PSYCHONEUROIMMUNOLOGIC PREDICTORS OF POST-SURGICAL OUTCOME IN WOMEN WITH ENDOMETRIAL CANCER

By

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To Fiona Jensen

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Endometrial cancer is the most common gynecologic cancer in the United States and is often co-morbid with conditions that confer high risk for post-surgical complications. Among surgical populations, psychosocial distress and maladaptive coping are associated with poorer surgical recovery. Similarly, cortisol, a stress hormone, may serve as an important mediator of the relationship between psychosocial factors and impaired immunity during the peri-operative period. Few studies have examined psychoneuroimmunologic predictors of oncologic surgical. The present study explored the relations among pre-surgical psychosocial stress, pre-surgical emotional support, pre-surgical diurnal cortisol slope, and indices of surgical outcome (e.g., length of hospitalization, severity of post-surgical complications, time to post-surgical ambulation, and post-surgical systemic immune response), among 75 women undergoing total abdominal hysterectomy with bilateral salpingo oophorectomy (TAH-BSO) for suspected endometrial cancer. It was hypothesized that a less complicated surgical recovery would be predicted by less pre-surgical psychosocial stress, more normal diurnal cortisol production, and greater emotional support. Participants completed a pre-surgical psychosocial interview and collected pre-surgical saliva samples for analysis of diurnal cortisol output. Surgical outcome data was abstracted from medical records.

Greater perceived emotional support from primary support person was significantly associated with less elevated post-surgical WBC count and was marginally associated with lower post-surgical pain ratings. More elevated pre-surgical indices of cortisol were significantly associated with more elevated post-surgical WBC count and lower post-surgical pain ratings. Contrary to hypothesis, psychosocial stress was not significantly related to indices of surgical recovery or indices of cortisol. Length of hospitalization, severity of post-surgical complications, and time to post-surgical ambulation were not significantly associated with psychoneuroimmunologic predictors. The findings of the present study extend the literature examining psychoneuroimmunologic predictors of surgical outcome by identifying relations among pre-surgical emotional support, pre-surgical indices of cortisol, post-surgical WBC count, and post-surgical pain ratings. They provide preliminary data for future research to examine psychoneuroimmunologic relations during the peri-operative period 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 40,880 new cases estimated in 2005 (American Cancer Society [ACS], 2005). It is also the second-most-deadly gynecologic cancer in the United States, with approximately 7,310 deaths expected from endometrial cancer in 2005 (ACS, 2005). The five-year survival rate for patients with endometrial cancer is 84% (ACS, 2003). Endometrial cancer primarily affects postmenopausal women, with the peak incidence of onset during the sixth and seventh decades (Dorigo & Goodman, 2003).

Pathophysiology of Endometrial Cancer

Endometrial cancer commonly presents as an overgrowth of the cells in the endometrium, which is the innermost layer of the body of the uterus. Approximately 90% of endometrial cancers are pathologically classified as endometrial adenocarcinomas (ACS, 2003). Endometrial cancer is thought to result from a progression from endometrial hyperplasia (pre-malignant cells) to atypical hyperplasia to malignant cells (Dorigo & Goodman, 2003). Endometrial cancer, like breast and ovarian 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). The luteal phase of menstruation is characterized by the production of progesterone, resulting in the cessation of endometrial proliferation and the eventual sloughing of endometrial cells (Cyr & Skelton, 2003). A shift in the balance between the amount of estrogen and progesterone produced by the ovaries, resulting in elevated levels of unopposed estrogen and unchecked proliferation of endometrial cells, has been implicated as a risk factor for endometrial cancer (ACS, 2003). Additional 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, 2003). Recent evidence suggests that genetics may also play a role in the development of endometrial cancer, given the higher risk for developing endometrial cancer among women with a history of colon, ovarian, or breast cancer (Dorigo & Goodman, 2003).

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). An additional 11% 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 total abdominal hysterectomy with bilateral salpingo oophorectomy (TAH-BSO). Pelvic irradiation or chemotherapy may be necessary if the pelvic lymph nodes are positive for cancer. Advanced stages of endometrial cancer involve the metastatic spread of the tumor to the cervix, ovaries, abdominal organs, or other sites (ACS, 2003).

Despite the favorable survival rate, high rates of comorbid conditions such as obesity, hypertension, and diabetes, as well as advanced age, confer an increased risk for acute post-surgical complications such as thromboembolism, infection, and wound healing complications among women with endometrial cancer (Tozzi, Malur, Koehler, & Schneider, 2005). These post-surgical complications pose potential threats to both physical and psychosocial well-being. Although great advances in medical practice and technology have significantly improved patients' surgical outcomes and recovery, post-surgical complications have not been eliminated entirely, thus suggesting that additional risk factors may contribute to poorer surgical outcome (Kopp et al., 2003). In the search to identify such risk factors, impaired psychosocial functioning has emerged as a potentially important risk factor for poorer surgical outcome.

Psychosocial Predictors of Surgical Outcome

Research examining the relationship between psychosocial functioning and surgical outcome has been generally heterogeneous in nature. Studies include a variety of pre-surgical psychosocial predictors, types of surgery, types of anesthesia (general versus local), and follow-up period (acute versus long-term follow-up). Additionally, researchers have examined various distinct indices of surgical outcome. This diversity of outcome variables may reflect the different aspects of surgical recovery, such as restoration of function, quality of life, cost effectiveness, and medical outcome variables. Thus, in order to obtain a comprehensive picture of surgical recovery, it may be important to evaluate a variety of outcomes.

Post-surgical Pain

Post-surgical pain is an important index of post-surgical outcome, given its relationship with both psychosocial and physical well-being. Uncontrolled main is a major predictor of psychosocial distress, including anxiety (Noyes, Holt, & Massie, 1998) and depression (Massie & Popkin, 1998). In addition to its potential deleterious effects on quality of life, post-surgical pain may also compromise the immune response to surgery and place individuals at increased risk for post-surgical complications. Moreover, there is evidence that the immunosuppressive effects of pain may be independent of the immunosuppression associated with surgical tissue trauma. For example, Liebeskind (1991) found that pain without tissue damage was associated with decrements in natural killer (NK) cell activity, as well as decreased lymphocyte proliferation. Additionally, both acute and persistent post-surgical pain have been associated with impaired wound healing (McGuire et al., 2006). Given the overlapping relationships between psychosocial distress, pain and immune functioning, distressed individuals may be at risk for not only increased post-surgical pain, but also for impaired post-surgical immune functioning (Kiecolt-Glaser, Page, Marucha, MacCallum, Glaser, 1998).

Several predictors of greater post-surgical pain have been identified in the general surgery literature. Walch et al. (2005) found that individuals exposed to greater sunlight during hospitalization following spinal surgery experienced marginally less pain, and consumed significantly less analgesic medication per hour than individuals exposed to lower levels of sunlight. Greater exposure to sunlight during hospitalization was also associated with decreased perceived stress (Walch et al., 2005). Katz et al. (2005) examined predictors of acute post-surgical pain among women undergoing breast cancer surgery and found that greater pre-surgical anxiety predicted clinically meaningful acute pain in the two days following surgery.

