Disease Stage and VEGF		0.10	
Distress and Neuroimmune Dysregulation			0.08
VEGF and Neuroimmune Dysregulation			0.49
IL-6 and Neuroimmune Dysregulation			0.40
Cortisol AUCi and Neuroimmune Dysregulation			0.42

Table 3-8. Unstandardized regression weights

1. Postoperative Complications Model	**Estimate**	**S.E.**	**C.R.**	***P***
VEGF and Distress	0.14	0.38	0.36	0.72
Cortisol AUCi and Distress	0.57	1.23	0.46	0.65
Pain and Distress	1.50	0.52	2.88	0.00
PSQI Global and Distress	0.67	0.23	2.88	0.00
Total SIGH-AD and Distress	0.75	0.24	3.17	0.00
Post-operative Complications and Cortisol	-0.01	0.01	-0.60	0.55
Post-operative Complications and VEGF	0.09	0.05	1.95	0.05
2. Disease Stage Model	**Estimate**	**S.E.**	**C.R.**	***P***
VEGF and Distress	0.18	0.38	0.48	0.63
Cortisol AUCi and Distress	0.57	1.23	0.47	0.64
Pain and Distress	1.48	0.52	2.86	0.00
PSQI Global and Distress	0.68	0.24	2.86	0.00
Total SIGH-AD and Distress	0.75	0.24	3.17	0.00
FIGO Disease Stage and Cortisol	-0.06	0.03	-2.18	0.03
FIGO Disease Stage and VEGF	0.09	0.10	0.90	0.37
3. Distress and Neuroimmune Dysregulation	**Estimate**	**S.E.**	**C.R.**	***P***
Distress and Neuroimmune Dysregulation	0.03	0.08	0.38	0.71
Pain and Distress	1.53	0.52	2.92	0.00
PSQI Global and Distress	0.65	0.22	2.92	0.00
Total SIGH-AD and Distress	0.76	0.24	3.16	0.00
VEGF and Neuroimmune Dysregulation	3.66	3.82	0.96	0.34
IL-6 and Neuroimmune Dysregulation	0.99	0.90	1.10	0.27
Cortisol AUCi and Neuroimmune Dysregulation	10.05	9.11	1.10	0.27

