RELATIONSHIPS AMONG PERCEIVED STRESS, SLEEP QUALITY, AND
DIURNAL CORTISOL IN ENDOMETRIAL CANCER PATIENTS:
A PILOT STUDY

By

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To Fiona Jensen

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Psychosocial factors (e.g., stress and sleep quality) are associated with abnormal

stress-hormone production (including flattened diurnal cortisol slopes) among individuals

with cancer. Research suggests that abnormal cortisol production may have significant

clinical implications for those with cancer. In particular, research has concluded that

greater disease severity is associated with diurnal cortisol dysregulation; and that

abnormal diurnal cortisol slope predicts earlier mortality among individuals with

metastatic cancer. Relations among perceived stress, sleep quality, and diurnal cortisol

slope have been examined mainly in breast cancer. To date, no studies have examined

these relations among women with endometrial cancer, the most common gynecologic

cancer and the fourth-most-common malignancy among women in the U.S. The present

feasibility study examined relations among pre surgical perceived stress, sleep quality,

and diurnal cortisol slope in 15 women with suspected endometrial adenocarcinoma.

It was hypothesized that greater perceived stress and poorer sleep quality would be associated with abnormal (e.g., flattened) diurnal cortisol slopes. Participants completed a psychosocial interview and provided saliva samples for analysis of diurnal cortisol output. Results revealed significant relationships between greater perceived stress and poorer sleep latency ($r = .65$, $p < .05$), greater number of negative life events and poorer global sleep quality ($r = -.92$, $p < .001$), and greater impact of negative life events and poorer global sleep quality ($r = -.92$, $p < .05$). Contrary to hypothesis, stress was not significantly related to diurnal cortisol. This study provides preliminary data to support future research examining predictors of diurnal cortisol and the relationship between diurnal cortisol and post surgical outcomes among women with endometrial cancer.

CHAPTER 1
INTRODUCTION

Epidemiology of Endometrial Cancer

Endometrial cancer is the most common gynecologic cancer in the United States,

with approximately 40,000 new cases estimated in 2004 (American Cancer Society

[ACS], 2004). It is also the second-most-deadly gynecologic cancer in the United States,

with approximately 7,000 deaths expected from endometrial cancer in 2004 (ACS, 2004).

The 5-year survival rate for patients with endometrial cancer is 84% (ACS, 2003a).

Endometrial cancer primarily affects postmenopausal women, with the peak incidence of

onset during the sixth and seventh decades (Dorigo & Goodman, 2003). Endometrial

cancer is approximately twice as common among White women compared to Black

women.

Pathophysiology of Endometrial Cancer

Endometrial cancer typically presents as an overgrowth of the cells in the

endometrium, which is the innermost layer of the body of the uterus. Almost 90% of

endometrial cancers are endometrial adenocarcinomas (ACS, 2003b). It is hypothesized

that endometrial cancer results from a progression from hyperplasia (pre-malignant cells),

to atypical hyperplasia of the endometrium, to malignant cells (Dorigo & Goodman,

2003). Like breast cancer and ovarian cancer, endometrial cancer is an

endocrine-mediated disease. During the follicular phase of menstruation, estrogen

unopposed by progesterone stimulates the proliferation of endometrial cells (Cyr &

Skelton, 2003). During the luteal phase of menstruation, progesterone is produced,

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resulting in the cessation of endometrial proliferation and the eventual sloughing of endometrial cells (Cyr & Skelton, 2003). A change in the balance between the amount of estrogen and progesterone produced by the ovaries, resulting in increased levels of unopposed estrogen and unchecked proliferation of endometrial cells, has been implicated as a risk factor for endometrial cancer (ACS, 2003b). Other known risk factors for endometrial cancer include exogenous use of estrogen (unopposed by progesterone), use of Tamoxifen (a selective estrogen-receptor-modulator treatment for breast cancer), early menarche, late menopause, infertility, obesity, and diabetes (ACS, 2003b). Recent evidence points to the role of genetics in the development of endometrial cancer; with women with a history of colon, ovarian, or breast cancer at a potentially higher risk for developing endometrial cancer (Dorigo & Goodman, 2003).

Staging and Treatment of Endometrial Cancer

The surgical staging of endometrial cancer is determined by cytology and pathology results from pelvic washings, total abdominal hysterectomy with bilateral salpingo oophorectomy (TAH-BSO), and pelvic lymph-node biopsies. Seventy-five percent of endometrial cancer diagnoses occur at Stage I, which is defined by the restriction of the original tumor to the endometrium (Dorigo & Goodman, 2003). Eleven percent of endometrial cancer diagnoses occur at Stage II and 11% occur at Stage III (Dorigo & Goodman, 2003). Standard treatment for early-stage endometrial cancer involves a TAH-BSO. Pelvic irradiation may be necessary if the pelvic lymph nodes are positive for cancer. Later stages of endometrial cancer involve the spreading of the tumor to the cervix, ovaries, abdominal organs, or other sites (ACS, 2003b).

Psychoneuroimmunology and Endometrial Cancer

Overview of Psychoneuroimmunology

Psychoneuroimmunology (PNI) is the study of the relations among psychosocial factors, neuroendocrine functioning, immunity, and health outcomes. Historically, much of that research has examined the relations among stress (laboratory-devised and naturalistic, acute and chronic); stress moderators and mediators (e.g., affect, mood, social support, personality, coping style, and health behaviors); and immune functioning in various populations, such as healthy populations, infectious diseases, cancer, wound healing, HIV, and autoimmune diseases (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002a). The study of PNI factors in cancer is becoming and increasingly important area of research.

Stress and Hypothalamic-Pituitary-Adrenal (HPA) Axis Functioning

Stress is defined by Lazarus and Folkman (1984) as "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being" (p. 19). This definition includes both primary and secondary appraisals, which, according to Lazarus and Folkman (1984), describe the initial evaluation of an event or situation's relevance to one's well-being (primary appraisal) and an evaluation of the resources available to deal with this potential threat (secondary appraisal). According to this view of stress, it is not just the occurrence of an event that poses a threat to well-being, but also the person's appraisal or perception of that threat.

When a situation is perceived as stressful, the Hypothalamic-Pituitary-Adrenal (HPA) axis becomes activated, causing a cascade of hormones to be produced that may (in turn) negatively impact immunity and health outcome. The paraventricular nucleus of

the hypothalamus releases corticotropin-releasing factor (CRF), which stimulates the pituitary gland. In response to this stimulation, the pituitary gland releases adrenocorticotropic hormone (ACTH). Finally, the release of ACTH results in the secretion of glucocorticoids from the adrenal cortex. One particular glucocorticoid (cortisol) is a steroid hormone that follows a circadian rhythm. It is regulated by the suprachiasmatic nuclei (SCN) in the hypothalamus, which causes cortisol to peak in concentration in the blood around waking, and decline steadily throughout the day (Stone et al., 2001).

Both physical and psychosocial factors can be responsible for the circadian dysregulation of cortisol (Mormont & Levi, 1997). Moreover, both acute and chronic stressors have been linked to dysregulated cortisol. In particular, acute stressors such as boot camp (Hellhammer, Buchtal, Gutberlet, & Kirschbaum, 1997), challenging mental tasks (Kirschbaum, Pruessner, Stone, & Federenko,1995), and lumbar puncture (Bohnen, Terwel, Twijnstra, & Markerink, 1992) have been associated with higher levels of cortisol. Altered cortisol profiles have also been found among individuals experiencing chronic stress, such as individuals experiencing interpersonal violence (Seedat, Stein, Kennedy, & Hauger, 2003) and unemployment (Ockenfels, Porter, Smyth, Kirschbaum, Hellhamer et al., 1995).

Under normal conditions, increases in circulating glucocorticoids act on the hypothalamus to inhibit further secretion of CRF and, subsequently, the secretion of ACTH from the pituitary gland. This negative feedback loop causes an inhibition of stress-induced HPA activation when a situation is no longer perceived as stressful. However, high, sustained levels of perceived stress override this negative feedback loop,

resulting in dysregulation of circulating cortisol (McEwen, 1998). This sustained

dysregulation of cortisol can have significant implications for health and immunity.

Cortisol, Immunity, and Health Outcome

Historically, much of the PNI literature has examined daily mean cortisol levels

(e.g., measured via a 24-hour urine collection) as the outcome variable of interest.

However, recent research has begun to move its focus from examining how much cortisol

an individual produces in a 24-hour period; to how much an individual's diurnal cortisol

slope deviates from the "normal" slope, defined as a peak on awakening followed by a

steep, steady decline throughout the day, with a trough at midnight (Anders, 1982; Stone

et al., 2001). This "normal" slope is contingent on the absence of significant external

stimulation and is robust among healthy individuals experiencing typical daily life (Stone

et al., 2001). Alterations in the diurnal cortisol slope can assume various forms, including

a flattened slope, abnormal peaks, and abnormal troughs.

The potential mediating effects of circadian disruption on the relationship between

psychosocial functioning and progression in diseases (such as cancer) warrants an

examination of diurnal cortisol dysregulation (Sephton & Spiegel, 2003). According to

Sephton and Spiegel (2003), circadian rhythms may reflect the regulatory competence of

the stress response via its ability to activate and de-activate when appropriate. Circadian

disruption of HPA axis functioning has not only been linked to psychosocial stress (e.g.,

Yehuda, 2002) but also to cancer progression. Using animal models of cancer, Filipski et

al. (2002) found that ablation of the SCN, which regulates circadian rhythm, resulted in

faster tumor growth and earlier mortality. In studies with humans, greater circadian

disruption has been found among patients with more-advanced cancer (Sephton &

Spiegel, 2003). Sephton and Spiegel (2003) posit that this phenomenon may reflect

dysregulation in behavioral variables related to both circadian disruption and disease progression, such as sleep quality (Sephton & Spiegel, 2003). Specifically, they note that disease progression may be associated with experiences (Such as pain or psychosocial distress) that interfere with sleep quality. Furthermore, poor sleep quality has been related to impaired endocrine and immune functioning linked to cancer progression (Vgontzas & Chrousos, 2002). Thus, Sephton and Spiegel (2003) suggest that behavioral variables (such as sleep quality) related to the cancer experience may partially explain the relationship between circadian disruption and disease progression. Circadian disruption appears to be of special relevance in endocrine-mediated cancers, in which endocrine circadian rhythms (such as cortisol) appear notably disrupted (Sephton & Spiegel, 2003). In fact, dysregulated diurnal cortisol has been identified in women with endocrine-mediated cancers such as breast cancer (Abercrombie et al., 2004; Sephton, Sapolsky, Kraemer, & Spiegel., 2000; Touitou, Bogdan, Levi, Benavides, & Auzeby., 1996) and ovarian cancer (Touitou et al., 1996).

One way in which diurnal cortisol dysregulation is thought to affect disease progression is through its suppressive effects on the immune system. For example, Miller, Cohen, and Ritchey (2002) posit that chronic stress impairs the ability of the immune system to respond to glucocorticoids. When infection or injury occurs, the immune system mounts an inflammatory response to assist with the healing process. Glucocorticoids, such as cortisol, regulate the inflammatory response to infection and injury by terminating the inflammatory cascade once it is no longer needed. However, when glucocorticoid production remains elevated for prolonged periods of time (e.g., under conditions of chronic stress), white blood cells respond by downregulating the

number and/or function of receptors that bind glucocorticoids, leading to a decreased

ability of white blood cells to respond to the anti-inflammatory actions of cortisol.

Consistent with this "glucocorticoid resistance hypothesis" (Figure 1-1), Miller et al.