Several investigations of psychosocial predictors of gynecologic surgical outcome have focused on post-operative pain and analgesic use as measures of surgical outcome. Preliminary support for the influence of pre-operative psychosocial functioning on gynecologic surgical pain was demonstrated by Kain, Sevarino, Alexander, Pincus, and Mayes (2000), who found that pre-operative anxiety predicted post-operative pain among women undergoing abdominal hysterectomy. In an extension of Kain et al.'s (2000) findings, Cohen, Fouladi, and Katz (2005) examined pre-operative distress and coping as predictors of post-operative pain and morphine consumption. Although pre-operative distress predicted greater post-operative pain and morphine consumption, this relationship was no longer significant when pre-operative coping was controlled for (Cohen et al., 2005). Moreover, the use of more passive coping strategies was associated with elevated pain and morphine consumption post-operatively (Cohen et al., 2005).

Post-Surgical Length of Hospitalization

Post-surgical length of hospitalization provides an estimate of speed of recovery following surgery and thus constitutes another important index of surgical outcome. Post-surgical length of hospitalization dependent upon factors related to insurance, institutional policies, the availability of home caregiving, and medical status. Despite its multifactorial nature, post-surgical length of hospitalization remains a clinically important measure of physical recovery given its reflection of the physical impact of surgery, physical aspects of recovery, behavioral aspects of recovery, and healthcare costs (Contrada et al., 2003). Longer length of post-surgical hospitalization may be associated with a number of negative health outcomes including post-surgical complications and infection (Bratzler & Hunt, 2006). McGuire et al. (2006) found that shorter length of hospitalization following gastric bypass surgery was marginally related to faster wound healing and that acute post-surgical pain was associated with a longer post-surgical hospitalization. Moreover, recent research suggests that behavioral and psychosocial factors may play a role in post-surgical length of hospitalization. Specifically, Oscarsson, Poromaa, Nussler, and Lofgren (2006) compared length of hospitalization for women undergoing minimally invasive surgery (laparascopic supravaginal hysterectomy) with women undergoing standard surgery (abdominal supravaginal hysterectomy) and found no differences between the two groups. Thus, the authors concluded that post-surgical length of hospitalization may depend more upon patient expectations and factors during the acute post-surgical period than on the surgical procedure itself (Oscarsson et al., 2006). Recent research has begun to elucidate some of the specific behavioral and psychosocial factors that may impact length of post-surgical hospitalization. Krohne and Slangen (2005) investigated the relationship between emotional support and duration of post-surgical hospitalization among individuals undergoing maxillofacial surgery and found that patients receiving more emotional support were hospitalized approximately 1.5 fewer days than individuals receiving less emotional support. Contrada et al. (2004) found additional support for the relationship between interpersonal coping and post-surgical duration of hospitalization in a study that examined religiousness among individuals undergoing coronary artery bypass graft (CABG). In addition to its use as a coping strategy, religiousness has been posited to be associated with social support networks. Contrada et al. (2004) found that individuals with stronger religious beliefs had significantly shorter hospitalization periods following CABG.

Post-Surgical Complications

The incidence of post-surgical complications not only contributes to post-surgical length of hospitalization but also serve as an important indicator of surgical outcome independent of their relationship to duration of hospitalization. Common post-surgical complications include surgical site infections, sepsis, cardiovascular complications, respiratory complications, and thromboembolic complications (Bratzler & Hunt, 2006). Post-operative complications are associated with longer post-surgical hospitalizations, as well as increased cost. Dimick et al. (2004) examined hospital costs associated with surgical complications. Increased cost per patient included $1398 for infectious complications, $7789 for cardiovascular complications, $52,466 for respiratory complications, and $1810 for thromboembolic complications (Dimick et al., 2004). Although post-surgical mortality has decreased substantially, the development of post-operative complications remains a significant index of post-surgical outcome. Among women undergoing hysterectomy, both insurance status, as well as race/ethnicity have been associated with the incidence of post-surgical complications. Women on Medicaid were more likely to have a post-surgical complication than privately insured women and Black women were more likely to have a post-surgical complication than White women, despite equivalent quality of care (Hakim, Benedict, & Merrick, 2004). There is also emerging evidence that behavioral and psychosocial factors may also be associated with greater risk for post-surgical complications. For example, Contrada et al. (2004) found individuals with stronger religious beliefs had fewer post-surgical complications. Moreover, the relationship between religious beliefs and length of hospitalization was mediated by the number of post-operative complications (Contrada et al., 2004). Kopp et al. (2003) provided further support for the relationship between interpersonal coping and surgical outcome, finding that life satisfaction and social support predicted surgical recovery without complications among a general surgery population.

Wound Healing Complications

Wound healing complications constitute an important category of post-surgical complications and an important index of recovery among individuals undergoing surgery. The wound healing process consists of a series of carefully orchestrated phases (See Figure 1-1). Comorbid conditions such as obesity, malnutrition, renal dysfunction, alcoholism, anemia, diabetes, tobacco use, immunosuppression, peripheral vascular disease, cancer, and advanced age may confer risk for wound healing complications (Schimp et al., 2004). Surgical wound healing complications may be described by the following categories: incisional separation, incomplete dehiscence/superficial separation, complete dehiscence, and evisceration (Schimp et al., 2004). Treatment for wound complications is both time-consuming, expensive, and may require prolonged hospitalization or specialized wound care (Schimp et al., 2004). Among gynecologic oncology patients, the incidence of incomplete and complete dehiscence ranges from two to five percent (Morrow, 1996).

Kiecolt-Glaser and colleagues have accumulated strong evidence that stress impairs wound healing, particularly during the early wound healing cascade (see Kiecolt-Glaser et al., 1998 for review). For example, delayed wound healing has been demonstrated among Alzheimer's caregivers (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995), among mice subject to restraint stress (Padgett, Marucha, & Sheridan, 1998), among dental students during examination time (Marucha, Kiecolt-Glaser, & Favagehi, 1998), and among couples during a conflict discussion (Kiecolt-Glaser et al., 2005). The relationship between psychosocial distress and impaired wound healing is proposed to be mediated by the effects of psychosocial distress on immune functioning. Indeed, Glaser et al. (1999) found that individuals who had a lower number of cytokines in the wound environment were also likely to have elevated stress levels, negative affect, and number of negative life events. Although the majority of wound healing research has been carried out under controlled conditions and involves standardized laboratory-induced wounds, several studies have examined psychosocial predictors of wound healing and relevant immune variables in the surgical context. Broadbent, Petrie, Alley, and Booth (2003) examined psychosocial predictors of wound healing and wound-relevant immune variables among individuals undergoing inguinal hernia surgery and found that greater pre-surgical worry about the surgery was associated with decreased matrix metalloproteinases 9 (MMP9) at the wound site. Moreover, greater pre-surgical perceived stress was associated with decreased IL-1ß at the wound site (Broadbent et al., 2003). In a sample of individuals undergoing gastric bypass surgery, McGuire et al. (2006) found that both acute and persistent post-surgical pain were associated with slower wound healing of a standardized punch biopsy wound placed at the same time as surgery.