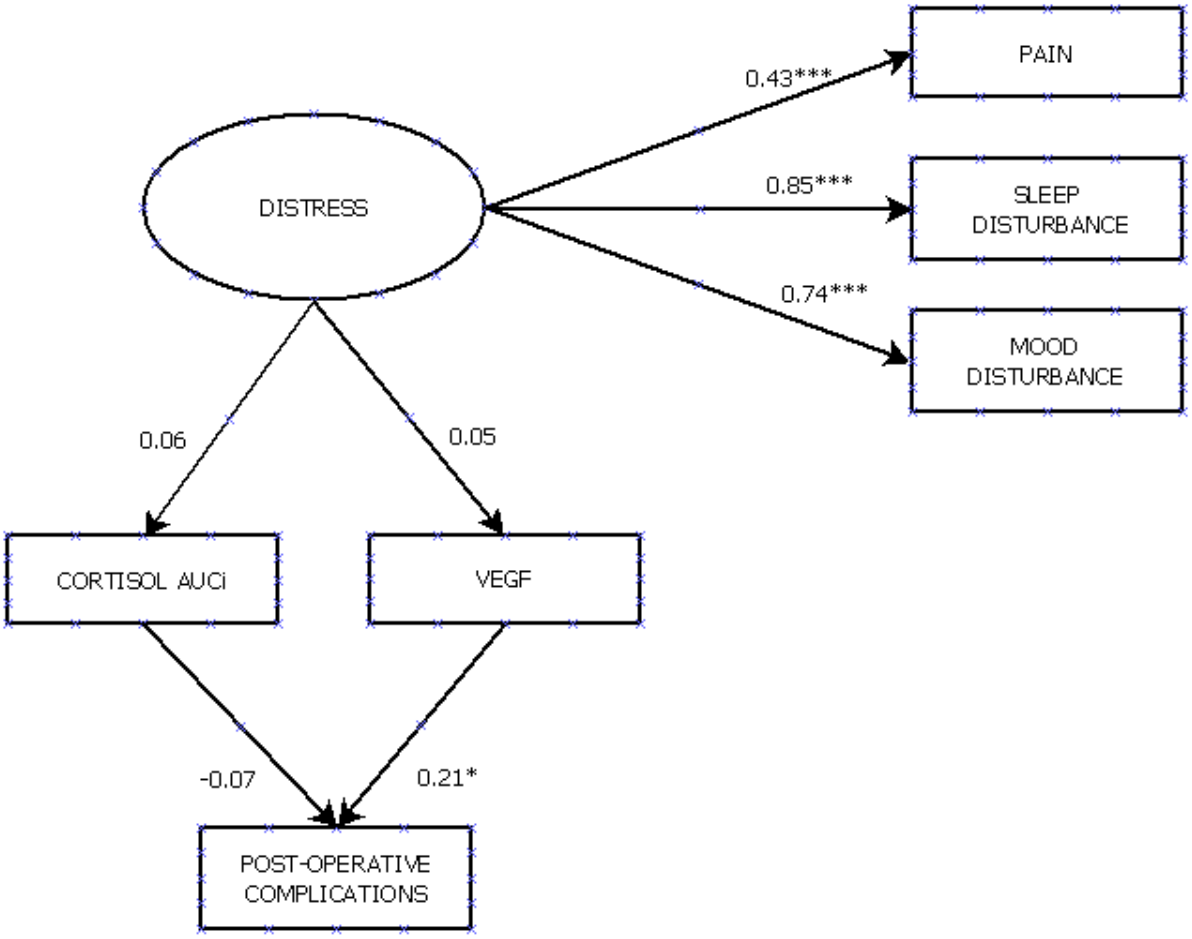


Figure 3-1. Postoperative complications model with standardized regressions

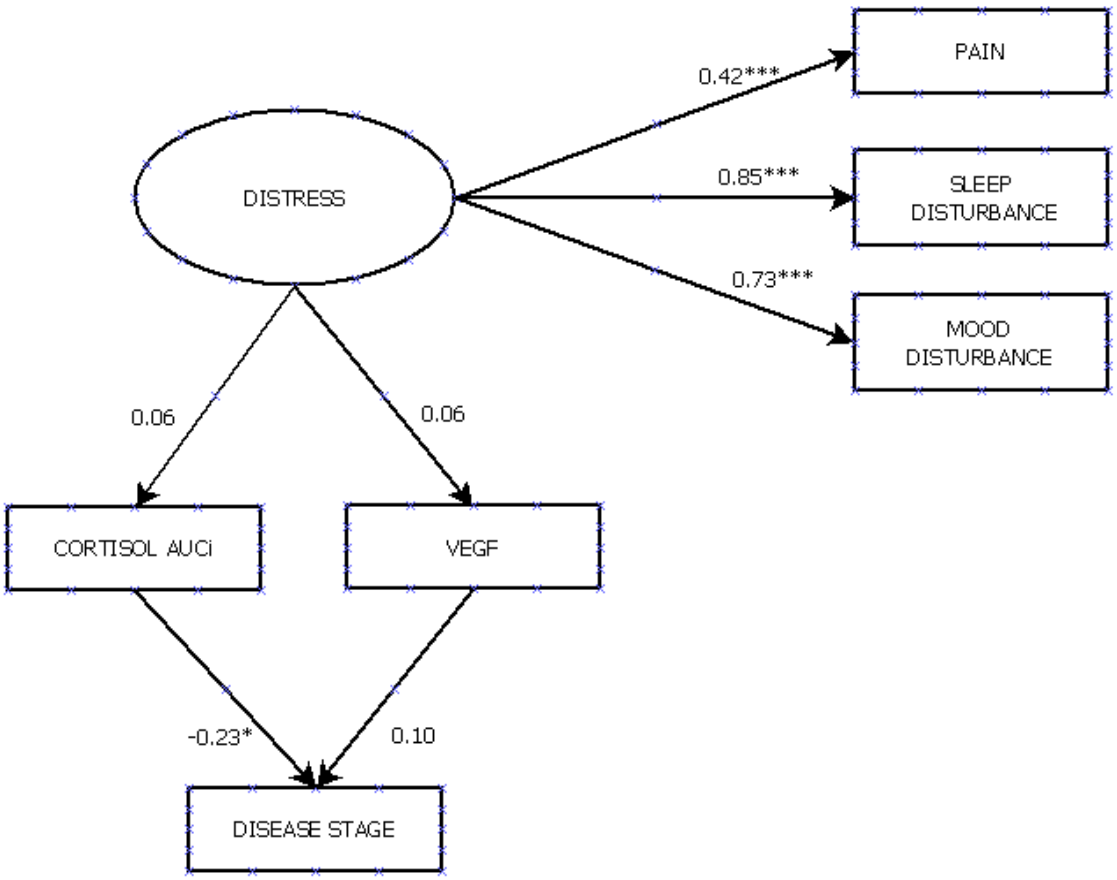


Figure 3-2. Disease stage model with standardized regressions

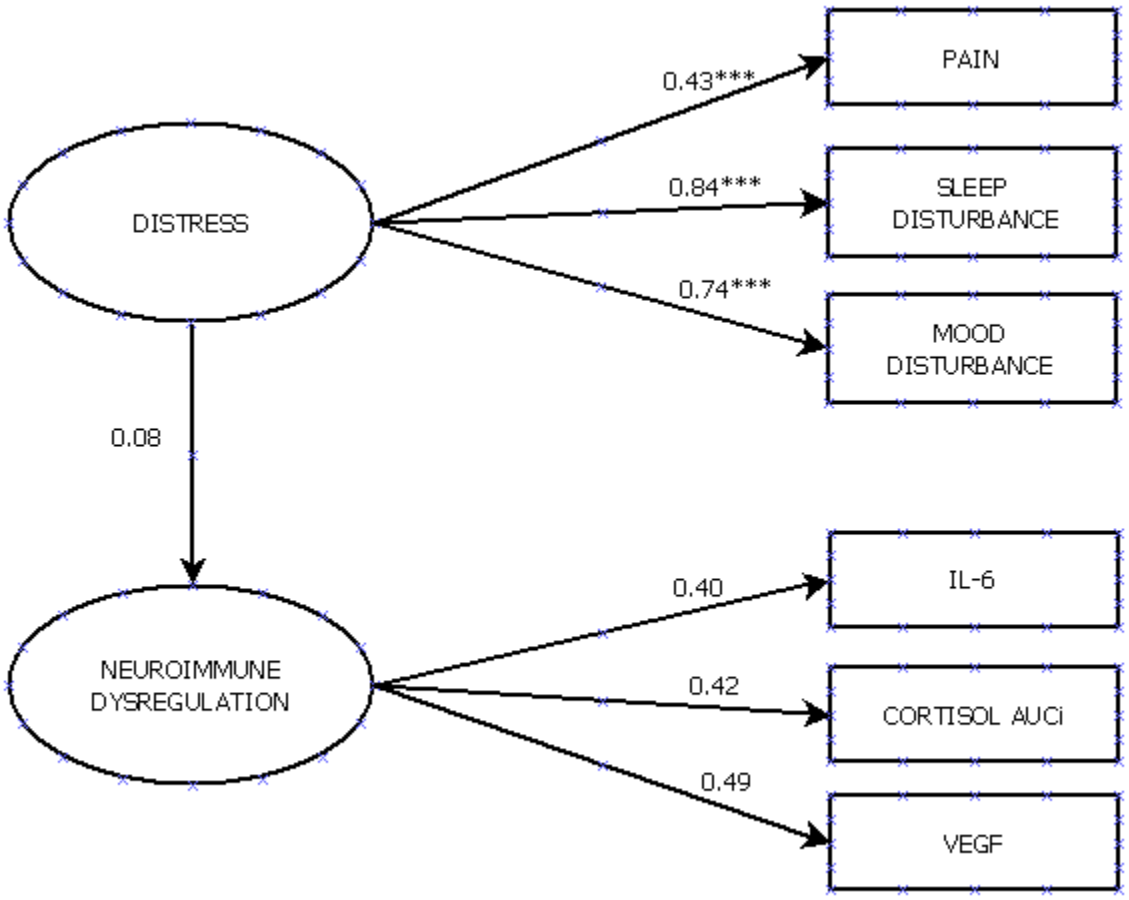


Figure 3-3. Distress and neuroimmune dysregulation model with standardized regressions

CHAPTER 4
DISCUSSION

Primary Aims

Approximately 43,000 women are diagnosed with endometrial cancer each year in the US and many of these women experience distress as part of their experience with cancer (ACS 2010 and Vitek, Rosenzweig & Stollings, 2007). Distress can include a number of symptoms, but research has focused on a specific cluster of symptoms which include mood disturbance, sleep disturbance and pain. Psychoneuroimmunology literature has found that mood disturbance (Sephton et al., 2000), pain (Thornton et al., 2010), and sleep disturbance (Rich et al., 2005) are associated with cortisol and cytokine production patterns that portend poorer clinical outcomes in cancer; however, no literature has investigated this set of symptoms and their association with neuroimmune function in women with endometrial cancer. Furthermore, the relations among these symptoms at the presurgical timepoint could be relevant to clinical status and outcomes in this population, such as disease stage and incidence of postoperative complications. Therefore, the current study aimed to examine the direct and indirect relationships among presurgical distress, presurgical neuroimmune dysregulation and post-surgical clinical outcomes among women undergoing TAH-BSO for suspected endometrial cancer.

This study demonstrated significant relationships among pain, sleep and mood disturbance, which can be collectively labeled as Distress, in women with endometrial cancer. These relationships were still present after controlling for relevant control variables of Age, BMI and Comorbidity. The correlations suggested that prior to surgery, high levels of pain, sleep disturbance and psychological distress may occur concurrently