(2003) note that chronic stress may impair glucocorticoids' ability to inhibit the

production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6

(IL-6), and tumor necrosis factor- α (TNF-α). These pro-inflammatory cytokines are

released by white blood cells and serve to direct white blood cells to the location of injury

or infection, initiate the production of other molecules in the inflammatory response, and

improve certain white blood cells' ability to kill. However, sustained, high circulating

levels of these cytokines can be toxic and damaging (Munck & Guyre, 1991), particularly

among individuals with cancer (Kelley et al., 2003).

↑ Chronic Stress

↓

↑ Glucocorticoid Dysregulation

↓

↓ Glucocorticoid Binding Receptors

↓

↓ Immune System's Anti-Inflammatory Response to Cortisol

↓

↑ Pro-Inflammatory Cytokines, Inflammatory Response

Resistance to Glucocorticoids
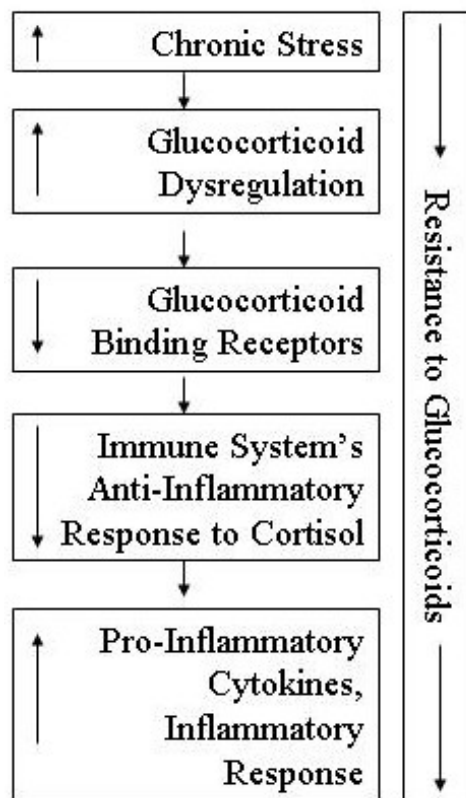
Figure 1-1. Glucocorticoid resistance model

Another important process in the inflammatory response is angiogenesis, which is the development of new vascular structures. As part of the inflammatory response, angiogenesis facilitates vascular permeability and blood flow to the source of the inflammation, which allows for the migration of leukocytes to the site (Frantz, Vincent, Feron, & Kelly, 2005). Angiogenesis is also integral in the development and progression of malignant tumors. Primary solid tumors typically grow for a period of time without vascularization, reaching a diameter of one to two millimeters (Folkman, 1990). This period of avascular growth is followed by the onset of angiogenesis, which stimulates nearby blood vessels for tumor perfusion, leading to tumor progression and in some cases, metastasis (Folkman, 1990; Kerbel, 2000). Early investigation into the potential biobehavioral mediators of pro-angiogenic cytokines, such as vascular endothelial growth factor (VEGF) suggest that endocrine mediators, such as cortisol, enhance VEGF production (Lutgendorf et al., 2003). Thus, cortisol dysregulation may also affect disease progression in cancer through enhanced angiogenesis.

Another way in which diurnal cortisol dysregulation is thought to affect disease progression via the immune system is through alteration of the balance between T helper 1 (Th1) and T helper 2 (Th2) cytokine responses. The Th1 immune response, which is linked to the production of interleukin-12 (IL-12), among other cytokines, facilitates cellular immunity. The Th2 immune response, which is linked to the production of cytokines such as interleukin-4 (IL-4), interleukin-6 (IL-6), and interleukin-10 (IL-10), facilitates humoral immunity and the inhibition of cellular immunity (Sparano, Lathers, Achille, Petruzzelli, & Young, 2004). A shift in the balance of the Th1/Th2 immune

response toward Th2 dominance is associated with more advanced disease in cancer patients (Sparano et al., 2004).

Glucocorticoids, such as cortisol, appear to impact the Th1/Th2 balance during nocturnal sleep. Petrovsky and Harrison (1997, 1998) found that nocturnal sleep promoted a shift toward Th1 dominance which is possibly mediated by the cortisol nadir typically found during early sleep. Furthermore, Dimitrov, Lang, Fehm, and Born (2004) found that corticosteroids altered the Th1/Th2 balance, producing a Th2 dominant response by inhibiting the Th1 cytokines. Thus, in light of the findings described above in which Th2 dominance is found among more advanced disease, dysregulated nocturnal cortisol not only threatens to disrupt the Th1/Th2 balance but may promote disease progression through inducing Th2 dominance.

The immunosuppressive effects of cortisol have also been linked to natural killer cells, an important component of innate immunity. Natural killer cells exert cytotoxic effects against viruses and neoplastic cells and may inhibit tumor growth and metastasis (Herberman, 1985; Trinchieri, 1989; Whiteside & Herberman, 1995). Cortisol has been shown to inhibit natural killer cell activity in peripheral blood leukocytes (Gatti et al., 1987). Among individuals with cancer, cortisol-induced suppression of natural killer cell activity may lead to tumor growth and/or metastasis.

Sleep Quality as a Mediator of the Relationship between Chronic Stress and Dysregulated Cortisol

Reduced sleep quality may be one of the most important biobehavioral mediators of the relationship between chronic stress and dysregulated cortisol. Although largely a subjective construct, sleep quality encompasses various quantitative sleep-related

variables, such as duration of sleep, sleep latency, and sleep disruption (Buysse, Reynolds, Monk, Berman, & Kupfer., 1989).

Like cortisol, poorer sleep quality has also been linked to higher levels of stress (Hall et al., 2000). Several studies have identified relationships between sleep quality and stress in healthy populations. In a study examining sleep disturbance in healthy middle-age women, Owens and Matthews (1998) found that greater perceived stress and tension were associated with insomnia. Neylan et al. (2002) investigated sleep quality among police officers and found that general stressors related to police work were associated with poorer sleep quality. Research has also investigated the relationship between sleep quality and stress among disease populations. Shapiro, Bootzin, Figueredo, Lopez, and Schwartz (2003) found that high levels of distress were associated with poorer sleep quality in breast cancer patients. Cruess et al. (2003) found that HIV positive patients with greater distress reported the greatest sleep disturbance. More extreme forms of stress, such as Post-Traumatic Stress Disorder (PTSD) have also been linked to sleep quality. Jacobsen et al. (1998) found that greater PTSD symptomatology was associated with poorer sleep quality in women who underwent autologous bone marrow transplants for breast cancer.

In addition to its association with stress, the literature suggests that sleep quality is also related to cortisol production. Specifically, poor sleep quality has been directly linked to greater diurnal cortisol dysregulation (Spiegel, Leproult, & Van Cauter, 1999). In a study utilizing a sleep laboratory, Spiegel et al (1999) examined the result of sleep debt on endocrine function and found that sleep debt was associated with cortisol dysreglation as defined by elevated plasma cortisol concentration in the afternoon and

early evening compared to a non-sleep debt condition. Similar disruptions were seen in salivary cortisol, with the rate of decrease between 4:00 PM and 9:00 PM six times slower in the sleep debt condition than in a non-sleep debt condition (Speigel et al., 1999). The authors posit that these results could be indicative of impairment in hippocampal regulation of negative feedback of the HPA axis.

The relationship between sleep quality and diurnal cortisol dysregulation has also been examined outside the context of sleep laboratories. Miller et al. (2002) found that parents of child cancer patients had significantly worse sleep quality and significantly flatter diurnal cortisol slopes compared to parents of healthy children. Thus, several studies in the literature identify a link between sleep quality and diurnal cortisol dysregulation in both laboratory and natural settings.

The immunosuppressive properties of poor sleep quality highlight its clinical significance among disease populations. One potential pathway by which sleep quality may act on immunity is via the effects of cortisol dysregulation on the pro-inflammatory cytokines. As mentioned above, poor sleep quality is linked with cortisol dysregulation, which may result in an inability to adequately regulate pro-inflammatory cytokines. In fact, cytokines are important in the modulation of sleep and sleep loss affects their prevalence in circulation (Mullington, Hinze-Selch, & Pollmacher, 2001). Moreover, as part of their role in the primary response to infection, cytokines are sensitive to sleep loss and increase during sleep deprivation (Mullington et al., 2001). According to Kelley et al. (2003), pro-inflammatory cytokines in the brain cause various sickness behaviors including a change in sleep patterns. This response is a natural response to infection and serves to promote resistance to pathogens and recovery (Kelley et al., 2003). According

to the glucocorticoid resistance model (Miller et al., 2003) the immunosuppressive effects of cortisol dysregulation result in a failure to suppress overactivity of pro-inflammatory cytokines. Thus, pro-inflammatory cytokines' association with sickness behavior and sleep changes could be exacerbated by cortisol dysregulation.

Another potential pathway by which sleep quality may act on immunity is via the ability to mount an adequate Th1 cytokine production pattern. As described earlier, the nocturnal balance between Th1 and Th2 cytokines is critical for an effective immune response (Dimitrov et al., 2004a). Several sleep-related variables appear to play a role in this important balance. Dimitrov, Lange, Tieken, Fehm, and Born (2004) highlight the importance of the slow wave sleep (SWS), which is characteristic of the early part of nocturnal sleep, as playing an important role in the suppression of glucocorticoids, which appears to favor Th1 cellular immunity. The importance of the early part of sleep is further reinforced by the fact that the circadian peak in Th1/Th2 cytokines occurs during this part of sleep (Petrovsky & Harrison, 1997). Thus, poor sleep quality, particularly during the early part of nocturnal sleep, may result in an inability to mount an adequate Th1 cellular immune response.

Reduced cellular immunity may have deleterious implications for disease progression among people with cancer. In a study of Th1 (cellular immunity) and Th2 (humoral immunity) immune responses among patients with head and neck cancer, Sparano et al. (2004) found that concentrations of interleukin-12 (IL-12), a cytokine involved in cellular immunity, were higher among patients with early stage tumors (Stages 1-2) than in patients with more advanced tumors (Stages 3-4). IL-12 levels were also higher among patients who did not have nodal metastases compared to patients who

had nodal metastases (Sparano et al., 2004). Perhaps more striking than the findings that cellular immunity was associated with early-stage disease variables, Sparano et al. (2004), found that levels of interleukin-10 (IL-10) and interleukin-6 (IL-6) (Th2 cytokines) were higher in more advanced tumors than early-stage tumors. IL-10 levels were also higher among patients with nodal metastases compared to those with no nodal metastases (Sparano et al., 2004). Thus, the literature suggests that an imbalance in the Th1/Th2 immune response, resulting in reduced cellular immunity, is associated with tumor progression and metastasis.

Applications of Psychoneuroimmunology to Cancer

Over the past several decades, advances in the understanding of the psychoneuroimmunologic relations involved in disease have been applied increasingly to the study of health and quality of life in cancer. PNI studies have primarily examined how psychosocial factors are associated with immune/endocrine factors that may promote progression to cancer in persons at risk for the disease, and promote progression, metastases, and recurrence in persons with cancer and in cancer survivors (Antoni, 2003). The application of PNI principles to cancer is based on the hypothesis that the cancer experience may engender stress and decreased quality of life, which may be associated with immune and neuroendocrine dysregulation, which may in turn affect disease progression and response to treatment (Antoni, 2003). In fact, the psycho-oncology literature is replete with evidence that individuals with cancer have higher levels of stress than healthy controls. Sources of stress for cancer patients include uncertainty, lack of personal control, waiting for results, communication with spouses and children, feelings of guilt, fears of dying, threat of disfigurement, the rigor of treatment, fatigue, financial

burden, social isolation, fear of recurrence, sexual difficulties, and vocational difficulties (Spiegel, 1997; Vess, Moreland, Schwebel, & Kraut, 1988).