Proposed Mechanisms of the Relationship between Peri-Operative Psychosocial Functioning and Surgical Outcome

The findings mentioned above suggest that psychosocial factors may play an important role in various indices of surgical outcome across diverse surgical populations. Although few studies have specifically examined the potential mechanisms of the relationships between psychosocial functioning and indices of surgical outcome, both behavioral and immune mechanisms have been proposed to account for these relationships.

Behavioral Mechanisms

Engagement in health promoting behaviors may serve as one modulator of the relationship between psychosocial functioning and surgical outcome. For example, health behaviors may impact surgical outcome via their effect on the type and amount of anesthetic agent used, their effect on the extent of surgery, and via direct effects on immune functioning (Kiecolt-Glaser et al., 1998). Greater psychosocial distress is associated with poorer health behaviors (Kiecolt-Glaser et al., 1998). Furthermore, adaptive interpersonal coping may confer benefits to pre-operative health, which may in turn serve as a protective factor during the peri-operative period (Contrada et al. 2004). Indeed, a number of pre-operative health factors have been identified as risk factors for impaired post-operative recovery, such as smoking status, hypertension, diabetes, and hypercholesterolemia (Peterson et al., 2002). However, it is unknown whether these indices of pre-operative health mediate the relationship between psychosocial functioning and post-surgical outcome. Additionally, health promoting behaviors are also important in the acute post-surgical period. For example, psychosocial distress may be associated with poor compliance with post-surgical recommendations for behaviors relevant to recovery such as proper breathing and ambulation (Kiecolt-Glaser et al., 1998).

Immune Mechanisms

In addition to behavioral modulators of the relationship between psychosocial functioning and post-surgical outcome, psychoneuroimmunologic (PNI) relations may also modulate this relationship. For example, social support is associated with improved immune functioning (Uchino, 2006) as well as improved wound healing capabilities (Kiecolt-Glaser et al., 1998). Several studies have also examined PNI relations during the peri-operative period. Greater depression is associated with decreased post-surgical lymphocytes and NK cells (Tjemsland, Soreide, Matre, & Malt, 1997). Increased pre-surgical state anxiety predicted a blunted neuroendocrine response to surgery (Pearson, Maddern, & Fitridge, 2005). Thus, psychosocial functioning may influence immune functioning during the peri-operative period, which may in turn influence surgical recovery.

Surgical Immune Response and Risk for Complications

In addition to the psychosocial stress associated with surgery, the surgical experience is also associated with substantial physical stress and trauma which affect immune functioning. The post-surgical immune response is characterized by hyperinflammation and immunosuppression, both of which may contribute to the development of post-surgical complications (Menger & Vollmar, 2004). Typically, the local immune response to surgery involves activation of the inflammatory cascade in order to prevent infection and to initiate tissue rebuilding, whereas the systemic response involves leukocytosis, neutrophilia, and lymphocytopenia (Salo, 1992). It should be emphasized that both the activated and depressed components of immune response to surgery are *adaptive* physiologic responses that enhance post-surgical survival (Salo, 1992). However, the excessive inflammation and immunosuppresson associated with surgical recovery also put individuals at risk for the development of complications and wound healing impairments (Salo, 1992).

Several aspects of surgery contribute to altered immune functioning during recovery. For example, the role of general anesthesia during surgery is to maintain homeostasis, thereby decreasing the stress response to surgery. As a result, general anesthesia is associated with a suppression of cell-mediated immunity (Salo, 1992; Ben-Eliyahu, 2003). Moreover, the suppression of cell-mediated immunity observed with general anesthesia is attenuated in regional anesthesia in which the nociceptive impulses are blocked regionally or at the level of the spinal cord (Ben-Eliyahu, 2003). Blood transfusions also impact peri-operative immune functioning by decreasing cell-mediated immunity (Ben-Eliyahu, 2003; Salo, 1992). Finally, the tissue trauma associated with the surgical procedure itself has been linked to altered immune functioning during the peri-operative period. Surgical trauma is related to hypoperfusion of tissue resulting in tissue ischemia, which subsequently alters neuroendocrine and immune functioning (Salo, 1992). The relationship between surgical tissue trauma and altered immunity is further strengthened by findings that minimally invasive surgical procedures are associated with attenuated cell-mediated immunity suppression and cytokine misbalance (Ben-Eliyahu, 2003; Menger & Vollmar, 2004).

Modulators of the Surgical Immune Response

Neuroendocrine functioning has been implicated in the modulation of the immune response to surgery. One pathway by which neuroendocrine factors appear to modulate immune response to surgery is through sympathetic nervous system (SNS) activation and release of catecholamines. Catecholamines, such as epinephrine and norepinephrine, suppress cell-mediated immunity (Ben-Eliyahu, 2003). The immunosuppressive effects of catecholamines are further supported by evidence that the suppression of cell-mediated immunity is attenuated by administration of beta adrenergic antagonists (Nelson & Lysle, 1998).

Activation of the hypothalamic pituitary adrenal (HPA) axis and elevated levels of its end-product, glucocorticoids, have also demonstrated strong immunosuppressive effects during the peri-operative period. Glucocorticoids, such as cortisol, increase post-surgically (Ben-Eliyahu, 2003; Pearson et al., 2005). Glucocorticoids also act synergistically with catecholamines by increasing beta adrenergic receptor density (Antoni et al., 2006). Glucocorticoids exert immunosuppressive effects by decreasing circulating lymphocytes, decrease monocytes functioning, decrease NK cell activity, and decrease cytokine production (DeKeyser, 2003). Increases in glucocorticoids are also associated with elevated levels of IL-6, a cytokine that functions to downregulate pro-inflammatory immune responses and to enhance anti-inflammatory immune responses (Menger & Vollmar, 2004). Specifically, glucocorticoid dysregulation also negatively impacts levels of IL-1β and TNF-α, two pro-inflammatory cytokines that are integral in the early wound healing response (Kiecolt-Glaser et al., 1998). Glaser et al. (1999) found elevated levels of salivary cortisol, a glucocorticoid, among individuals who produced low numbers of cytokines in the fluid of standardized blister wounds.

Psychosocial Stress and Cortisol

Cortisol has increasingly become a variable of interest in psychoneuroimmunologic (PNI) research, given its relationship with both psychosocial stress and immune functioning. The relationship between psychosocial stress and cortisol results from HPA axis activation. When a situation is perceived as stressful, the 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, follows a circadian rhythm regulated by the suprachiasmatic nuclei (SCN) in the hypothalamus (Stone et al., 2001). The SCN 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. 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. However, altered cortisol production has also been found among individuals under chronic life stress, such as individuals experiencing interpersonal violence (Seedat, Stein, Kennedy, & Hauger, 2003) and unemployment (Ockenfels, 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.