in this sample of women. While sample size may have limited power of the correlation analysis, further examination using more advanced statistical methods (SEM) supported the initial evaluation. As expected, the proposed SEM model's latent factor of Distress represented the shared variance of the measured variables representing these constructs.

Additionally, the proportion of women experiencing symptoms of Distress in this sample of women was comparable to other samples of cancer patients (Thompson & Shear, 1998; Bradley et al., 2006; Lutgendorf et al., 2001; Portenoy et al., 1994; Rummans et al., 1998). When compared to other patients with chronic illness, the current sample of women contained a similar percentage of patients with poor sleep quality (30% with PSQI>8; Carpenter & Andrykowski 1998). Variable levels of pain have been reported among cancer patients (42-63%, Rummans et al., 1998), and the current sample fits within this range, with 63.6% reporting symptoms of pain prior to surgery.

While the latent factor of Distress could be utilized in SEM, the proposed model had to be modified to evaluate the initial aims of the study. Modifications were made to improve the structural model, specifically the latent factors of Neuroimmune Dysregulation and Negative Clinical Outcomes, which may not have been fully represented by only two measured variables per latent factor (Kline, 2005). The two modified SEM models demonstrated good overall fit to the data and built upon the initial correlation matrix. Although the study did not identify significant direct or indirect relationships among Distress, Neuroimmune Dysregulation and Negative Clinical Outcomes as latent factors, significant relationships were found between specific neuroimmune markers and negative clinical outcomes.