Sleep quality has emerged as another indicator of decreased quality of life related to the cancer experience. Research with heterogeneous samples of cancer patients found that between 30 and 50% of newly diagnosed patients suffered from sleep difficulties (Savard & Morin, 2001). Furthermore, Owen, Parker, and MacGuire (1999) found that cancer patients experienced poorer sleep quality and more daytime dysfunction than healthy participants. Several studies assessing sleep quality in breast cancer patients found that between 61% (Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002) and 63% (Koopman et al, 2002) of breast cancer patients reported some type of sleep disturbance or poor sleep quality. Furthermore, breast cancer patients with poor sleep quality reported impairments in their ability to engage in daily tasks as well as lower levels of energy (Fortner et al., 2002). The perceived stress and impaired sleep quality experienced by cancer patients has the potential to negatively impact not only quality of life and psychosocial well-being, but also immune and neuroendocrine functioning.

A number of studies have found a link between stress and immunity among cancer patients. In an extensive review of the PNI findings related to cancer, Kiecolt-Glaser, Robles, Heffner, Loving, and Glaser. (2002b) report that psychological distress has been linked to impaired ability to repair damaged cellular DNA involved in cancer as well as the inhibition of apoptosis (Kiecolt-Glaser et al., 2002). Specifically, psychosocial stress has been linked to decreased methyltransferase synthesis, which plays an important role in DNA report in certain forms of tumors (Glaser, Thorn, Tarr, Kiecolt-Glaser, & D'Ambrosio, 1985). In a study of malignant melanoma, Fawzy et al. (1993) found that

psychosocial factors were related to faulty apoptosis, which is a process involving programmed cell death that is important in the defense against cancer cells.

The HPA axis has also been a particular focus of PNI research examining the effect of stress on cancer progression. It is hypothesized that the suppressive effects of cortisol on T-lymphocytes and natural killer cell cytotoxicity may interfere with the immune system's surveillance of cancer cells (Antoni, 2003). A recent study among women with metastatic breast cancer suggests that stress related to marital status may be associated with dysregulated diurnal cortisol (Sephton et al., 2000). Moreover, Luecken, Dausch, Gulla, Hong, & Compass (2004) found altered diurnal cortisol among women with breast cancer meeting PTSD criteria. Thus, evidence is mounting that stress is associated with altered neuroendocrine functioning among people with cancer.

In addition to its association with immune and neuroendocrine functioning, stress has also been linked to disease outcomes in cancer. In a study examining stress and disease outcome in women who were HIV and HPV positive, Pereria et al. (2003b) found that stressful life events predicted an increased likelihood of developing squamous intraepithelial lesions (SIL), the pre-malignant phase of cervical cancer. Findings from the animal literature also suggest the role of stress in cancer progression. In a study utilizing stress paradigms among rats, Ben-Eliyahu, Page, Yirmiya, and Shakhar. (1999) found that stress-induced suppression of natural killer cell activity was related to tumor development. Similar studies with mice have also highlighted the role of stress in tumor metastasis (e.g., Kanno, Wakikawa, Utsuyama, & Hirokawa, 1997).

In light of the findings pointing to the relationship between psychosocial stress and altered immune/endocrine functioning and disease outcome, evidence exists that stress-

reduction interventions may be able to counteract these relationships by reducing stress and improving immune/endocrine functioning. McGregor et al. (2004) examined the effects of a 10-week cognitive-behavioral stress management (CBSM) intervention on psychosocial and immune functioning among women with early stage breast cancer. She found that women receiving the CBSM intervention displayed more benefit-finding and improved lymphocyte proliferation compared to women in the control condition. Cruess et al. (2000b) also examined the effects of a 10-week CBSM intervention with women with early stage breast cancer. He reported that women who participated in the intervention showed increased benefit finding and reductions in serum cortisol compared to women in the control condition. Furthermore, psychosocial interventions among women with breast cancer have been shown to normalize cortisol responsivity to acute stress (van der Pompe, Antoni, & Heijnen, 1996).

Among PNI studies of cancer affecting women, the majority of research has focused on virally- and endocrine-mediated cancers such as cervical cancer, breast cancer, and ovarian cancer. In addition to the sources of stress related to the cancer experience stated above, women with gynecologic cancers face additional concerns related to sexuality and reproductive health (Anderson & Lutgendorf, 2000). Sexual dysfunction is common among women with gynecologic cancer treatment (Andersen, Anderson, & de Prosse, 1989) and younger women with gynecologic cancer may be faced with concerns regarding reproductive potential in the future (Anderson & Lutgendorf, 2000). Thus, the unique stressors associated with these cancers coupled with the role of immune and endocrine factors in their development and progression have recently made them the focus of PNI research.

Cervical cancer is a virally-mediated cancer that is thought to develop in conjunction with decreased immune surveillance (Antoni, 2003). Cervical cancer is linked to Human Papillomavirus (HPV) (Brisson et al., 1994; Katase, Teshima, Hirai, & Hasumi, 1995) and its progression appears to be increased among women who are immunosuppresseed (Penn, 1981). Research into the PNI relations among cervical cancer have highlighted several psychosocial factors such as stressful life events that are associated with immune factors that control HPV-induced progression to cervical cancer (Pereira et al., 2003).

Relations among psychosocial factors and immune factors associated with negative outcomes have also been found among endocrine-mediated cancers such as breast and ovarian cancer. Levy et al. (1990) found that various psychosocial factors such as perception of high quality emotional support from a spouse or intimate other, perceived social support from the physician, and active social support seeking as a coping strategy predicted higher NK activity among early stage breast cancer patients. Moreover, Tjemsland, Soreide, Matre, & Malt (1997) found that psychosocial factors such as anxiety and depression were associated with lymphocytes during the perioperative period. Immune response to laboratory stressors has also been examined among women with breast cancer. van der Pompe et al. (1998) found that women with breast cancer had a delayed NK cell activity response to a laboratory speech task compared to healthy women. Among women with ovarian cancer, psychosocial factors such as helplessness and worthlessness have been associated with higher levels of immune factors that promote tumor growth, such as VEGF (Lutgendorf et al., 2002).

Much of the PNI research on endocrine-mediated cancers has focused on the HPA axis and diurnal cortisol dysregulation. Touitou et al. (1996) investigated diurnal patterns of serum cortisol in breast cancer and ovarian cancer patients. Fifty-three percent of breast cancer patients and 75% of ovarian cancer patients had abnormal patterns of cortisol, defined as higher than normal mean cortisol, erratic peaks and troughs, and flattened diurnal slopes (Touitou et al., 1996). These findings are a cause for concern in light of Sephton et al.'s (2000) findings that flatter diurnal cortisol slopes predicted shorter survival time in women with metastatic breast cancer. In a subsequent study utilizing a healthy control group, Abercrombie et al. (2004) found that women with metastatic breast cancer had significantly flatter cortisol slopes than healthy controls. Thus, the PNI literature suggests that not only do women with endocrine-mediated cancer display diurnal cortisol dysregulation, but that this dysregulation is associated with poor health outcomes and mortality. In light of these findings, it is surprising that no research to date has examined diurnal cortisol among endometrial cancer, another common endocrine-mediated cancer.

Importance of Psychoneuroimmunology in Endometrial Cancer

Endometrial cancer represents an important but under-studied population in the PNI cancer literature. A number of factors lend support to the need for more extensive study of the PNI relations in women with endometrial cancer. First, as stated previously, endometrial cancer is the most common gynecologic malignancy. Second, women with endometrial cancer represent a highly stressed population with significant quality of life deficits during and after treatment. In a study that examined global perceptions of quality of life (satisfaction with the ability to carry out daily activities, overall physical condition during the last week, and overall quality of life during the past week) among women with

endometrial cancer immediately post-treatment, Klee and Machin (2001) found that global evaluations of quality of life of women with endometrial cancer were lower compared to age- and partner status-matched healthy women. Furthermore, at one month post-treatment, ratings of overall quality of life during the past week were still lower among women with endometrial cancer compared to controls (Klee & Machin, 2001). In a qualitative study of sexual functioning among women with endometrial cancer, Juraskova et al. (2003) identified a number of concerns regarding sexuality, including feelings of loss related to removal of reproductive organs, fear related to resuming sexual activity, and concerns about sexual desirability. The impact of the endometrial cancer experience on levels of stress and quality of life may pose threats to endocrine and immune functioning.

Third, endometrial cancer primarily affects older, postmenopausal women. The geriatric nature of this population raises important concerns related to immune senescence and the increased opportunity for disease and infection (Butcher & Lord, 2004). Aging has been associated with alterations in immune functioning and dysregulation (Lutgendorf & Costanzo, 2003). In addition to its association with higher levels of pro-inflammatory cytokines (Han & Meydani, 2000), aging is also related to changes in HPA axis functioning, such as flattened diurnal cortisol slope (Deuschle et al., 1997), and slower HPA recovery after stress (Sapolsky, Krey, & McEwen, 1986). Lutgendorf and Costanzo (2003) posit that these changes may result in sustained circulating stress hormones, such as cortisol, after cessation of stressors.

Fourth, there is some evidence for cortisol dysregulation among women with endometrial cancer. Mollerstrom, Carlstrom, Lagrelius, and Einhorn (1993) found that

endometrial cancer patients had higher cortisol levels than both healthy controls and women being treated for non-malignant post-menopausal bleeding. However, it is important to note that no published studies to date have examined diurnal cortisol dysregulation among women with endometrial cancer.

Finally, an intact immune response is critical for maintaining health and well-being among women with endometrial cancer. There is some preliminary research that psychosocial factors, such as stress and poor social support, are associated with pro-angiogenic cytokine production patterns among individuals with cancer (Lutgendorf et al., 2002). This has important implications for women with endometrial cancer. For example, VEGF, is elevated in women with endometrial cancer, compared to healthy women (Reynolds, Grazul-Bilska, & Redmer., 2002). Elevation of VEGF is also related to shorter disease-free survival in women with endometrial cancer (Chen et al., 2001). In addition to VEGF, interleukin-8 (IL-8) has been implicated in tumor angiogenesis. IL-8 has been found to be elevated in women with early stage endometrial cancer (Chopra, Dinh, & Hannigan, 1997). Recent evidence suggests that cortisol induced the production of VEGF from ovarian cancer cell lines (Lutgendorf, et al, 2003). Thus, dysregulated cortisol, possibly associated with increased stress, may pose a threat for angiogenesis among women with endometrial cancer.

In addition, intact immune functioning is critical to recovery from surgery. Antoni (2003) has highlighted the importance of investigating pre-surgical stress reduction and its impact on post-surgical immune functioning. This illustrates the importance of pre-surgical immune functioning for post-surgical recovery, an issue relevant to endometrial cancer, given that surgery represents its primary form of treatment.

In spite of the cogent reasons to investigate the PNI relations among women with endometrial cancer, no research has examined PNI relations in this population. Furthermore, little research has examined PNI relations in a disease population during the acute pre-surgical period.

Current Study

A number of studies have found dysregulated diurnal cortisol profiles in patients with endocrine-mediated cancer (Sephton et al., 2000; Touitou et al., 1996; Abercrombie et al., 2004). The immunosuppressive effects of cortisol raise concern that dysregulated cortisol in cancer patients may be associated with poorer health outcomes. The paucity of research examining variables related to cortisol is surprising considering the potential deleterious effects of dysregulated diurnal cortisol on cancer patients. Although evidence exists for relationships between stress and sleep quality, stress and diurnal cortisol, and sleep quality and diurnal cortisol, no study to date has focused on the relationships among these variables in women with endometrial cancer.