Psychosocial Stress, Cortisol Dysregulation, and Surgical Outcome

The surgical experience is characterized by both psychosocial and physical stress. Consequently, stress may be associated with neuroendocrine dysregulation and subsequent complications among individuals during the peri-operative period. Padgett et al. (1998) found that the delayed wound healing observed among mice under restraint stress was associated with elevated cortisol and that this relationship was attenuated by the blocking of glucocorticoid receptors. Additionally, Glaser et al. (1999) found that greater stress was associated with both greater cortisol, as well as lower production of pro-inflammatory cytokines in wound fluid. Pearson et al. (2005) examined state anxiety during the acute pre-operative period and found that it was associated with a blunted cortisol response during the intra-operative period. Although neither anxiety nor intra-operative cortisol was associated with post-operative complications, these findings provide compelling evidence that PNI relations may be similar in studies of both controlled and standardized tissue damage, as well as in studies of surgical tissue damage.

Psychosocial Predictors of Peri-Operative Neuroendocrine Functioning and Surgical Outcome

Psychosocial Stress

Given the well-established link between psychosocial distress and impaired immunity, numerous studies have examined psychosocial stress as a predictor of peri-operative neuroendocrine functioning and surgical outcome. One form of psychosocial distress, perceived stress, has been positively associated with cortisol dysregulation following laboratory controlled tissue damage (Glaser et al., 1999). Additionally, perceived stress is associated with an impaired pro-inflammatory response at the wound site among individuals undergoing inguinal hernia surgery (Broadbent et al., 2004). Although cortisol was not examined as a mediator of the relationship between perceived stress and impaired pro-inflammatory response in this study, glucocorticoids have been identified as key modulators of the impaired pro-inflammatory response early in the wound healing cascade.

Interpersonal Coping

Findings from Cohen et al. (2005) suggest that, among women undergoing major gynecologic surgery, pre-operative coping strategies may be better predictors of post-operative pain outcomes than psychosocial distress. In addition, Manyande et al. (1995) report that the use of an active coping imagery intervention prior to surgery was associated with lower cortisol, lower heart rate, and less pain during the peri-operative period. Furthermore, the association between passive coping and poorer surgical outcome is consistent with previous research findings linking passive coping with poorer health behaviors (Singh et al., 1996), poorer immunity (Goodkin, Fuchs, Feaster, Leeka, & Rishel, 1992), and poorer health outcomes (Leserman et al., 2002) among individuals with HIV. Moreover, passive coping is often associated with maladaptive interpersonal coping (Pereira et al., 2004). Interpersonal coping involves the way in which individuals interact with their social environment when faced with stressors. Interpersonal coping has been demonstrated to be an influential factor in individuals' exchanges with the health care system and adherence (Pereira et al., 2004). Specifically, maladaptive interpersonal coping is hypothesized to negatively impact health behaviors and health outcomes via its association with behavioral disengagement and avoidant coping (Cohen, Gottlieb, & Underwood, 2001). Additionally, interpersonal coping may be of particular significance to women, given the relational cultural theory's assertion that women commonly identify themselves through their relation to others (Jordan, Kaplan, Miller, Stiver, & Surrey 1991).

Purpose of Study

Although findings among general surgery populations suggest that psychosocial functioning is associated with objective indices of poorer post-surgical outcome, such as longer post-surgical hospitalization and more post-surgical complications, no published study to-date has examined these variables among women undergoing gynecologic oncology surgery. The present study will extend findings from the general surgery population to examine relationships between psychosocial functioning and indices of post-surgical outcome (post-surgical systemic immune response, post-surgical complications, time to ambulation, and post-surgical duration of hospitalization) among women undergoing TAH-BSO for suspected endometrial cancer, a population that is considered to be at an elevated risk for poor surgical outcome as a result of their high rates of comorbid medical conditions (See Figure 1-2). The findings of the present study are expected to enhance the ability to screen for patients who may be at elevated risk for poorer post-surgical outcome based on psychosocial functioning. The findings are also expected to inform future research, including research examining the potential mechanisms of the relationship between pre-surgical stress, pre-surgical interpersonal coping, and post-surgical outcome, as well as the development of pre-surgical psychosocial interventions to improve post-surgical outcome.

Specific Aims

Aim 1: To examine the relations among pre-surgical psychosocial stress, pre-surgical diurnal cortisol slope, and indices of post-surgical recovery (systemic immunosuppression, post-surgical complications, time to ambulation, and length of post-surgical hospitalization) among women undergoing total abdominal hysterectomy with bilateral salpingo oophorectomy (TAH-BSO) for suspected endometrial cancer.

Hypothesis 1a: Women who report greater pre-surgical psychosocial stress will have a more complicated post-surgical recovery, including greater systemic immunosuppression, greater incidence of post-surgical complications, longer time to ambulation, and longer post-surgical hospitalization.

Hypothesis 1b: The relationship between pre-surgical psychosocial stress and a more complicated post-surgical recovery will be mediated by more abnormal diurnal cortisol slopes.

Aim 2: To examine the relations among pre-surgical emotional support, pre-surgical diurnal cortisol slope, and indices of post-surgical recovery (systemic immunosuppression, post-surgical complications, time to ambulation, and length of post-surgical hospitalization) among women undergoing total abdominal hysterectomy with bilateral salpingo oophorectomy (TAH-BSO) for suspected endometrial cancer.

Hypothesis 2a: Women who report greater pre-surgical emotional support will have a less complicated post-surgical recovery, including less systemic immunosuppression, lower incidence of post-surgical complications, shorter time to ambulation, and shorter post-surgical hospitalization.

Hypothesis 2b: The relationship between pre-surgical emotional support and a less complicated post-surgical recovery will be mediated by a less abnormal diurnal cortisol slope.

Aim 3: To examine whether pre-surgical emotional support moderates the potential relations among pre-surgical psychosocial stress and indices of post-surgical recovery among women undergoing total abdominal hysterectomy with bilateral salpingo oophorectomy (TAH-BSO) for suspected endometrial cancer.

Hypothesis 3: Among women with high pre-surgical psychosocial stress, those who report less emotional support will have a more complicated post-surgical recovery, including greater systemic immunosuppression, greater incidence of post-surgical complications, longer time to ambulation, and longer post-surgical hospitalization, than those who report greater use of peri-operative adaptive interpersonal coping.