Contrary to hypotheses, SEM analysis did not find significant relationships between Distress and cortisol AUCi, but the study did find a positive trend between symptoms of distress and cortisol AUCi. It is possible that the retrospective assessment of mood disturbance and sleep disturbance combined with the preoperative pain ratings did not accurately represent the symptoms experienced at the time of cortisol collection. There may also be other symptoms of distress that could add to the shared variance of the latent factor of Distress, making the positive relationship with cortisol AUCi stronger. Future studies could try to assess symptoms of distress on the same days as cortisol collection and incorporate other relevant symptoms of distress.

Research on the relationship between symptoms of distress and neuroimmune markers, such as cortisol, has been impeded by methodological variability, which leads to difficulty interpreting results. Specifically, the variable methods of measurement and operationalization of cortisol has led to inconsistent results regarding the relationship between symptoms of distress and cortisol output (Chida & Steptoe, 2009 and Vedhara et al., 2006). For example, characteristics of poor sleep quality have been associated with lower cortisol awakening response (CAR) in saliva, which may reflect a blunting or "wearing out" of the HPA axis (Backhaus, Junghanns, & Hohagen, 2004). The current study utilized AUCi, which doesn't fully account for changes in CAR due to time of sample collection (fewer morning samples). The accuracy of sample collection by participants may influence the strength of the positive relationship between symptoms of distress and cortisol AUCi, due to lower overall values of AUCi when morning sample collection is later than expected. Future studies evaluating the relationship between Distress and cortisol production may benefit from separately assessing CAR (expecting

lower values) and AUCi (expecting higher values), which may better elucidate how cortisol production can be influenced by symptoms of Distress.

There was also no significant relationship found between Distress and VEGF levels in this sample. However, the relationship between Distress and VEGF had a similar effect size to the relationship between Distress and AUCi, suggesting that symptoms of distress may promote the release of both of these neuroimmune markers. With regard to methodology of VEGF assessment, the current study evaluated depression over the past month and utilized serum VEGF levels. Research that has identified relationships between VEGF and mood disturbance in women with gynecologic cancer often utilized plasma VEGF levels (Lutgendorf et al., 2008). It may be that the plasma values are slightly higher than serum, leading to a positive, but not significant, relationship between Distress and VEGF levels.

Symptoms of distress included in this study have been individually associated with different neuroimmune markers, including, but not limited to, greater VEGF (Lutgendorf et al., 2008; Mills et al., 2005 and Guess et al., 2009) and cortisol levels (Antoni et al., 2009; Vedhara et al., 2003; Tennant & Hermann, 2002); therefore, a more comprehensive neuroimmune profile may better explain the shared variance associated with symptoms of distress. Also, the presence of multiple components of distress may influence neuroimmune function differently than the solitary effects of one symptom, so future studies should further evaluate the cumulative effects of Distress on specific immune parameters.

Another aim of the current study was to evaluate the relationship between neuroimmune dysregulation and negative clinical outcomes. There was no significant

relationship found between VEGF levels prior to surgery and disease stage. . Studies that have found a relationship between VEGF and disease progression have been conducted using VEGF levels in cytosol, which are usually much higher than serum levels (Lutgendorf et al., 2003 and Chen et al., 2001). Since there was a positive, but not significant, relationship between serum VEGF levels and disease stage in this sample, future studies evaluating this relationship may find stronger associations using cytosol VEGF levels. Furthermore, examining the direct relationship between preoperative VEGF levels and long-term survival or relapse, rather than examining disease stage as a proxy for survival, may clarify relationship between VEGF and cancer progression.

While the association between higher levels of VEGF prior to surgery and disease stage was not significant, higher levels of VEGF were significantly associated with greater postoperative complications. Specific examination of VEGF levels in women with endometrial cancer further supported the concept that higher levels of pro-inflammatory markers prior to surgery may lead to worse clinical outcomes (Kaireviciute et al., 2010). Since there are a number of different cytokines implicated in the effects of inflammation on clinical outcomes in cancer, future SEM models could build upon these findings by evaluating other cytokines, such as IL-6 or Interferon-gamma, which have been implicated in the progression of disease and worse outcomes in cancer patients (Kaireviciute et al., 2010 and Savard et al., 2005).

The current study evaluated one other marker of neuroimmune dysregulation, changes in cortisol production. Particularly, cortisol AUCi prior to surgery was significantly associated with more advanced surgically stage disease; however, lower –

rather than higher – AUCi was associated with more advanced disease at diagnosis. There are several possible explanations for these results. Most notably, cortisol dysregulation can be operationalized in many different ways, which is one source of inconsistency among the literature on the effects of psychosocial symptoms on cortisol indices (Vedhara et al., 2006). In the present study, cortisol dysregulation was operationalized as higher cortisol production (AUCi), indicating overstimulation of the HPA axis, but the inverse relationship between cortisol and disease stage suggested that HPA axis understimulation is a stronger correlate of advanced disease stage than overstimulation. Lower AUCi levels may co-occur with other indicators of HPA axis understimulation, such as lower CAR, flatter cortisol slope, or elevated evening cortisol levels. In general, these indicators represent a "blunted" release of cortisol found in the presence of chronic stress, pain, sleep disturbance (Geiss et al., 2005 and Backhaus, Junghanns, & Hohagen, 2004). The current results fit within the research on the relationships of cortisol dysregulation (flattened slope) and mortality, especially if surgical disease stage was considered a proxy for survival in women with endometrial cancer (Sephton et al., 2000).