The purpose of the current study was to examine the relations among perceived stress, sleep quality, and diurnal cortisol slope pre-surgically in women with endometrial cancer. Specifically, the current study first sought to assess for dysregulation of diurnal cortisol slopes among women with endometrial cancer. We hypothesized that compared to women with benign gynecologic disease, women with endometrial cancer would have more abnormal diurnal cortisol slopes in terms of flatter slopes, abnormal peaks, and abnormal troughs. Secondly, the current study sought to assess for relations among perceived stress, sleep quality, and diurnal cortisol slope among women with endometrial cancer. We hypothesized that greater perceived stress as well as poorer sleep quality would be associated with more abnormal diurnal cortisol slopes. Finally, the current

study sought to assess whether sleep quality mediates the relationship between perceived stress and diurnal cortisol slope. We hypothesized that poorer sleep quality would mediate the relationship between greater perceived stress and abnormal diurnal cortisol slope.

CHAPTER 2
METHODS

Design

The current study was cross-sectional in design. Fifteen women with suspected endometrial cancer attended a single session in which they underwent a psychosocial interview as well as provided four saliva samples per day for the three days preceding the psychosocial interview. The measures in the battery of psychosocial interviews related to this study assessed a variety of variables related to stress and sleep quality. Analyses examined both the relationships between individual variables as well as a mediational hypothesis between the variables.

Participants

The study sample consisted of 15 women with suspected endometrial adenocarcinoma. Thirty-two women were approached for study recruitment, of which 6 women declined to participate in the study, citing the following reasons: "Having surgery too soon," "Too much to handle," "A wreck all the time-don't want to," "Don't have the time," and "Too much going on right now." Eleven women were deemed ineligible due to the following reasons: pre or perimenopausal status, previous cancer history, not fluent in English, and not having surgery at UF & Shands. Of the 15 women who provided informed consent to participate in the study, complete data were collected from 13. All women participating in the study underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) with or without pelvic lymph node dissection for suspected primary endometrial adenocarcinoma, were post-menopausal, and were fluent

in spoken English. Women were excluded from the study if they met any of the following criteria: (1) a post-TAH-BSO diagnosis of endometrial sarcoma, (2) Stage IV endometrial adenocarcinoma, (3) a previous history of cancer, (4) recurrent endometrial carcinoma, (5) metastasis to the uterine corpus from another site, (6) pre-surgical chemotherapy or radiotherapy, (7) current psychotic disorder or suicidal intent. The stage of endometrial cancer was determined by pathologists post-operatively, with 2 women (14.3%) classified as Stage 0, 7 women (50%) classified as Stage I, 4 women (28.6%) classified as Stage II, and 1 woman classified as Stage II/III endometrial cancer. Patients underwent endometrial biopsy a mean of 20.58 (SD = 8.35) days prior to participating in the study. Table 2-1 lists the demographic characteristics of participants.

Procedures

All participants were recruited from the Shands & UF Gynecologic Oncology Clinics in Gainesville, Florida. Potential participants were identified through consultation with attending physicians, residents, and medical students and were notified of the opportunity for participation by their physicians at their surgical consultation visit. If a patient indicated that she was interested in participating, she was introduced to a study staff member who provided her with detailed information about study participation. If she agreed to participate, she underwent informed consent procedures and provided written informed consent. Participants then underwent a brief psychiatric screening interview (described below). If this was unremarkable, they were then provided with a salivary cortisol collection kit and instructed to collect their saliva samples at home for three consecutive days prior to their pre-operative visit. At the pre-operative clinic visit (mean of 9.9, $SD = 6.4$ days after consultation visit), participants underwent a two-hour psychosocial interview (described below) and peripheral venous blood draw. Participants

were compensated $20. The University of Florida Health Sciences Institutional Review

Board approved all study procedures.

Table 2-1. Demographic characteristics of study participants

Demographic Characteristics	
N	15
Age, Mean (SD)	61.57 (11.29)
Highest degree (% of sample)	
Less than high school	30.8
High school/GED	38.5
Some college	15.4
Bachelor's degree	13.3
Household income (% of sample)	
Less than $5,000	7.7
$5,000-$11,999	7.7
$12,000-$15,999	15.4
$16,000-$24,999	30.8
$25,000-$34,999	7.7
$35,000-$49,999	23.1
$50,000-$74,999	7.7
$75,000-$99,999	0.0
$100,000 or greater	0.0
Don't Know	7.7
Race (% of sample)	
American Indian	0.0
Asian	0.0
Native Hawaiian/Pacific Islander	0.0
Black/African American	7.7
White	92.3
Ethnicity (% of sample)	
Hispanic/Latino	0.0
Not Hispanic/Latino	100.0
Marital Status (% of sample)	
Married	84.6
Divorced	7.7
Widowed	7.7
Employment Status (% of sample)	
Working full-time	23.1
Working part-time	7.7
Keeping house/raising children	7.7
Retired	61.5

Psychosocial Screening and Assessment

The brief psychiatric screening interview assessed for current suicidal ideation, psychotic symptoms, and borderline or antisocial personality disorder. Current suicidal ideation was measured with the Beck Scale for Suicide Ideation (BSS; Beck & Steer, 1991). The BSS is a 21-item, self-report measure of the presence and severity of suicidal ideation. The reliability of the BSS is well established, with coefficient alphas ranging from .87-.90 (Beck & Steer, 1991). The concurrent validity of the BSS is demonstrated by moderate to high correlations with other measures of suicidal constructs (Beck & Steer, 1991). Although little published data exist regarding the use of the BSS as a screening tool among cancer populations, it has been used extensively among inpatient and outpatient psychiatric populations (Pinninti, Steer, Rissmiller, Nelson, & Beck., 2002). No participants with current suicidal ideation were excluded from further participation.

The Psychotic Screening Module of the Structured Clinical Interview for DSM-IV for non-clinical populations (SCID-NP; Spitzer, Williams, Gibbon, & First, 1992) was used to assess for psychotic symptoms and Axis II pathology if clinically indicated. The SCID-NP is a semi-structured interview for making DSM-IV Axis I psychotic diagnoses in non-psychiatric populations. If the results of the screening were unremarkable, participants underwent a two-hour psychosocial interview conducted by a trained researcher at the pre-operative visit.

Perceived stress was measured with the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983). The PSS is a 14-item scale measuring the degree to which situations in the past month are perceived as stressful. The scale was developed to evaluate the degree to which people find their lives "unpredictable, uncontrollable, and

overloading." Participants use a 5-point Likert scale ranging from "Never" to "Very Often" to indicate how often they have experienced each item in the past month. Higher scores on the PSS indicate higher levels of perceived stress. The PSS has coefficient alpha reliability in healthy samples ranging from .84 to .86 (Cohen et al., 1983) and has good reliability in studies of individuals with physical illness (coefficient alpha .86-.89; Soderstrom, Dolbier, Leiferman, & Steinhardt, 2000). The PSS is moderately correlated with life stress measures (r =.20-.35) as well as with psychological and medical constructs such as depressive symptomatology (r =.76) and physical symptomatology (r=.52) (Cohen et al., 1983). The validity of the PSS has also been demonstrated in gynecologic samples (Kain, Sevarino, Alexander, Pincus, & Mayes, 2000).

Life event stress was measured with an abbreviated version of the Life Experiences Survey (LES; Sarason, Johnson, and Siegel, 1978) modified by Leserman and colleagues at the University of North Carolina for use with chronically ill populations. This 30-item life stress measure measures the number of stressful events during the past 6 months as well as the impact of those life events.

Depression and anxiety were measured with the Structured Interview Guide for the Hamilton Anxiety and Depression Scale- Modified (SIGH-AD; Williams, 1988): The SIGH-AD is a semi-structured interview guide based on the Hamilton Anxiety Scale (Hamilton, 1959) and the Hamilton Depression Scale (Hamilton, 1960). The SIGH-AD has been used previously among chronically ill populations (e.g., Cruess et al., 2002).

Sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is a 19-item interview quantitatively and qualitatively assessing sleep quality in the past month. The questions comprise the following component scores:

sleep duration, sleep latency, and frequency/severity of sleep problems. Seven component scores are yielded: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. The PSQI also produces a global sleep quality score which ranges from 0-21, with higher scores indicating lower sleep quality. The PSQI has good reliability (Cronbach's alpha = .83) (Buysse et al., 1989) and is correlated with reports of sleep problems and fatigue (r = .65-.43), tension/anxiety (r = .50), depression (r = .50), and vitality (r = -.53) in breast cancer patients (Carpenter & Andrykowski, 1998).

Physiological Assessment

Salivary Cortisol

Salivary cortisol is a reliable reflection of free cortisol levels in the blood (Kirschbaum & Hellhammer, 1994). Participants were asked to collect saliva samples at 8:00 AM, 12:00 PM, 5:00 PM, and 9:00 PM each day for three consecutive days prior to their pre-operative visit. Participants collected samples at home with Salivette (Sarstedt, Inc., Newton, NC) devices, which consist of a cotton role encased in a plastic centrifuge tube. In an effort to facilitate the collection of samples, participants were provided with watchlike devices (Watchminder, Inc., Irvine, CA) that were programmed to vibrate at each collection time. Participants were instructed to use the Salivette device to collect a saliva sample each time the watchlike devicevibrated. Because non-compliance with the sampling schedule can affect the validity of the cortisol levels (Kudielka, Broderick, & Kirschbaum, 2003), watchlike devices were programmed to display a "code word" each time the device vibrated that disappeared after approximately 5 minutes. Participants were asked to write the "code word" for each sample on the label of the corresponding Salivette. No samples were excluded from analyses due to an incorrect "code word".

Samples for which the "code word" was missing as a result of device malfunction were not excluded from analyses. Samples were refrigerated or kept in an insulated cooler until participants returned them at their pre-operative clinic visit and were transported to the College of Nursing Biobehavioral Research Laboratory.

Saliva samples were centrifuged for 15 minutes at 3000 RPM and aliquots were frozen at -70ºC until assayed. Cortisol levels were assessed using a commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kit (Salimetrics, Inc., State College, PA). ELISA is laboratory technique frequently used in studies involving immune factors such as antigens and antibodies, as well as hormones. It consists of a surface with an antibody attached to it. The antibody will connect itself to the substance being measured (e.g., the hormone of interest). A mixture of a purified version of the substance being measured mixed with an enzyme and the test sample are added to the test system. If there is none of the substance of interest present in the test sample, then only the substance of interest connected with enzyme will bind to the surface. This results in a change in the color of the solution, which can be measured with a plate reader to determine how much of the substance of interest is present in the test sample.

ELISA measures the concentration of cortisol using a microtiter plate which is coated with rabbit antibodies to cortisol. Standard and unknown cortisol competes with cortisol linked to horseradish peroxidase for the antibody binding sites. Following a period of incubation, the unbound components were washed away and the bound cortisol was measured by the reaction with the substrate. This reaction produced a blue color which was read on a standard plate reader. ELISA is based upon the principle that the

intensity of the color is proportional to the concentration of cortisol. A darker color indicates lower concentrations of cortisol

Biobehavioral Controls

Cortisol can be affected by medical and demographic variables other than stress. For this reason, information about participants' age, disease stage, medication use, and comorbid illnesses was abstracted from medical records. These variables have been traditionally examined as potential confounds in analyses with physiologic outcomes. Disease stage has been linked to more dysregulated diurnal cortisol patterns (Touitou et al., 1995) and higher mean cortisol levels (Abercrombie et al., 2004). A number of studies have found relationships between cortisol and the use of certain medications such as thyroid medication (Adam & Gunnar, 2001) and medication for cancer treatment (Sephton et al., 2000).

Sociodemographic characteristics were measured with the MacArthur Sociodemographic Questionnaire (MSQ; Adler, Epel, Castellazzo, & Ickovics, 2000). The MSQ is a questionnaire developed by the MacArthur Foundation that assesses subjective and objective social status. To assess subjective social status, participants indicate their perceived standing in the community and the country by marking their standing on a picture of a ladder with ten rungs. A variety of traditional socioeconomic status questions such as education level, employment status, and income assess objective social status.