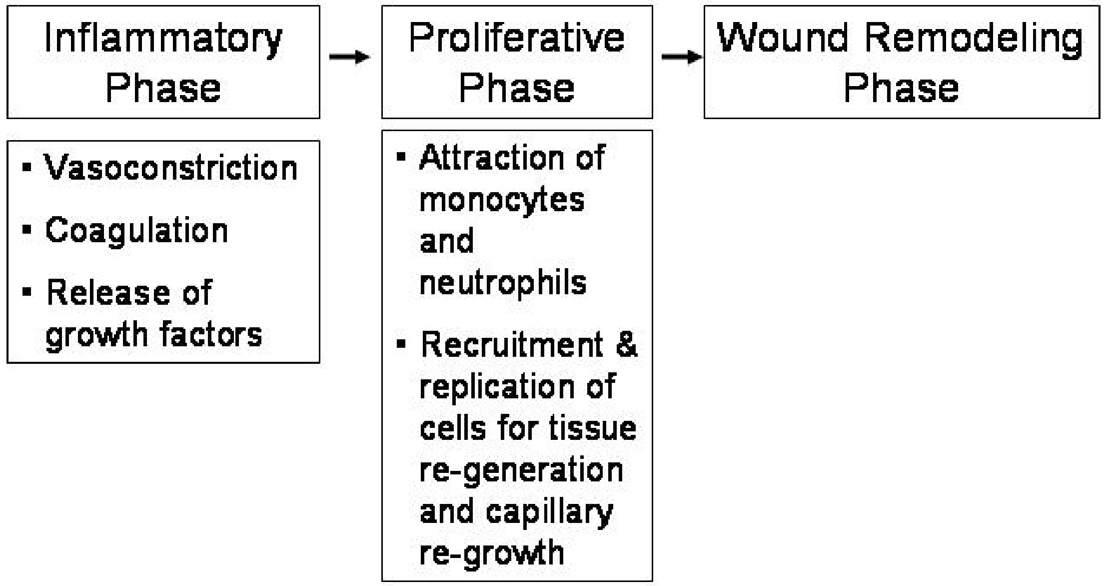

Figure 1-1. Wound healing cascade (Adapted from Kiecolt-Glaser et al., 1998).

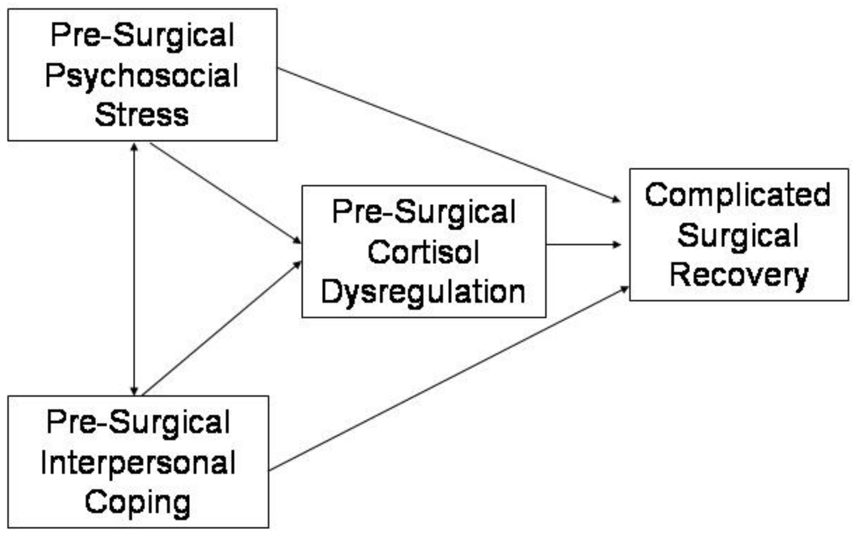

Figure 1-2. Theoretical model.

CHAPTER 2
METHODS

Design

The design of the present study is prospective. The sample consists of 75 women with suspected endometrial cancer scheduled to undergo TAH-BSO. Participants were recruited from the UF&Shands Gynecologic Oncology Clinic in Gainesville, FL. Participants completed a psychosocial interview approximately one day prior to TAH-BSO surgery and collected saliva samples for the quantitation of pre-surgical salivary cortisol levels. Surgical outcome data (from the time of surgery until discharge) were abstracted from medical records. This study was conducted in accordance with the rules and regulations of the Institutional Review Board (IRB) of the University of Florida and is IRB approved (protocol no. 69-2004). Figure 2-1 displays the study design.

Participants

Inclusion criteria for participants in the present study included: (a) women undergoing TAH-BSO with or without pelvic lymph node dissection for either (i) an abnormal endometrial biopsy concerning for endometrial cancer or (ii) a complex adnexal mass without ascites or omental caking concerning for Stage I gynecologic malignancy, and (b) fluency in spoken English. Exclusion criteria for participants in the present study included: (a) recurrent endometrial carcinoma, (b) metastasis to the uterine corpus from another site, (c) pre-surgical chemotherapy or radiotherapy, (d) current psychotic disorder, and (e) current suicidal intent/plan. Because the diagnosis of endometrial cancer is based on post-surgical pathology, it was possible that women included in the proposed study were diagnosed post-surgically with pre-cancerous or benign disease. Based on preliminary data, it was expected that less than 10% of participants would eventually be diagnosed with benign disease. Table 2-1 summarizes the demographic characteristics of participants.

Procedures

Participants were recruited from the Gynecologic Oncology Clinic at UF&Shands Medical Plaza. Potentially eligible participants were identified at their treatment consultation visit through consultation with attending physicians, residents, medical students, and nurse practitioners. Potentially eligible participants were notified of the opportunity to participate in a research project by one of the previously listed health care providers. If a patient expressed interest in participating, she met with a trained researcher who provided an overview of the study and answered any questions the patient had. If a patient stated that she would like to participate in the study, she underwent an informed consent process in which she read and signed the IRB-approved Informed Consent Form. Following informed consent, she underwent a brief screening assessment. If the results of the screening assessment were unremarkable, a psychosocial assessment interview was be scheduled for the day of the participant's pre-operative medical appointment at the Gynecologic Oncology Clinic. At the time of the pre-operative appointment, participants underwent a one-hour psychosocial interview in a private room in the Gynecologic Oncology Clinic. Following the psychosocial interview, participants were be reimbursed $20 for meal and parking expenses. No psychosocial data was collected on the day of surgery.

Post-surgical complication data was obtained from inpatient and outpatient medical records during the period from the date of surgery until the date of discharge. Biobehavioral data (e.g., age, disease stage, medications, co-morbid illnesses) were abstracted from medical records and were also based on participants' self-report.

Psychosocial Assessment

The following psychological/psychiatric measures were completed prior to study entry to determine participants' eligibility:

Beck Scale for Suicide Ideation (BSS; Beck & Steer, 1991-1993): 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). Women who reported current suicidal ideation, intent, or plan were referred immediately to the Psycho-Oncology Clinic at the Psychology Clinic (under the supervision of Deidre Pereira, Ph.D., licensed psychologist) as well as Psychiatry. Women reporting current suicidal ideation, intent, or plan were not eligible for participation in this study (see exclusion criteria noted above).

Psychotic Screening Module of the Structured Clinical Interview for DSM-IV for non-clinical populations (SCID-NP; Spitzer, Williams, Gibbon, & First, 1992). The SCID-NP is a semi-structured interview for making DSM-IV Axis I psychotic diagnoses in non-psychiatric populations. The SCID-NP has been used widely as a brief screening measure of psychotic disorders among patients with medical illness, such as HIV (e.g., Penedo, et al., 2003). Women with current psychotic symptoms were referred immediately to Psychiatry for evaluation and treatment. Women with current psychotic symptoms were not eligible for participation in this study (see exclusion criteria noted above).