Cortisol levels consistently demonstrated negative associations with clinical outcomes in the SEM models presented, indicating cortisol dysregulation due to inhibited production of cortisol in this sample. However, lower cortisol AUCi was not significantly associated with postoperative complications in this study. Since cortisol can promote a Th2 immune response (indirectly inhibiting the proinflammatory response), cortisol dysregulation due to blunted HPA reactivity may lead to greater inflammation after surgery, leading to worse surgical outcomes in this population (Antoni et al., 2006;

Irwin et al., 2003 and Sato et al., 2002). This indirect effect of cortisol may partly explain the negative relationship between cortisol AUCi and postoperative complications in this study.

While the current study focused on HPA dysregulation, symptoms of Distress could influence both sympatho-adreno-medullary (SAM) and HPA systems, and these two systems could work together to influence clinical outcomes in cancer (Antoni, 2009). These two systems influence different parts of the adrenal gland, with the SAM axis (catecholamines) tied to adrenal medullary function and the HPA axis tied to adrenal cortex function (glucocorticoids and inflammation; Antoni, 2009). For example, research has identified relationships among catecholamines (epinephrine and norepinephrine) and symptoms of distress, including pain, depression and fatigue (Thornton, Andersen and Blakely 2010). Catecholamines (plasma norepinephrine) have also been found to mediate the relationship between depression and surgical outcomes associated with inflammation in heart disease, and similar relationships may be present in women with cancer (Dao et al., 2010). While cortisol AUCi was not significantly associated with VEGF levels in this study, cortisol and catecholamines may synergistically promote VEGF production (Antoni et al., 2006). This suggests that future research may be able to build upon the current results by incorporating catecholamines as a marker of activation of the SAM axis, which could improve the shared variance explained by the latent factor of Neuroimmune Dysregulation. This addition may improve the likelihood of examining mediation as a primary aim in a similar SEM model.

There could be a number of other reasons why mediation could not be evaluated in the current study. It is also possible that symptoms of Distress could directly influence

catecholamines and cortisol, to subsequently influence inflammation (Antoni, 2006). Future studies could also consider utilizing two separate latent factors to represent neuroendocrine response (cortisol and catecholamines) and inflammatory responses (Th1 and Th2 cytokines). The current study focused on promotion of cell-mediated (Th1) immunity, but future studies may also want to consider the inhibition of humoral (Th2) immunity in the context of distress (Dimitrov et al., 2004). Future models could investigate other markers of inflammation, such as interferon gamma, tumor necrosis factor and IL-6, in the context of tumorigenesis and surgical recovery, as well as symptoms of distress (Dimitrov et al., 2004; Kaireviciute et al., 2010 and Savard et al., 2005).

Both IL-6 and tumor necrosis factor have been implicated in the presence of daytime fatigue, which is a symptom of distress that could further improve the model by strengthening the theoretical relationship between distress and neuroimmune dysregulation in models that build upon these findings (Vgontzas & Chrousos 2002). Research has suggested that fatigue may play a significant role in the quality of life of cancer patients, as well as patients suffering from depression, chronic sleep and/or pain disturbance, and that higher levels of plasma IL-6 may represent the systemic effect of these symptoms (Clevenger et.al., 2012 and Heffner et al., 2011). It is possible that fatigue is another critical component of the relationship between Distress and Neuroimmune dysregulation that has not been integrated in the models evaluated by this study.

The inclusion of different measured variables and modification of the current methodology could strengthen the latent factors in the current SEM model. Hopefully,

these suggested changes would allow further evaluation of potential mediation among Distress, Neuroimmune Dysregulation and Negative Clinical Outcomes in this population, as well as other target populations.

Exploratory Analysis

To build upon the study aims, serum IL-6 was added to the original model, allowing evaluation of the relationship between Distress and Neuroimmune Dysregulation using SEM. IL-6 was added for several reasons. First, IL-6 levels have been implicated in the bidirectional relationship between pain and sleep, and greater levels of IL-6 may represent the physiological effect of Distress in patients (Heffner et al., 2011). Second, IL-6 has been identified as a key inflammatory marker in this population of women, as higher levels were found in women with endometrial cancer compared to women with benign disease (Bellone et al., 2005). Third, IL-6 has been implicated in the process of angiogenesis, promoting tumor metastasis, and may promote development and progression of endocrine driven cancers, such as endometrial cancer (Cozzolino et al. 1993 and Dossus et al., 2010). Fourth, IL-6 may indirectly facilitate postoperative complications, such as anemia and impaired immune function (Maccio et al., 2012). Thus, adding IL-6, an anti-inflammatory marker, to the model may have improved the ability of the model to identify relationships between clinical outcomes and distress-associated neuroimmune dysregulation. The addition of IL-6 to the Neuroimmune Dysregulation latent factor was also intended to improve the stability of the factor by increasing the number of measured variables from two to three.