<div align="center">

Statistical Procedures

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Statistical Analyses

The distributions of all variables were examined to confirm that parametric tests could be employed. Relations among biobehavioral control variables and salivary cortisol

slope were then tested using correlations. Biobehavioral control variables significantly

related to salivary cortisol slope at $p \leq .10$ were controlled for in subsequent analyses.

Calculation of Salivary Cortisol Slope

Previous research has found that diurnal slope is related to health outcome (i.e.,

severity of disease, mortality) whereas mean cortisol levels or "area under the curve" may

not be (Abercrombie et al., 2004; Sephton et al., 2000). Thus, we elected to look at

cortisol diurnal slope as opposed to mean level or area under the curve. Diurnal cortisol

slope was calculated using the methods of Abercrombie et al. (2004) and Sephton et al.

(2000). Cortisol concentrations were log transformed. A series of multiple regressions

with the time of sample collection as the outcome variable and the cortisol value for each

day (4 timepoints X 3 days) as the predictor variables was performed individually for

each participant to quantify each person's diurnal cortisol slope (ß). Smaller ß values

indicate steeper (normal) slopes and larger ß values indicate flattened slopes, abnormal

peaks, and abnormal troughs (abnormal).

Analyses for Specific Aims

To assess whether perceived stress and sleep quality were related to diurnal cortisol

slope, multiple linear regression was performed with perceived stress and global sleep

quality as the predictor variables and mean diurnal cortisol slope as the outcome variable.

To assess whether global sleep quality mediated the relationship between perceived stress

and mean diurnal cortisol, the methods of Baron and Kenny (1986) were used. In order

for data to mediation to be supported, three conditions must be met. First, the

hypothesized predictor variable, perceived stress, must be related to the outcome variable,

mean diurnal cortisol slope. Next, perceived stress must be related to the mediating

variable, global sleep quality. Finally, the relationship between perceived stress and mean

diurnal cortisol slope must be weakened (partial mediation) or eliminated (full mediation) when the mediating variable, global sleep quality, is controlled. Throughout this process, the mediator, global sleep quality, must remain significant. A hierarchical linear regression was performed to test for mediation, with mean diurnal cortisol slope as the dependent variable, perceived stress as the block 1 predictor, and global sleep quality as the block 2 predictor.

Power and Sample-Size Considerations

The small sample size of the current study warranted an examination of effect sizes in the literature and a determination of the power necessary to carry out the statistical analyses. A small number of studies have examined psychoneuroimmunologic aspects of women with gynecologic malignancies or those at-risk for developing gynecologic malignancies (e.g. Byrnes et al., 1998; Lutgendorf et al., 2002; Pereira et al, 2003a; Pereira et al., 2003b). Among women with or at-risk for gynecologic cancer, the effect sizes for the relationship between psychosocial variables and immune variables fall in the "medium" to "large" range. Most studies examining psychoneuroimmunologic aspects of cancer have focused on the breast cancer population. A review of this literature reveals effect sizes between psychosocial and immune variables in the "small" to "medium" range, according to Cohen's effect size conventions (Tjemsland et al.,1997; Turner-Cobb et al., 2004; Turner-Cobb et al., 2002). One study examining cortisol in breast cancer patients reported "large" effect sizes for the relationship between psychosocial variables and cortisol (Giese-Davis, Sephton, Abercrombie, Duran & Spiegel, 2004). Table 2-2 lists calculated effect sizes for the relationship between psychosocial and immune variables in the cancer literature.

NCSS PASS software was used to perform a power analysis for the current study.

Power analysis revealed that a sample size of 15 provides 50% power to detect an R^2 of

0.30 attributed to two independent variables using an F-test with a significance level

(alpha) of 0.05. Figure 2-2 illustrates the results of the power analysis.

Table 2-2. Psychoneuroimmunology effect sizes

Study	Population	f^2	r	d
Lutgendorf et al., 2002	Ovarian cancer		.59	
Pereira et al., 2003a	Pre-cervical cancer	.37		
Pereira et al., 2003b	HIV + , HPV + women	.14-.32		
Byrnes et al., 1998	Pre-cervical cancer		.29-.39	
Turner-Cobb et al., 2004	Metastatic breast cancer		.21	
Turner-Cobb et al., 2002	Metastatic breast cancer		.17-.19	
Tjemsland et al., 1997	Operable breast cancer		.24-.39	
Giese-Davis et al., 2004	Metastatic breast cancer			.70-.90
Corcos et al., 2004	Healthy young women		.55	
Lutgendorf et al., 1999	Healthy older women		.24-.35	
Suarez et al., 2003	Healthy men		.27-.57	
Segerstrom & Miller, 2004	Meta-Analysis		.21-.41	
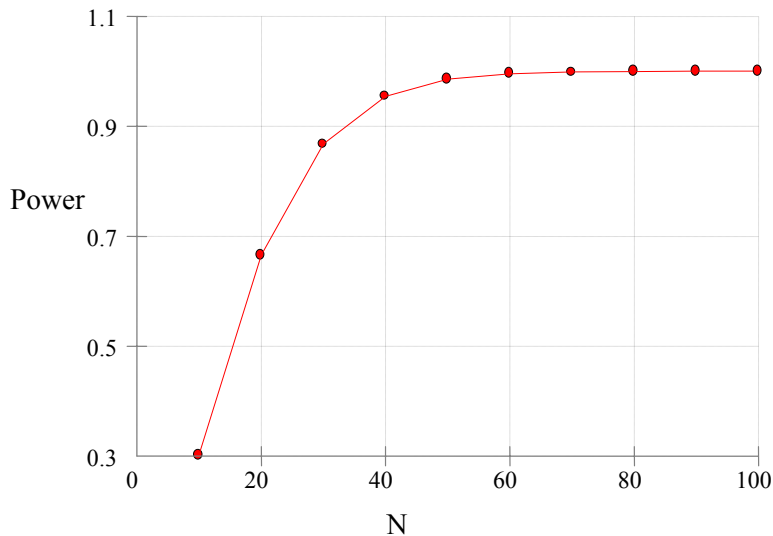
Figure 2-2. Power analysis by sample size

CHAPTER 3
RESULTS

Control Variables and Preliminary Analyses

Raw cortisol values were log transformed prior to calculating diurnal slope as per

the methods of Sephton et al. (2000). The diurnal cortisol slopes for all three days were

averaged to create a mean diurnal cortisol slope. Pearson bivariate correlations were

performed to assess relations among continuous biobehavioral control variables and the

main variables of interest. Independent samples t-tests were conducted to determine

whether any relations existed among categorical biobehavioral control variables and the

main variables of interest (Tables 3-1 and 3-2). According to the published PSQI scoring

system, greater values on global sleep quality and all sleep components are indicative of

greater sleep dysfunction. However, for the purposes of the analyses below, PSQI global

sleep quality values were reverse scored such that greater values indicated better sleep

quality.

Relations Among Control Variables and Stress

The use of corticosteroid medication had been designated a priori as an important

biobehavioral control variable; however, the use of corticosteroid medication was only

documented in one participant, thus precluding the ability to examine corticosteroid use

as a control variable in this study.

Furthermore, there was a significant relationship between family income and

impact of negative life events ($r = .79$, $p = .007$), such that greater family income was

associated with greater impact of negative life events. A marginally significant

relationship emerged between family income and number of negative life events ($r = .52$, $p = .086$).

A significant relationship emerged between greater depressive symptomatology and greater number of negative life events ($r = .69$, $p = .013$) as well as greater impact of negative life events ($r = .86$, $p = .013$). A significant relationship also emerged between greater anxiety and greater number of negative life events ($r = .69$, $p = .013$), as well as greater impact of negative life events ($r = .90$, $p = .000$).

Relations Among Control Variables and Sleep Quality

A marginally significant negative relationship also emerged between global sleep quality and depressive symptomatology ($r = -.56$, $p = .073$), and a significant negative correlation emerged between global sleep quality and anxious symptomatology ($r = -.61$, $p = .045$).

Relations Among Control Variables and Cortisol

Analyses revealed no significant relationships between our biobehavioral control variables and mean cortisol slope or mean morning cortisol levels.

Descriptive Results

Participants reported a mean perceived stress level of 20.30 ($SD = 7.41$). An independent samples t-test revealed that the mean in the current study was not significantly different than the mean perceived stress ($M = 21.5$, $SD = 2.8$) reported by a sample of 17 metastatic breast cancer patients in a study by Abercrombie et al. (2004) ($t = .60$, $p = .55$).

Participants reported a mean global sleep quality score of 5.73 ($SD = 3.23$). This is below the clinical cutoff of 8 specified by Carpenter and Andrykowski (1998) for use in clinical populations. However, three participants had global sleep quality scores in the

clinically significant (≥ 8) range. Mean scores on the seven components of global sleep quality are reported in Table 3-3. An independent samples t-test was conducted to test whether the global sleep quality and sleep component scores in the current study differed significantly from those reported in a sample of breast cancer patients (Carpenter & Andrykowski, 1998). The independent samples t-test revealed no significant difference between global sleep quality in the current study and the Carpenter & Andrykowski (1998) study ($t = .93$, $p = .35$). Independent samples t-tests on the sleep component scores revealed a marginally significant difference between subjective sleep quality in the current study and the Carpenter & Andrykowski (1998) study ($t = 1.82$, $p = .07$), with women in the current study reporting better subjective sleep quality compared to women with breast cancer. Participants reported taking a mean of 19.64 minutes to fall asleep in the past month ($SD = 17.87$). They reported receiving a mean of 6.82 hours of sleep per night in the past month ($SD = 1.56$). 23.7% of participants reported that they had taken sleep medication at least once during the past month.

Dysregulation of Diurnal Cortisol Slopes

The first aim of the current study was to assess for dysregulation of diurnal cortisol slopes among women with endometrial cancer. The mean log-transformed morning cortisol values and diurnal slopes are shown in Table 3-4. Figure 3-1 displays the mean diurnal cortisol slope across days and participants.

To assess for patterns of dysregulation in diurnal cortisol slopes, individual diurnal slopes were plotted for each participant (Figure 3-2). Slopes were considered dysregulated if the slope increased or failed to decrease at any time point after 8:00 A.M. Using this criteria for dysregulation, 66.7% of participants had an abnormal slope as defined by an abnormal peak or a flattening of the slope after 8:00 A.M. Due to the lack

of cortisol data available for the two participants who had benign gynecologic disease, analyses comparing diurnal slopes for women with endometrial cancer and those with benign gynecologic disease were not conducted. However, future research in this area is warranted.

Table 3-1. Continuous control variables: Correlations with cortisol, stress, and sleep quality

Continuous control variables	Cortisol slope (mean)	Cortisol in AM (mean)	Perceived stress	Global sleep quality	Depressive sx	Anxious sx	Number stressful events	Impact negative events
Age	-.16 (.68)	-.17 (.66)	.07 (.84)	-.22 (.52)	-.54 * (.06)	-.52*(.07)	-.15 (.65)	-.38 (.28)
	N = 9	N = 9	N = 10	N = 11	N = 13	N = 13	N = 12	N = 10
BMI	-.13 (.74)	-.14 (.72)	.02 (.95)	.27 (.43)	.45 (.12)	.20 (.52)	.36 (.25)	.23 (.53)
	N = 9	N = 9	N = 10	N = 11	N = 13	N = 13	N = 12	N = 10
Highest year in school	.14 (.73)	.27 (.49)	.00 (.99)	-.21 (.54)	.05 (.86)	.29 (.34)	-.26 (.42)	-.16 (.66)
	N = 9	N = 9	N = 10	N = 11	N = 13	N = 13	N = 12	N = 10
Family income	.21 (.58)	-.06 (.88)	.37(.30)	.44 (.17)	.61 ** (.03)	.80**(.00)	.52 *(.09)	.89**(.00)
	N = 9	N = 9	N = 10	N = 11	N = 13	N = 13	N = 12	N = 10
Depression	-.16 (.67)	-.08 (.84)	.49 (.15)	.56 *(.07)	--	--	.69** (.01)	.86**(.00)
	N = 9	N = 9	N = 10	N = 11			N = 12	N = 10
Anxiety	-.05 (.90)	.04 (.92)	.45 (.20)	.61**(.05)	--	--	.69**(.01)	.90**(.00)
	N = 9	N = 9	N = 10	N = 11			N = 12	N = 10

Note: Table values represent Pearson bivariate correlation scores; values in parentheses represent *p*-values. $* = p < .10$, $** = p < .05$.