The following psychosocial variables were measured at the pre- surgical assessment as part of specific aims:

Demographics

The MacArthur Sociodemographic Questionnaire(MSQ; Adler, Epel, Castellazzo, & Ickovics, 2000) 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. The MSQ was completed at participants' pre-operative visit (approximately one day prior to surgery).

Medical comorbidity

The Charlson Comorbidity Index (Charlson, Pompei, Ales, MacKenzie, 1987) was used to assess medical comorbidity. The Charlson Comorbidity Index is a weighted index that takes into account the number, as well as severity of comorbid diseases.

Pre-surgical life stress

An abbreviated measure of the Life Experiences Survey (LES; Sarason, Johnson, & Siegel, 1978) was used to measure pre-surgical life stress. This abbreviated LES measure was devised by Leserman and colleagues at the University of North Carolina for use with chronically ill populations. The version that will be used in the proposed research has been further tailored for use with cancer patients by Pereira and Jensen at the University of Florida by anchoring health items to the experience of being diagnosed with cancer (LES-Cancer, LES-C). This 34-item life stress measure assesses the number of negative life events during the past 6 months. Additionally, participants use a 5-point scale ranging from "Not Stressful" to "Extremely Stressful" to rate the impact of each negative life event when it occurred.

Emotional support from primary support person

The Sources of Social Support Scale (SSSS; Carver, 1999) was used to assess emotional support. The SSSS is a 50-item self-report questionnaire measuring receipt of both positive and negative emotional and instrumental social support from spouse/partner, friends, adult female family members, other family members, and health care providers. For each item, participants rate the frequency with which they receive a specific type of social support using a 5-point Likert scale ranging from "Not at all" to "A lot." For the present study, self-reported receipt of positive emotional support from spouse/partner was used in the specific aims. For women without a spouse/partner, the self-reported receipt of positive emotional support from friends was used.

The following psychosocial variables were measured at the pre- surgical assessment as part of exploratory analyses:

Pre-surgical perceived stress

The Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) was used to measure pre-surgical perceived stress. 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, et al., 2000).

Total emotional support from all sources

The Sources of Social Support Scale (SSSS; Carver, 1999) was used to assess *total* emotional support from the following sources: spouse/partner, friends, adult female family members, other family members, and health care providers. A more comprehensive description of this measure can be found in the previous section.

Physiologic Assessment

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. Because non-compliance with the sampling schedule can affect the validity of the cortisol levels (Kudielka, Broderick, & Kirschbaum, 2003), participants were encouraged to note the time of sample collection if it deviated from the times specified above. 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 for preparation and storage.

Saliva samples were centrifuged for 15 minutes at 3000 RPM and aliquots were frozen at -70ºC until assayed. Cortisol assays were conducted at the Behavioral Medicine Research Center Neuroendocrinology Laboratory in the Department of Psychology at the University of Miami and at Salimetrics Inc. (State College, PA) by trained laboratory personnel. 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.

Salivary Cortisol Slope Calculation

A growing body of research has examined diverse aspects of cortisol in response to psychosocial factors. Vedhara, Stra, Miles, Sanderman, & Ranchor (2006) describe four measures of cortisol commonly measured in PNI research: area under the curve with respect to ground (AUCg), area under the curve with respect to increase (AUCi), early morning cortisol peak, and diurnal cortisol slope. Although often used interchangeably under the umbrella of “cortisol”, recent research suggests that these measures of cortisol may reflect varied and distinct processes. For example, diurnal cortisol is a measure of the pattern of cortisol production over time, whereas the early morning peak, which is considered to be a proxy measure of diurnal cortisol, is representative of HPA axis reactivity to waking (Vedhara et al., 2006). In contrast, the AUC approach is calculated on based upon the trapezoid formula in order determine the overall production of cortisol over time (Vedhara et al., 2006). Thus, AUCg reflects the basal HPA activity whereas AUCi reflects HPA reactivity (Vedhara et al., 2006). Based on findings suggesting 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, Sapolsky, Kraemer, & Spiegel, 2000), cortisol diurnal slope was examined as the primary measure of cortisol and AUCg, AUCi, mean daily cortisol, and morning cortisol were examined as secondary measures of cortisol. Diurnal cortisol slope were be calculated using standard linear regression. This method is consistent with that reported by Abercrombie et al. (2004), Sephton et al., (2000), Giese-Davis, Sephton, Abercrombie, Duran, and Spiegel (2004), Giese-Davis, Dimiceli, Sephton, and Spiegel (2006), and Vedhara et al. (2006). Because the normal diurnal cortisol slope is characterized by a peak upon waking followed by a subsequent decline throughout the day (Stone et al., 2001), cortisol concentrations were log transformed in an effort to normalize the distribution and linearize the change in cortisol over the day (Vedhara et al., 2006). A series of 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 were performed individually for each participant to quantify each person's diurnal cortisol slope using unstandardized beta weights. Based upon previous research (e.g., Vedhara et al., 2006), unstandardized beta weights closer to zero are indicative of more abnormal diurnal slopes (characterized by flattened slopes, abnormal peaks, and abnormal troughs), whereas unstandardized beta weights further from zero are indicative of more normal diurnal slopes.

Although hierarchical linear modeling (HLM) may also be an appropriate form of cortisol slope estimation (e.g., Stone et al., 2001), the linear regression model described above has demonstrated equivalent results with HLM (Rogosa & Saner, 1995). Additionally, given that among 90% of healthy individuals, the diurnal cortisol slope is characterized by a peak upon waking followed by consistent decline (Stone et al., 2001), the use of a linear model is appropriate.

Diurnal cortisol slope was identified as the measure of cortisol in the specific aims. Mean daily cortisol, mean morning cortisol, AUCg, and AUCi were designated as the measures of cortisol in exploratory aims.

Surgical Outcome Assessment

The following surgical outcome variables were measured during the post-surgical hospitalization period as part of specific aims:

Severity of post-surgical complications

Data regarding participants' post-surgical complications were abstracted from medical records. Information was abstracted from operative reports, discharge summaries, diagnostic testing reports, and Gynecologic Oncology and nursing notes documented within patients' paper and electronic medical charts on the hospital unit as well as at the UF&Shands Gynecologic Oncology Clinic. The determination of whether an event/condition constituted a complication was determined based on the gynecologic surgery literature (e.g., Nichols & DeLancey, 1995; Tozzi et al., 2005; Vasilev, 2000). Figure 2-2 lists the events and conditions that will be classified as complications for the proposed study. The severity of each complication was rated on a scale from 1 (minimally severe) to 3 (extremely severe) by a board-certified gynecologic oncologist (Daylene Ripley, MD). The weighted sum of documented post-operative complications was utilized as the outcome of interest. It should be noted that the validity of this method of data collection is dependent upon the accuracy and consistency of documentation by healthcare providers in the medical record. Thus, in an effort to obtain the most comprehensive information regarding individuals' post-surgical recovery, all available sources of information regarding post-surgical recovery in the medical record was reviewed. Three additional raters who were blinded to study design and hypotheses reviewed medical records and rated post-surgical complications to establish inter-rater reliability with the primary rater ($\alpha = .92$).