The exploratory model was identified. The Distress factor was consistently associated with pain, sleep disturbance and mood disturbance and the Neuroimmune Dysregulation factor was equally associated with the three different neuroimmune

markers (VEGF, cortisol AUCi and IL-6). The addition of IL-6 was not only intended to improve the structural model, but also to better explain the relationship between the latent factor of Distress and Neuroimmune Dysregulation; however, the exploratory model did not demonstrate a significant relationship between these latent factors. As previously explained, there could be other theoretical components missing from this model, such as a critical symptom of Distress (i.e. fatigue), a neuroimmune marker representing activation of the SAM axis (catecholamines), or other inflammatory markers (Th1 or Th2 cytokines) that are part of the complex relationship between symptoms of Distress, Neuroimmune Dysregulation and Negative Clinical Outcomes. Unfortunately, the relationships with Negative Clinical Outcomes could not be evaluated, likely due to the structural weakness of the latent factor of Negative Clinical Outcomes.

Evaluation of other clinical outcomes, such as survival, length of hospitalization and time to relapse, may improve the SEM models presented in this study. As surgical improvements are made, these women are more likely to undergo laparoscopic surgery, which has a different set of associated outcomes, such as longer surgical time, that would be worth evaluating as well (Janda et al., 2010 and Mourits et al., 2010). Additionally, the disease stage outcome variable is ordinal, rather than continuous, and is not normally distributed, which also impacted the original model structure and conflicted with assumptions of SEM (i.e. normality). Inclusion of more continuous measures of relevant health outcomes in cancer could allow the latent factor of Negative Clinical Outcomes to be evaluated using a similar SEM model. Also, the postoperative complications variable only represented acute complications (prior to discharge), but symptoms of distress and levels of neuroimmune markers may play a

greater role on intraoperative or long-term complications after surgery (Ben-Eliyahu 2003), suggesting a more longitudinal evaluation of the associations among these variables.

Clinical Significance

Pain, sleep disturbance and mood disturbance all coexist among this population prior to surgery. This cluster of symptoms has been found among other health populations and at varying timepoints across the cancer experience (Theobald et al., 2004). This is a notable set of symptoms because they have been the target of many evidence based treatments, such as cognitive-behavioral therapy (CBT). CBT addressing these specific symptoms has been shown to modify levels of key inflammatory markers following treatment, supporting the concept of a bidirectional relationship among symptoms and physiological changes (Pigeon et al., 2008). Future research evaluating potential mechanisms by which distress is associated with clinical outcomes should incorporate more than one measure of cortisol dysregulation (CAR and evening cortisol levels), as well as other markers of cell-mediated immunity (interferon gamma). Specifically, these neuroimmune parameters have been associated with symptoms of distress, have demonstrated sensitivity to cognitive behavioral interventions and have been associated with disease progression (Vedhara et al., 2006; Antoni et al., 2009; and Savard et al., 2005).

Intervention targeting symptoms of distress and neuroimmune dysregulation prior to surgery may improve the quality of life of cancer patients throughout the cancer experience. Given the potential effects of cognitive behavioral interventions on these specific components of distress in cancer, further evaluation of potential mediation among these presurgical symptoms, levels of neuroimmune markers and clinical

outcomes may support future randomized control trials of psychological interventions prior to surgery in cancer patients (Theobald, 2004; Dalton et al., 2004; Davidson et al., 2001; Antoni et al., 2009; Kwekkeboom et al., 2010). Furthermore, these symptoms may progressively worsen as patients initiate treatments for cancer, such as radiation and chemotherapy, which can have side effects of increased pain and changes in sleep (Guess et al., 2009 and NCI, 2009). Future longitudinal studies could determine if these symptoms of distress fluctuate during the cancer experience and if there is a more favorable time for delivering an intervention targeting the effects these symptoms may have on clinical outcomes in cancer, like relapse or survival.

The current study focused on the preoperative status (distress and neuroimmune dysregulation) and acute postoperative complications in endometrial cancer using the CTCAE coding system. The CTCAE identified similar rates of postoperative complications and provided an added level of systematic detail compared to previous studies evaluating acute complications following TAH-BSO (Janda et al., 2010 and Mourits et al., 2010). This system provided a reliable method of identifying and rating severity of complications in this population and could be utilized in other studies evaluating surgical outcomes. However, the CTCAE accounted for complications in a comprehensive set of organ systems, but the neuroimmune markers and distress symptoms evaluated in this study may have more notable effects on specific categories of complications, such as cardiovascular or immune system complications (Kaireviciute et al., 2010 and Maccio et al., 2012). Targeting these categories of postoperative complications identified by the CTCAE may improve the current theoretical and structural model and clarify what postoperative outcomes may be improved by

addressing specific preoperative symptoms of distress and neuroimmune markers in this population.