Relations Among Perceived Stress, Global Sleep Quality, and Diurnal Cortisol Slope

The second aim of the current study was to assess for relations among perceived stress, global sleep quality, and diurnal cortisol slope among women with endometrial cancer. Pearson bivariate correlations were performed to assess for relations among perceived stress, global sleep quality, and diurnal cortisol slope. Once again, to assist with ease in interpreting PSQI sleep quality results, PSQI global sleep quality values were reverse scored such that greater values indicated better sleep quality.

Contrary to hypothesis, mean diurnal cortisol slope was not significantly associated with either perceived stress ($r = -.38$, $p = .36$) or global sleep quality ($r = -.29$, $p = .49$). Moreover, there was not a significant relationship between perceived stress and global sleep quality ($r = .49$, $p = .16$). There were no significant relationships between mean

morning cortisol levels and perceived stress ($r = .15$, $p = .72$) or global sleep quality

($r = .39$, $p = .34$) (Table 3-5).

Table 3-2. Categorical control variables: Relations with mean cortisol slope, perceived stress, and sleep quality

Categorical control variables	Cortisol slope (mean)	Cortisol in AM (mean)	Perceived stress	Global sleep quality	Depressive sx	Anxious sx	Number stressful events	Impact negative events
Tumor stage	-.65(.54) $N = 9$	-.22(.83) $N = 9$	-.75 (.48) $N = 10$	-.99(.35) $N = 11$	-.06 (.97) $N = 13$	-.23(.82) $N = 13$	-.65 (.53) $N = 12$	-.86 (.42) $N = 10$
Medication: thyroid	-.98(.36) $N = 9$	-.34(.74) $N = 9$	1.21 (.26) $N = 10$	.82 (.43) $N = 11$	-.23 (.82) $N = 13$	-.98(.35) $N = 13$	.83 (.42) $N = 12$	.43 (.68) $N = 10$
Medication: beta blockers	.21 (.84) $N = 9$	-.43(.68) $N = 9$	-.77 (.46) $N = 10$	-.79(.45) $N = 11$	-1.38(.19) $N = 13$	.19 (.15) $N = 13$	-1.10 (.30) $N = 12$	-.76 (.47) $N = 10$

Note: Table values represent Independent t-test scores; values in parentheses represent p-values.. * = $p < .10$, ** = $p < .05$.

Table 3-3. Mean PSQI global and sleep component scores

Sleep quality component	Endometrial cancer (current study)		Breast cancer (Carpenter & Andrykowski, 1998)	
	Mean	SD	Mean	SD
Global sleep quality	5.73	3.23	7.00	4.40
Subjective sleep quality	0.55	0.52	1.00	0.80
Sleep latency	1.18	0.60	1.20	1.00
Sleep duration	0.64	1.21	1.10	0.90
Sleep efficiency	0.55	1.04	0.80	1.10
Sleep disturbance	1.36	0.50	1.40	0.60
Use of sleep medication	0.73	1.27	0.60	1.10
Daytime dysfunction	0.73	0.65	0.90	0.80

Note: The above scores on Global Sleep Quality and the sleep components range from 0 to 3 with higher scores indicative of greater sleep dysfunction.

Table 3-4. Mean morning and diurnal slope cortisol values

	Morning day 1	Morning day 2	Morning day 3	Morning mean	Slope day 1 (ß)	Slope day 2 (ß)	Slope day 3 (ß)	Mean slope (ß)
Mean	-1.43	-1.11	-2.17	-1.55	-.56	-.54	0.00	-0.46
SD	1.35	1.12	1.53	0.97	0.52	0.46	0.62	0.44

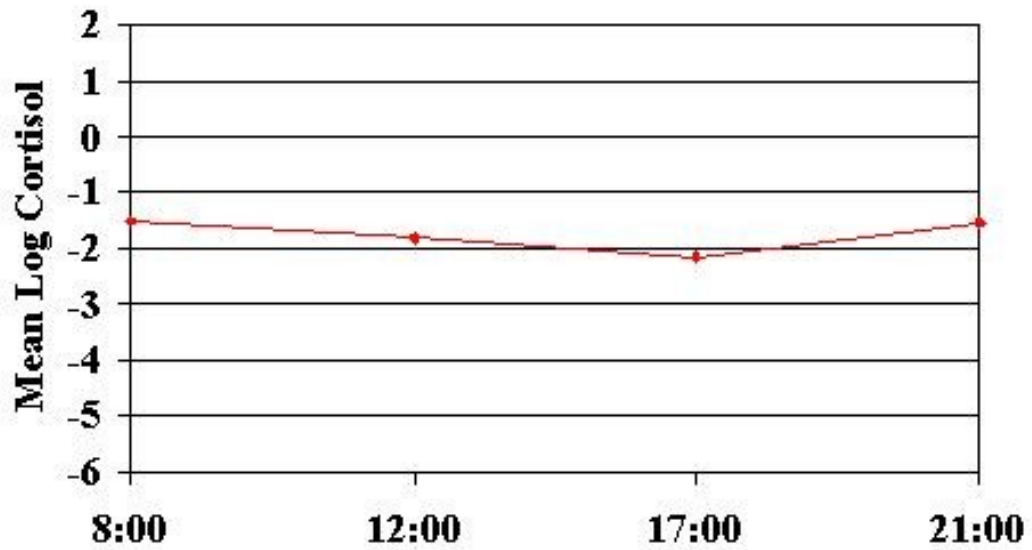Note: Morning values are the log-transformed concentrations at 8:00

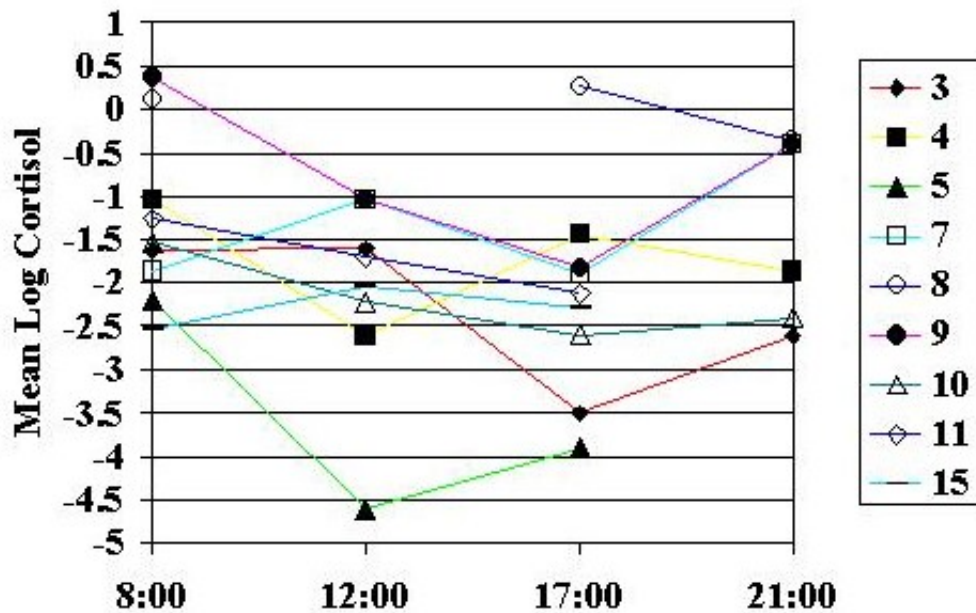Figure 3-1. Mean cortisol slope across days

Figure 3-2. Individual mean cortisol slopes

In an effort to further explore the relations among perceived stress, sleep quality, and diurnal cortisol, additional Pearson bivariate correlations were conducted between perceived stress, components of sleep quality, diurnal cortisol, and mean morning cortisol

levels (Table 3-5). Once again, to assist with ease in interpretation of results, subjective sleep quality, sleep duration, and sleep efficiency were recoded such that lower values indicated greater sleep dysfunction.

The analyses revealed that sleep latency was significantly related to perceived stress ($r = .65$, $p = .042$), indicating that longer sleep latency is associated with higher levels of perceived stress. The analyses also revealed a significant relationship between the use of sleep medications and mean diurnal cortisol slope ($r = .79$, $p = .019$), with more frequent use of sleep medications associated with more abnormal diurnal cortisol slopes. Analyses also revealed a trend toward a significant negative association between subjective sleep quality and mean morning cortisol ($r = .-67$, $p = .068$) such that poorer subjective sleep quality was associated with higher mean morning cortisol values. Mean morning cortisol level was not significantly associated with perceived stress, sleep latency, or the use of sleep medications,.

Due to the lack of an expected significant relationship between perceived stress and cortisol, Pearson bivariate correlations were performed to examine the relations among sleep quality, cortisol and alternative measures of stress used in this research. (Table 3-6). The sum of the number of stressful life events experienced in the 6 months prior to study entry was significantly related to poorer global sleep quality ($r = -.94$, $p = .000$). Greater number of stressful life events was also associated with the following PSQI components: poorer subjective sleep quality ($r = -.62$, $p = .043$), longer sleep latency ($r = .81$, $p = .002$), shorter sleep duration ($r = -.88$, $p = .000$), and poorer sleep efficiency ($r = -.82$, $p = .002$). The sum of the impact ratings of all negatively appraised stressful life events experienced in the 6 months prior to study entry ("greater impact of negative life events") was also

significantly related to poorer global sleep quality ($r = -.92$, $p = .000$). Greater impact of negative life events was also associated with longer sleep latency ($r = .89$, $p = .001$), shorter sleep duration ($r =-.89$, $p = .001$), and poorer habitual sleep efficiency ($r =-.75$, $p = .020$). Neither greater number of stressful life events nor greater impact of negative life events was significantly associated with mean diurnal cortisol slope or mean morning cortisol levels.

Table 3-5. Correlations among perceived stress, sleep quality components, and cortisol

	Perceived stress	Global sleep quality	Sleep latency	Sleep medication	Subjective sleep quality	Mean cortisol slope	Mean AM cortisol
Perceived stress	—	49 (.16) N = 10	.65**(.04) N = 10	.17 (.65) N = 10	.35 (.32) N = 10	-.38 (.36) N = 8	.15(.72) N = 8
Global sleep quality	.49 (.16) N = 10	—	.70*(.02) N = 11	.49 (.13) N = 11	.63* (.04) N = 11	-.29 (.49) N = 8	.39 (.34) N = 8
Sleep latency	.65 **(.04) N = 10	.70*(.02) N = 11	—	-.06 (.86) N = 11	.61**(.05) N = 11	-.40(.33) N = 8	.12 (.77) N = 8
Sleep medication	.17 (.65) N = 10	.49 (.13) N = 11	-.06 (.86) N = 11	—	-.21 (.55) N = 11	.79**(.02) N = 8	-.04(.92) N = 8
Subjective sleep quality	.35 (.32) N = 10	.63*(.04) N = 11	.61**(.05) N = 11	-.21 (.55) N = 11	—	-.48(.23) N = 8	.67*(.07) N = 8
Mean cortisol slope	-.38 (.36) N = 8	-.29(.49) N = 8	-.40 (.33) N = 8	.79**(.02) N = 8	-.48(.23) N = 8	—	-.49(.18) N = 9
Mean AM cortisol	.15 (.72) N = 8	.39 (.34) N = 8	.12 (.77) N = 8	-.04 (.92) N = 8	.67*(.07) N = 8	-.49 (.18) N = 9	—

Note: $* = p \le .10$, $** = p \le .05$

Mediation

The third aim of the current study was to assess whether global sleep quality mediated the relationship between perceived stress and diurnal cortisol slope among women with endometrial cancer. Although life stress was associated with poorer global sleep quality, and sleep quality components were associated with greater diurnal cortisol dysregulation, life stress was not associated with greater diurnal cortisol dysregulation. Therefore, mediation could not be tested.