Length of post-surgical hospitalization

The duration of participants' post-surgical hospitalization was abstracted from discharge summaries documented in participants' medical records.

Systemic immunosuppression

White blood cell (WBC) count is a clinically important index of systemic immune response during the acute post-surgical period. The post-surgical immune response is typically characterized by leukocytosis, neutrophilia, and lymphocytopenia (Salo, 1992). Participants' WBC counts during post-surgical hospitalization, as well as leukocyte subset differential percentages was abstracted from medical records. Less elevated WBC counts during post-surgical hospitalization is considered indicative of systemic immunosuppression.

Time to ambulation

Information about days to ambulation was abstracted from participants' discharge summaries as well as notes documented on patients' paper medical charts on the hospital unit. Time to ambulation was quantified as the post-operative day on which ambulation first occurred.

Biobehavioral variables

Information about participants' age, disease stage, medication use, comorbid illnesses, health behaviors (e.g., use of tobacco, alcohol, illicit drugs), additional surgical procedures (e.g., panniculectomy or hernia repair at the time of TAH-BSO), intra-operative complications (e.g., inadequate hemostasis), intra-operative blood loss, anesthetic dose, and post-operative analgesic use were abstracted from medical records. Additionally, the MSQ (see above) was used to measure sociodemographic control variables. These variables have been traditionally examined descriptively and as potential confounds in analyses with physiologic and disease outcomes. A priori biobehavioral control variables included age, FIGO stage, BMI, medical comorbidity, post-surgical pain, and length of surgery.

The following surgical outcome variables were measured during the post-surgical hospitalization period as part of exploratory analyses:

Post-surgical pain ratings

Information about participants' post-surgical pain ratings was abstracted from their vital signs as documented in their inpatient medical record. Pain ratings were based on a scale from zero to ten, with ten indicating the worst pain level.

Statistical Procedures

The distributions of all variables were examined to confirm that parametric tests could be used. Any variables with non-normal distributions were transformed accordingly. Relations among a priori biobehavioral control variables and outcome measures were tested using correlations. Biobehavioral control variables significantly related to outcome measures at $p \leq .05$ were controlled for in subsequent analyses.

Analyses of Specific Aims

Aim 1: To examine the relations among peri-operative psychosocial stress, pre-surgical diurnal cortisol slope, and indices of post-surgical recovery.

To examine support for hypothesis 1a, which states that women who report greater pre-surgical psychosocial stress will have a more complicated post-surgical recovery, a series of hierarchical linear regression models was used. For each hierarchical regression, biobehavioral control variables were entered as the Block 1 predictor, impact of negative life events (measured by the LES-C) were entered as the Block 2 predictor, and diurnal cortisol slope was entered as the Block 3 predictor. Separate regressions were planned for each of the following outcome variables: systemic immunosuppression, post-surgical complications, time to ambulation, and length of post-surgical hospitalization.

To examine support for hypothesis 1b, which states that pre-surgical diurnal cortisol slope will mediate the relationship between pre-surgical psychosocial stress and indices of surgical recovery, the methods specified by Baron and Kenny (1986) were used. In order for mediation to be supported, three conditions must be met. First, the hypothesized predictor variable, impact of negative life events, must be related to the outcome variable, index of post-surgical recovery. Next, impact of negative life events must be related to the mediating variable, diurnal cortisol slope. Finally, the relationship between impact of negative life events and index of post-surgical recovery must be weakened (partial mediation) or eliminated (full mediation) when the mediating variable, diurnal cortisol slope, is controlled. Throughout this process, the mediator, diurnal cortisol slope, must remain significant.

Aim 2: To examine the relations among peri-operative emotional support, pre-surgical diurnal cortisol slope, and indices of post-surgical recovery.

To examine support for hypothesis 2a, which states that women who report greater pre-surgical emotional support will have a less complicated post-surgical recovery, a series of hierarchical linear regression models was used. For each regression, biobehavioral control variables were entered as the Block 1 predictor, pre-surgical positive emotional support was entered as the Block 2 predictor, and diurnal cortisol slope was entered as the Block 3 predictor. Separate regressions were planned for each of the following outcome variables: systemic immunosuppression, post-surgical complications, time to ambulation, and length of post-surgical hospitalization.

To examine support for hypothesis 2b, which states that pre-surgical diurnal cortisol slope will mediate the relationship between pre-surgical emotional support and indices of surgical recovery, the methods specified by Baron and Kenny (1986) were used. In order for mediation to be supported, three conditions must be met. First, the hypothesized predictor variable, positive emotional support, must be related to the outcome variable, index of post-surgical recovery. Next, positive emotional support must be related to the mediating variable, diurnal cortisol slope. Finally, the relationship between positive emotional support and index of post-surgical recovery must be weakened (partial mediation) or eliminated (full mediation) when the mediating variable, diurnal cortisol slope, is controlled. Throughout this process, the mediator, diurnal cortisol slope, must remain significant.

Aim 3: To examine whether pre-surgical emotional support moderates the potential relations among peri-operative psychosocial stress and indices of post-surgical recovery.

To examine support for hypothesis 3, which states that among women with high pre-surgical psychosocial stress, those who report less pre-surgical emotional support will have a more complicated post-surgical recovery, the hierarchical regression methods specified by Aiken and West (1997) were planned. Biobehavioral control variables were entered as the Block 1 predictor. In the second block, the main effects of impact of negative life events and positive emotional support were entered. In the third block, the interaction between impact of negative life events and positive emotional support were entered.

Power and Sample Size Considerations

A small number of studies have examined psychosocial predictors of surgical outcome (e.g., Broadbent et al., 2004; Kopp et al., 2003; Krohne & Slangen, 2005). A review of this literature reveals effect sizes between psychosocial and immune variables in the “medium” to “large” range, according to Cohen’s effect size conventions (Broadbent et al., 2004; Kopp et al., 2003; Krohne & Slangen, 2005). 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 proposed study based upon the findings examining psychosocial predictors of length of hospitalization (Krohne & Slangen, 2005) and of post-operative complications (Contrada et al., 2004). Power analysis revealed that a sample size of 70 provides 80% power to detect a change in slope from 0 under the null hypothesis to .32 under the alternative hypothesis when the standard deviation of the X’s is 1, the standard deviation of Y is 1, and the two-sided significance level is .05 (See Figure 2-3).