According to the study results, inflammation may primarily influence surgical recovery, but neuroendocrine changes, such as cortisol dysregulation, may influence a different set of clinical outcomes, such as disease stage. Given the inconsistent literature regarding the effects of cortisol dysregulation (as defined by slope, CAR, AUC and mean values) on clinical outcomes in cancer, future research is needed to clarify how different aspects of cortisol dysregulation may influence cancer progression. Specifically, CAR has been strongly associated with psychological disturbance, as well as sleep disturbance, and this index of cortisol production may be a more sensitive indicator of impaired HPA reactivity and promotion of chronic inflammation that can occur in the context of cancer (Vedhara et al., 2006l Dimitrov et al., 2004 and Backhaus, Junghanns, & Hohagen, 2004).

Strengths and Limitations

The current study had several weaknesses worthy of discussion. Although SEM was utilized, causality can not be determined from the models presented in this study. A longitudinal, experimental study design is needed to establish causal relationships among the variables presented. Additionally, the women who withdrew from the study did not complete assessments prior to surgery, so no comparative analyses could be conducted between the included and excluded participants. This study was a secondary analysis of a larger study of women, limiting generalizability to Caucasian women with early stage endometrioid endometrial cancer. These women represent the majority of women diagnosed with endometrial cancer; however, the current study aims should also be evaluated in women suspected of having more advanced stage endometrial cancer.

Identifying women with possible metastasis and other types of histology (papillary serous or clear cell endometrial cancer) may increase the strength of relationships being evaluated by the current study, because these women may experience greater symptoms of distress prior to surgery, have higher levels of inflammation and be at greater risk of postoperative complications (Guess et al., 2009; Bellone et al., 2005; Ben-Eliyahu 2003 and Sorosky, 2008).

With regard to methodological concerns, the measures in this study all demonstrated strong psychometric properties, but they were not ideal for comparison across studies evaluating symptoms of distress in cancer. The SIGH-AD was modified for use in this population and a sum score of anxiety and depression symptoms was utilized, so there were no clinical cutoffs available to describe the clinical relevance of mood disturbance in this sample. Depression and anxiety may be interrelated, but could be independently associated with different neuroimmune markers and clinical outcomes. Future models could evaluate these symptoms separately and using generalizable measures, while also fully addressing multicollinearity (an assumption of SEM) between these symptoms.

Also, while the study measures were collected preoperatively, psychosocial data was collected as a retrospective assessment of the past month and biological data was collected on different preoperative days, typically with saliva collection occurring the three days prior to surgery and blood collection on the day of surgery. Collecting sleep quality ratings that were better correlated with saliva sampling days, as well as other pain measures (Brief Pain Inventory) that may provide more comprehensive evaluations of symptoms, may also improve the relationship between Distress and Neuroimmune

Dysregulation because the collection of data on symptoms of distress would better coincide with neuroimmune function prior to surgery. While the current study was targeting acute symptoms of distress prior to surgery, chronic life stress may influence the relationships among the variables in this study. The blunted HPA reactivity indicated by relationships with cortisol AUCi is characteristic of people facing chronic stress (i.e. long-term financial or marital stressors), so it is possible that the current sample included women with high and low levels of chronic life stress and that these women may have differing clinical and biological presentations prior to surgery. Future studies should further elucidate the effects of chronic life stress on the potential mediation among symptoms of distress, neuroimmune dysfunction and clinical outcomes in cancer.

With regard to assessment of pain prior to surgery, It is reassuring that the BPI demonstrated a strong positive association with the PCOQ item representing pain symptoms. However, the parent study did not administer both of these measures consistently to all participants, so sample size limited the measured variables that could be incorporated in the current statistical analyses. Sample size and missing data also limited the current study's ability to comprehensively evaluate the impact of relevant control variables. Due to the relationship between clinical outcomes in endometrial cancer and BMI, age and comorbid conditions, future SEM models evaluating relationships with clinical outcomes should incorporate these variables. Also, surgical disease stage could serve as another control factor if long-term clinical outcomes (i.e. survival) are included in future studies.

Furthermore, there may be other measured variables that could improve the SEM model presented in this study. The latent factor of distress may benefit from inclusion of a self-report measure of fatigue, which has also been associated with catecholamine and cytokine levels in patients with cancer (Blakely, 2010 and Vgontzas & Chrousos 2002). Studies show that fatigue may play an integral role in the relationships among sleep quality, pain levels and mood disturbance in cancer patients, as well as other health populations (Beck et al., 2005, Kwekkeboom et al., 2010 and Theobald et al., 2004).

This secondary analysis was also restricted to an a priori set of biological markers, salivary cortisol and serum levels of VEGF and IL-6. While blood samples were intended to be collected at the same time of day across participants, this was often difficult to achieve given that participants were required to be cleared for surgery on the day of the presurgical blood draw. Research on IL-6 levels in the context of sleep difficulty has suggested that there may be a circadian rhythm to the release of IL-6 which is disrupted by poor sleep, so future studies could find stronger relationships among IL-6 and symptoms of distress if all participant samples were collected at the same time of day (Vgontzas & Chrousos 2002). Catecholamines and other cytokines may be involved in the development and progression of symptoms and disease processes and research should build upon the current model by incorporating other relevant biological markers.