Table 3-6. Correlations among outcome variables and alternative measures of stress

	Number of negative life events	Impact of negative life events
Global sleep quality	.94 (.00)***	.92 (.00)***
	$N = 11$	$N = 9$
Subjective sleep quality	.62 (.04)**	.44 (.23)
	$N = 11$	$N = 9$
Sleep latency	.81 (.00)***	.89 (.00)***
	$N = 11$	$N = 9$
Sleep duration	.89 (.00)***	.89 (.00)***
	$N = 11$	$N = 9$
Sleep efficiency	.82 (.00)***	.75 (.02)**
	$N = 11$	$N = 9$
Sleep disturbance	.36 (.28)	.21 (.59)
	$N = 11$	$N = 9$
Use of sleep medication	-.13 (.71)	-.04 (.93)
	$N = 11$	$N = 9$
Daytime dysfunction	.45 (.17)	.40 (.28)
	$N = 11$	$N = 9$
Mean AM cortisol	.22 (.60)	-.02 (.97)
	$N = 8$	$N = 6$
Diurnal cortisol slope	-.34 (.41)	.00 (1.0)
	$N = 8$	$N = 6$

Note: $* = p \leq .10$, $** = p \leq .05$, $*** = p \leq .001$.

CHAPTER 4
DISCUSSION

Discussion of Results

The current study is the first to-date to investigate the relations among perceived stress, sleep quality, and diurnal cortisol slope among women with early stage endometrial cancer. The primary hypothesis of this study was that perceived stress and sleep quality would be related to greater diurnal cortisol slope dysregulation. Although the findings did not provide support for this hypothesis, the current study yielded a number of important preliminary findings. Among participants in the current study, impairments in global sleep quality were largely not clinically significant. These sleep quality findings are consistent with previous studies which have examined sleep quality in breast cancer patients (Carpenter & Andrykowski, 1998). However, it should be noted that impairments in sleep quality did emerge on the more objective measures of sleep quality, such as the use of sleep medications and sleep latency, the latter of which is assessed by the number of minutes it takes to fall asleep at night. Thus, although the results point to generally good sleep quality in the current sample, less subjective indicators suggest that participants in the current study did report experiencing some impairments in sleep quality, which may have been underrepresented by global sleep quality scores. This may reflect a response bias among this older population, which we have observed across various measures in the larger study in which participants had a tendency to underreport or minimize negative psychosocial experiences.

In addition to assessing sleep quality among women with endometrial cancer patients, the current study also examined a number of predictors of both global sleep quality and components of sleep quality. Among the biobehavioral control variables, greater depressive symptomatology and greater anxiety were associated with poorer sleep quality. A growing body of literature in psychosomatic medicine links poor sleep quality as measured both subjectively through self report as well as through polysomnography to depression (e.g., Buysse et al., 1998; Hall et al., 1997; Hall et al., 2000). The relationship between sleep quality and depression in the current study is not surprising, given that sleep disturbance is a key component in the evaluation of depressive symptomatology. Support for the associations between poor sleep quality and anxiety found in the current study is also well documented in the literature (e.g., Belanger, Morin, Langlois, & Ladouceur, 2004; Hall et al., 1997).

The current study also investigated the hypothesized relations among perceived stress and sleep quality. In terms of perceived stress during the past month, greater levels of perceived stress were associated with longer sleep latency. In contrast, when life event stress in the past six months was examined, a number of significant findings emerged. A greater number of negative life events in the past six months was significantly related not only to poorer global sleep quality, but also to sleep quality components such as poorer subjective sleep quality, longer sleep latency, shorter sleep duration, and poorer sleep efficiency. The reported impact of these negative life events in the past six months was also significantly associated with poorer global sleep quality, longer sleep latency, shorter sleep duration, and poorer sleep efficiency among women in the current study. These

findings suggest that greater life event stress, but not perceived stress, is associated with a variety of sleep quality components. Possible reasons for this are discussed below.

The pattern of findings related to stress and sleep quality prompts questions regarding why perceived stress was not associated with more aspects of sleep quality. Although the reason why perceived stress was not associated with components of sleep quality is unclear, it is possible that the PSS did not fully capture the life stress "distress" that participants were experiencing. Although the PSS has been used extensively in PNI studies (e.g., Burns, Carroll, Drayson, Whitnam & Ring, 2003; Ebrecht, Hextall, Kirtley, Taylor, Dyson et al., 2004; Motivala et al., 2003), the use of this instrument may have limited the findings, given that the PSS measures a rather narrow conceptualization of stress, namely self-reported appraisals of unspecified stressful situations during the past month. In contrast, the LES (Sarason, Johnson, Siegel, 1978) yielded a number of significant relationships with global sleep quality and its components. Compared to the PSS, the LES is a more comprehensive measure of stress, in that it assesses participants' emotional reactions to specific, relevant life stressors that may have been experienced. This may suggest that in this population it is vital to assess reactions to acute and chronic specific life stressors rather than simply appraisals of acute, global stress, Thus, future research should include measures of life event stress in addition to measures of perceived stress. Moreover, future research may also benefit from a more global examination of distress encompassing life event stress, depression, and anxiety.

Another important aim of the current study was to assess for diurnal cortisol slope dysregulation among women with endometrial cancer. The findings supported the hypothesis that women with endometrial cancer have dysregulated diurnal cortisol slopes,

with approximately two-thirds of the participants in the current study displaying abnormal diurnal cortisol slopes, as defined by an increased or flattened slope after 8:00 A.M. These findings are consistent with studies of other endocrine-mediated cancers such as breast cancer and ovarian cancer (Abercrombie et al., 2004; Sephton et al., 2000; Touitou et al, 1996), and are particularly concerning in light of Sephton et al.'s (2000) findings that abnormal diurnal cortisol slope predicted earlier mortality in metastatic breast cancer patients. Future research should assess whether abnormal diurnal cortisol slope predicts morbidity and/or earlier mortality among endometrial cancer patients.

In addition to assessing for diurnal cortisol dysregulation, the current study further examined possible predictors of abnormal diurnal cortisol slopes. The results did not reveal any significant relationships between diurnal cortisol and biobehavioral control variables. Although this lack of findings was unexpected, it is possible that the small sample size and the resulting lack of variance in the control variables accounted for the lack of significant relationships. Furthermore, although numerous studies have reported associations between diurnal cortisol dysregulation and severity of disease (Abercrombie et al., 2004; Sephton et al., 2000; Touitou et al, 1996), these studies included women with metastatic disease, whereas the current study only included women with early stage cancer. Thus, future research with a larger, more heterogeneous sample should be conducted to assess relations between cortisol and biobehavioral control variables.

Also contrary to hypothesis, the findings of the current study revealed no associations between perceived stress and measures of diurnal cortisol. Although this may be related to the use of the PSS as a measure of perceived stress, the findings also revealed no relationship between life event stress and measures of diurnal cortisol. Due to

the robust relationships among life event stress and components of sleep quality, the lack of a relationship between life event stress and diurnal cortisol is puzzling. Several factors may account for this. First, it is possible that six-month timeframe used in this version of the LES may not have been sensitive enough to recent stressors, given that recent stressors may impact diurnal cortisol more greatly at the time cortisol was measured in this study. Second, it may be that certain types of life events are more strongly related to cortisol than other types of life events. Future research is needed to address which types of stressful life events are associated with diurnal cortisol, particularly in important context of the peri-operative period. Third, a relationship between stress and cortisol may have been confounded by other measured or unmeasured biobehavioral variables. For example, it is possible that mood or social support may moderate a relationship between life stress and cortisol.

Contrary to the absence of associations between stress and sleep quality, the findings of the current study did reveal significant associations between several sleep quality components and measures of diurnal cortisol. Notably, the use of sleep medications was associated with greater diurnal cortisol slope dysregulation among women with endometrial cancer. There are several plausible explanations for this relationship. First, on the PSQI, the use of sleep medications is one of the more objective measures of impaired sleep quality. Once again, this may suggest that research among older, female cancer patients should utilize objective measures of sleep quality. Second, although not testable in the current study, it may be that the use of sleep medication alters diurnal cortisol slopes. Future research with a larger sample size should more closely examine the effect of sleep medication use on diurnal cortisol slopes.

The findings of the current study also revealed a trend toward a relationship between poorer subjective sleep quality and higher mean morning cortisol values. A number of recent studies have highlighted the importance of the cortisol awakening response as a marker of circadian disruption (Kudielka & Kirschbaum, 2003; Williams, Magid, & Steptoe, 2005). Specifically, higher cortisol awakening response has been linked to higher stress, depression, sleep disturbance, and earlier time of waking (Williams et al. 2004). Although the current study did not assess for time of waking on cortisol collection days, the cortisol concentration at 8:00 A.M. could be used as a proxy for the cortisol awakening response. It is possible that the trend toward a relationship between poorer subjective sleep quality and higher mean morning cortisol may support previous findings related to these constructs. Future research should further explore the psychosocial and biobehavioral predictors of cortisol awakening response as well as its association with disease outcome variables.

Implications of Findings

Although the current feasibility study is among the first to report relations among stress, sleep quality, and cortisol in women with early stage endometrial cancer, the findings of the current study must be interpreted with caution due to the small sample size of the current study. However, the results of the current study provide a foundation and rationale from which future larger scale studies can examine relations among these variables

There are a number of potential pathways which future research could explore to extend the findings of the current study. First, future studies on diurnal cortisol dysregulation among women with endometrial cancer should extend the findings of the current study by investigating the various patterns of dysregulation (i.e., flattened slope,

abnormal peak, abnormal trough) and their potential relations with both psychosocial

predictors and disease outcome variables. Thus far, studies examining dysregulated

cortisol among individuals with cancer have only differentiated between dysregulated

diurnal cortisol pattern and the "normal" diurnal cortisol pattern typically found among

healthy individuals. It is plausible that specific types of dysregulation may have more

deleterious effects on immune functioning and health than others. Similarly, the different

dysregulation patterns may be differentially associated with psychosocial factors. Thus,

future research should further explore the relations among psychosocial factors, patterns

of dysregulated diurnal cortisol, and immune and health outcomes.

Second, future research should examine diurnal cortisol during the post-surgical

recovery period and its relation with post-surgical outcomes such as post-operative

complications and wound healing. Wound breakdown, cellulitis, and lymphedema are

common post-operative complications among women with gynecologic cancer and have

been linked to infection and inflammatory immune response (Gould et al., 2001; van

Lindert, Symons, Damen, & Heintz, 1995). However, few studies have sought to identify

non-surgical predictors of post-operative complications among women with gynecologic

cancer. Numerous studies examining healthy populations have found that stress (e.g.,

academic examinations, caregiving for dementia patients) is associated with delayed

wound healing (Kiecolt-Glaser, Marucha, Malarkey, Mercado, Glaser, 1995; Marucha,

Kiecolt-Glaser, Favagehi, 1998; Padgett, Marucha, Sheridan, 1998). It is possible that the

effect of stress on wound healing occurs via the psychosocial "activation" of stress

hormones, such as cortisol, which can result in immune dysregulation and

immunosuppression during the wound healing process. Therefore, the effects of stress

and cortisol dysregulation during the post-operative period represents an important future direction for research and may have important implications for interventions targeted at reducing post-operative complications.

Study Limitations

Despite these implications, the results of this study should be considered in light of several limitations. First, although data suggesting pre-surgical relations among perceived stress, sleep quality, and diurnal cortisol among women with endometrial cancer is important to the understanding of the psychoneuroimmunologic relations in this disease, the cross-sectional design of this study precludes causal inferences about these relations. Future prospective studies are needed to elucidate the sequential relations among perceived stress, sleep quality, and diurnal cortisol slope and the causal mechanisms involved in these relations.

The study is also limited by various characteristics of the sample. The sample was largely composed of White women, with only one participant identifying her racial/ethnic background as Non-White. Although endometrial cancer is thought to be twice as common among White women compared to Black women, White women were over-represented in the current study's sample. Furthermore, the study sample's sociodemographic composition limits the generalizability of the results to older, middle SES women from the southern United States. Moreover, the sample may have been biased with regards to the amount of stress experienced by participants. Several women declined to participate in the study citing reasons such as, "too much to handle," "a wreck all the time," and "too much going on right now." Thus, it is possible that the patients experiencing the most stress were not included in the study, further limiting the generalizability of the findings.

The measurement of the constructs of interest presents another potential limitation for the current study. Specifically, the findings may have been limited by the measures chosen to assess the psychosocial predictors.

The measurement of sleep quality may have also been problematic in the current study. First, self-reported sleep quality depends upon participants' accurate reporting of their sleep experience and is therefore subject to over- or under-estimations. Future studies would benefit from the inclusion of objective measures of sleep, including polysomnographic methods or the use of actigraphy. Furthermore, although it is a commonly used measure of sleep quality, particularly in the health psychology literature, some have suggested that the complex scoring of the PSQI may jeopardize its validity (Beck, Schwartz, Towsley, Dudley, & Barsevick, 2004). Beck et al. (2004) propose that the re-coding and combining of responses required by the PSQI scoring paradigm results in decreased variance in the PSQI composite scores. Thus, it is recommended that future studies include additional self-report measures of sleep, such as sleep logs.

Compliance with saliva collection and storage poses another potential limitation to the accurate measurement of diurnal cortisol. Participants were asked to collect four samples each day, for three consecutive days. This sample collection schedule, which required that participants carry their saliva collection kit with them at all times, may have been burdensome to participants, particularly those at an advanced age. Compliance with saliva sampling is essential to the accurate measurement and interpretation of cortisol (Kudielka et al., 2003). In fact, diurnal cortisol slope can demonstrate a 100% change within 30 minutes (Kirschbaum & Hellhammer, 1994). Thus, in an effort to maximize compliance to the saliva sampling schedule, participants were instructed to wear

Watchminder devices which were pre-programmed to buzz at the four collection times. At each collection time, the Watchminder displayed a neutral codeword which participants were asked to write on the Salivette tube. These code words were only displayed briefly. Therefore, although the Watchminders did not serve as a perfect compliance check, they were intended to encourage compliance. However, it must be noted that there is no measure of the actual time each sample was taken. Future research should utilize better methods to record compliance, such as the use of electronic drug exposure monitors (see Kudielka et al., 2003).

Cortisol is a complex physiological variable that has been examined in complex and diverse ways within the behavioral science field. In the current study, cortisol was examined in terms of its diurnal slope, based on findings that dysregulation of diurnal slope is associated with negative outcomes such as advanced disease and mortality (Abercrombie et al., 2004; Sephton et al., 2000; Touitou et al., 1996). The examination of diurnal cortisol slope raises a number of issues that must be considered when interpreting the findings of the current study. First, although research examining neuroendocrine dysregulation and disease is increasingly focused on the significance of circadian disruption and diurnal slope, there is also evidence that mean level of cortisol, which was not examined in the current study, may also have important implications for those with cancer. Studies investigating mean cortisol levels often employ the area under the curve (AUC) method, which is derived from a trapezoid formula (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). In the current study, AUC was not selected as an outcome variable, given Sephton et al.'s (2000) findings that diurnal slope, not AUC, was associated with survival. Although an examination of AUC may have proved an

interesting endeavor, it was not consistent with our hypothesis of circadian rhythm dysregulation and thus, we do not report findings looking at overall mean cortisol level. However, it is also possible that there may be an interaction between AUC and diurnal slope, such that high stress is associated with high AUC X flat diurnal slope. Future research should examine this possibility.

The current study's saliva sample collection protocol also merits consideration when interpreting the findings. The current study used four saliva samples per day (8AM, 12PM, 5PM, 9PM) to plot the diurnal cortisol slope. Although previous studies examining diurnal cortisol slope among people with cancer have typically used four daily samples to plot the diurnal slope (e.g., Abercrombie et al., 2004; Sephton et al., 2000; Turner-Cobb et al., 2000), studies examining diurnal cortisol among healthy populations have used substantially greater numbers of daily samples (Kirschbaum et al., 1994; Kirschbaum, Kudielka, Gaab, Schommer, Hellhammer, 1999). Stone et al. (2001) raise concerns that a small number of unreliable samples could bias the estimation of the diurnal slope (Stone et al., 2001). Thus, it is possible that the four samples collected in the current study may not have been adequate for an accurate plotting of the diurnal slope. Furthermore, although numerous sampling protocols request that participants collect samples at pre-determined times (e.g., Abercrombie et al., 2004; Turner-Cobb et al., 2000;Sephton et al., 2000), others use the time of waking to set the timeline of sample collection for the day (Broderick, Arnold, Kudielka, & Kirschbaum, 2004; Kudielka & Kirschbaum, 2003; Miller et al., 2002). Using each participant's waking time to determine the sample collection times may produce a more accurate approximation of their diurnal cortisol slope, including the peak at waking which is found among healthy

individuals. Thus, although consistent with previously published studies examining diurnal cortisol among people with cancer, the sample collection methodology employed in the current study may not have achieved optimal approximation of participants' diurnal cortisol slope.

Finally, although the current study focused exclusively on diurnal cortisol dysregulation as the outcome variable, it did not explore the specific patterns of dysregulation. It is possible that specific dysregulation patterns (i.e., flattened, abnormal peaks, abnormal troughs) may differ in their association with psychosocial and disease variables. Future studies would benefit from an exploration of the specific dysregulation patterns and their relations with both psychosocial predictors as well as disease outcomes. In addition, Abercrombie et al. (2004) suggest that the effects of generalized circadian dysregulation may be more important than cortisol dysregulation in isolation. Future research is needed to investigate the role of other types of circadian dysregulation and to elucidate the causal mechanisms involved in circadian dysregulation among people with cancer.

The current study is also limited by a small sample size and the resulting lack of power to detect relations between the variables of interest. The small sample size is surprising, given that endometrial cancer is the most common gynecologic cancer and the fourth most common cancer among women (ACS, 2004). There are numerous potential explanations for the small sample size of the current study. First, it appears as though substantially fewer women presented to the UF & Shands Gynecologic Oncology Clinic compared to in past years. An examination of the number of women presenting to this site for treatment of endometrial cancer from the UF & Shands Tumor Registry revealed

that between the months of June and August of 2003, 14 women with newly diagnosed endometrial cancer presented for treatment. In contrast, only 2 women with newly diagnosed endometrial cancer presented for treatment between June and August of 2004. It is unlikely that this decrease in women presenting for treatment for newly diagnosed endometrial cancer represents a steep decline in the rates of endometrial cancer. Rather, we posit that women may be increasingly receiving treatment for endometrial cancer from their primary gynecologist, as opposed to gynecologic oncologists. According to guidelines for treatment established by the International Federation of Gynecology and Obstetrics (FIGO), low risk tumors that are unlikely to include nodal involvement may be safely operated on by general gynecologists (International Federation of Gynecology and Obstetrics [FIGO], 2000). Thus, it may be that general gynecologists are increasingly treating women with early stage endometrial cancer. Future studies may benefit from the inclusion of additional recruitment sites, such as general gynecologic practices.

A second potential explanation for the low number of women with endometrial cancer presenting to the UF & Shands clinic for treatment results from the numerous hurricanes that affected the region during the course of the current study. The hurricanes resulted in the closing of the gynecologic oncology clinic on several occasions and the subsequent cancellation of appointments. Furthermore, as the only clinic specializing in gynecologic oncology in the North Central Florida region, women receiving treatment often travel long distances to receive treatment at the clinic. The hurricanes and their subsequent damage may have prevented patients from farther away from traveling to the site of the current study.

Our sample size was further limited by the inclusion and exclusion criteria. Such stringent criteria are necessary to ensure internal validity in studies examining the relations between psychological and physiologic variables. However, it should be noted that the criteria employed resulted in a smaller pool of women who met eligibility criteria for recruitment. In spite of these sample size limitations and resulting lack of statistical power, we were able to uncover several hypothesized relations among life stress, sleep quality, and cortisol.

Consistent with the small overall sample size, we had substantially fewer participants in the comparison group than expected. The comparison group was composed of women receiving treatment for suspected endometrial cancer which, post-surgically was determined to be benign or pre-cancerous disease. It is possible that this smaller sample size in the comparison group also reflects the guidelines put forth by FIGO regarding who should perform the surgical treatment for women with low risk endometrial tumors. We posit that women with a possible diagnosis of benign or pre-cancerous disease may not be referred to gynecologic oncologists and may instead receive treatment from their primary general gynecologist. Thus, by recruiting exclusively at a gynecologic oncology clinic, the current study may have been less likely to recruit women who were ultimately determined to have benign or pre-cancerous disease. The lack of an appropriate comparison group poses several limitations for the current study limits the ability to determine whether those with endometrial cancer display greater diurnal cortisol dysregulation compared to those with benign disease who are receiving the same treatment and experiencing the same uncertainty pre-surgically.

Conclusions

The current feasibility study is the first to-date to explore the relations among stress, sleep quality, and diurnal cortisol pre-surgically among women with early stage endometrial cancer. The findings suggest significant relationships between stress and sleep quality. The results also revealed relationships between use of sleep medications and abnormal diurnal cortisol slope, as well as a trend toward a relationship between subjective sleep quality and mean morning cortisol level. Contrary to hypothesis, stress was not related to diurnal cortisol slope or mean morning cortisol level. This study provides preliminary data to support future research examining the relationship between psychosocial factors and diurnal cortisol among women with endometrial cancer. Future research is needed to further examine the predictors of dysregulated diurnal cortisol slopes as well as to examine relations between diurnal cortisol slope and post-operative outcomes in women with endometrial cancer.

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BIOGRAPHICAL SKETCH

Sally Jensen graduated summa cum laude from the University of Minnesota (Minneapolis, MN) in 2000, where she received a Bachelor of Arts degree in psychology and spanish. After graduation, Ms. Jensen was employed for three years as a Community Program Specialist in the University of Minnesota, Division of Epidemiology. At the Division of Epidemiology, Ms. Jensen worked on two community-based health-promotion research studies funded by the National Institutes of Health (NIH) involving the evaluation of behavioral strategies to prevent osteoporosis in girls and the evaluation of the effect of low-fat food availability in high schools on students' food choices. Ms. Jensen entered graduate school in the University of Florida Department of Clinical and Health Psychology in 2003. She is currently pursuing her Ph.D. in Clinical Psychology.