Salivary cortisol was operationalized as AUCi, but other cortisol indices, such as cortisol awakening response (CAR), may improve the understanding of the role of cortisol dysregulation in future models. PNI research has utilized various measures of

cortisol to identify dysregulation and incorporating multiple indices of cortisol dysregulation (CAR and AUCi) may better account for different neuroimmune changes associated with symptoms of distress. Cortisol AUCi and CAR are also highly dependent on the assumption that patients are collecting samples accurately, which introduces a certain amount of error associated with this measured variable. Much of the research on psychosocial factors and cortisol dysregulation has been conducted in laboratory settings, so comparisons with the current study should be made cautiously. Also, it may be fruitful to measure cortisol and VEGF/IL-6 within compartments other than saliva and serum, respectively. VEGF/IL-6 levels sampled from plasma or wound fluid have demonstrated significant relationships with symptoms of distress, which may be due to higher concentrations of these substances in these other compartments (Maccio et al., 2012).

Finally, one of the biggest limitations of the study was the clinical outcome data available, as this latent factor was limited to two measured variables and was not able to be evaluated as part of an SEM model. Perhaps use of multiple, continuous outcome data, such as survival or time to recurrence, may be more appropriate for evaluation using SEM in the future.

These limitations do not outweigh the various strengths of the current study. Utilization of SEM allowed a comprehensive evaluation of relevant measured variables in a systematic way, and this statistical approach accounted for any incomplete data using FIML. This methodology led to evaluation of models in a large sample size, which is not common in research with this population. Overall, the models that were evaluated demonstrated good fit to the data and were generated and modified based on

theoretical concepts. These models fit well within the established literature on the neuroimmune mediation of the relationship between psychological factors and clinical outcomes in cancer.

While mediation among latent factors could not be evaluated, important relationships in this population were unveiled. This is the first study to demonstrate the relationship among pain, sleep disturbance and mood disturbance (anxiety and depression) in women undergoing surgery for endometrial cancer. This symptom cluster has been established in other health populations, but not in a homogenous group of women diagnosed with endometrial cancer, an endocrine-driven cancer. The associations found between neuroimmune markers and clinical outcomes fit within the current literature and suggested that there may be different indices of SAM or HPA activity that could have different relationships with health outcomes. Utilizing highly structured methods of assessment (the CTCAE) with sound psychometric properties will facilitate replication of the current methodology in future studies with other health populations. Additionally, evaluation of pre and post surgical status is clinically meaningful, as these timpeoints are associated with symptoms of distress, and interventions around the time of surgery could aim to modify clinical outcomes, such as postoperative health.

Future research should build upon these findings by utilizing SEM approaches to better understand the complex pathways by which psychosocial factors influence clinical outcomes in cancer. Evaluation of other neuroimmune markers and clinical outcomes which are more appropriately suited for SEM may uncover relevant mediating

factors, which can be the target of future interventions in women with endometrial cancer, as well as other patients with chronic illness.

American Joint Committee on Cancer

Cervix Uteri Cancer Staging

7th EDITION

Definitions

Primary Tumor (T)

TNM CATEGORIES	FIGO STAGES	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a**	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)

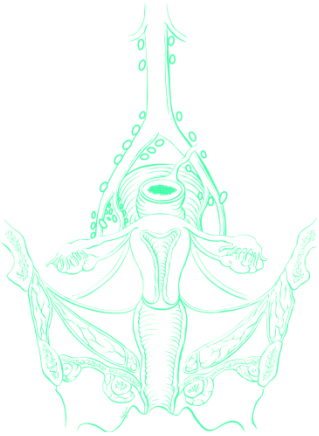
Regional Lymph Nodes (N)

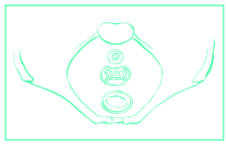
TNM CATEGORIES	FIGO STAGES	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIB	Regional lymph node metastasis

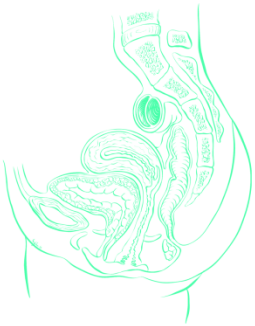
Distant Metastasis (M)

TNM CATEGORIES	FIGO STAGES	
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)

ANATOMIC STAGE/PROGNOSTIC GROUPS (FIGO 2008)			
Stage 0*	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIA1	T2a1	N0	M0
Stage IIA2	T2a2	N0	M0
Stage IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	Any N	M0
	T1–3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1







Notes

* FIGO no longer includes Stage 0 (Tis).

** All macroscopically visible lesions—even with superficial invasion—are T1b/IB.

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BIOGRAPHICAL SKETCH

Seema M. Patidar attended the University of North Carolina where she earned a Bachelor of Science in psychology, with a minor in chemistry in 2006. After graduating, Seema worked at Duke University Medical Center on a study examining the prognostic benefits of exercise and anti-depressant therapy in patients with heart disease.

In 2008, Seema was awarded an Alumni Fellowship and began her graduate studies in the University of Florida's Clinical and Health Psychology PhD. She has been a member of Deidre Pereira's research lab, conducting research in psycho-oncology, psychoneuroimmunology and women's health. She attained her MS in 2010 and completed her qualifying exams later that year. She is currently completing an APA accredited internship at the Boston Consortium and will receive her PhD in 2013.