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 studies that have examined relations among psychosocial functioning and cortisol, the effect sizes for the relationship between psychosocial variables and cortisol fall in the “medium” to “large” range. Table 2-3 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 proposed study based upon the findings of Gallagher-Thompson et al. (2006). Power analysis revealed that a sample size of 60 provides 81% power to detect a change in slope from 0 under the null hypothesis to .35 under the alternative hypothesis when the standard deviation of the X’s is 1, the standard deviation of Y is 1, and the two-sided significance level is .05. Given that the power analysis regarding the aims examining post-surgical recovery as outcome variable is greater than the sample size recommended by the power analysis examining cortisol as an outcome variable, the proposed study will use the conservative estimation of N = 70 (See Figure 2-4).

Table 2-1. Demographic characteristics of participants

Total *N*	75
N with psychosocial data	75
N with cortisol data	62
N with length of hospitalization data	75
N with post-surgical complications data	75
N with ambulation data	43
N with WBC data	75
Age, Mean (SD)	60.71 (9.65)
Highest Degree (% of sample)	
Less than high school	12.3
High School/GED	39.7
Associate degree	13.7
Bachelor's degree	17.8
Master's degree	9.6
Professional degree	1.4
Other	5.5
Household Income (% of sample)	
Less than $5,000	2.7
$5,000 - $11,999	5.4
$12,000 - $15,999	13.5
$16,000 - $24,999	9.5
$25,000 - $34,999	13.5
$35,000 - $49,999	14.9
$50,000 - $74,999	14.9
$75,000 - $99,999	4.1
$100,000 or greater	9.5
Don't know	5.4
Race (% of sample)	
Multiracial	1.3
Black/African American	8.0
White	90.7
Ethnicity (% of sample)	
Hispanic/Latino	5.3
Not Hispanic/Latino	94.7
Marital Status (% of sample)	
Married	56.2
Never married	4.1
Separated	2.7
Divorced	17.8
Widowed	19.2
Employment Status (% of sample)	
Working full-time	32.4
Working part-time	12.2
Unemployed	1.4
Keeping house/Raising children	6.8
Retired	47.3

Table 2-2. Surgical recovery effect sizes

Study	Population	*N*	R^2
Broadbent et al., 2003	Inguinal hernia surgery patients	47	.25 - .34
Kopp et al., 2003	General surgery patients	112	.04 - .76
Krohne & Slangen, 2005	Maxillofacial surgery patients	84	.25

Table 2-3. Psychosocial-cortisol effect sizes

Study	Population	*N*	*d*	R^2
Giese-Davis et al, 2004	Metastatic breast cancer	91	.90	
Giese-Davis et al., 2006	Metastatic breast cancer	29		.37
Vedhara et al., 2006	Breast cancer	59		.10
Gallagher-Thompson et al., 2006	Dementia caregivers and non-caregivers	83		.40
Turner-Cobb et al., 2004	Metastatic breast cancer	72		.04

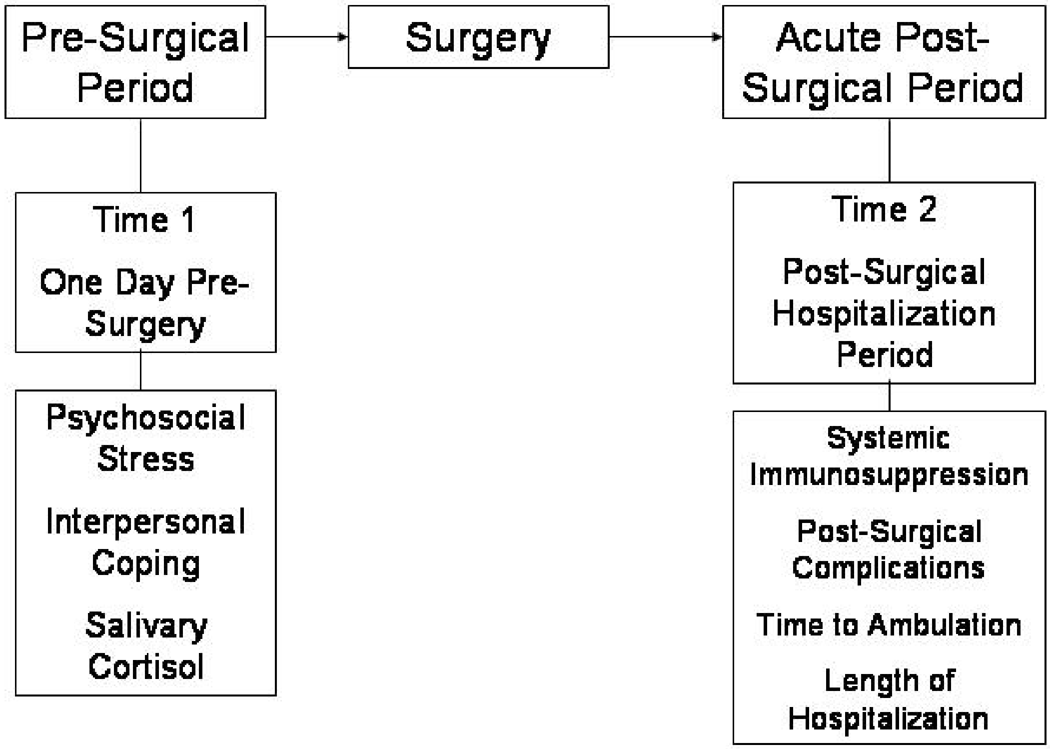

Figure 2-1. Design timeline.

Category	Complication
Immune	Sepsis
	Febrile
	Wound complication
	Infection
Cardiovascular	Arrhythmias
	Tachycardia
	Myocardial infarction
	Abnormal blood pressure
Gastrointestinal	Emesis
	Intestinal Fistula
	Slow return of bowel function
	Laryngospasm
	Severe nausea/vomiting
	Diarrhea
	Ileus
	Pancreatitis
	Bowel Obstruction
	GI tract Bleeding
Pulmonary	Brochospasm
	Pulmonary Embolism
	Pneumonia
	Atelectasis
	Pneumothorax
	Pulmonary edema
	Adult respiratory distress
	Respiratory infection
	Low O2 saturation
	Bronchial inflammation
	Cough with sputum
	Pleural effusion
	Perihilar airspace disease
	Hypoxic event
	Respiratory insufficiency
	Dyspnea
Hematologic	Deep Vein Thrombosis
	Thromboembolism
	Venous stasis
	Low hematocrit
	Transfusion
	Hypoxemia
	Superficial phlebitis
Renal	Low urine output
	Abnormal creatnine
	Uretal obstruction
	Urinary tract infection
	Acute renal failure
	Urinary fistula
	Bladder dysfunction
	Acute tubular necrosis
Procedure related	Central line hematoma
	Central line air embolism
	Venous catheter infection
	Venous catheter thrombosis
	Venous catheter obstruction
	Infection--paracentesis
	Adverse medication response
Miscellaneous	Pain
	Post-surgical ascites
	Hypothermia
	Decubitus ulcer
	Delirium
	Dizziness
	Pelvic hematoma
	Aspiration
	Lymphocyst
Peritoneal	Pneumoperitoneum
Cerebrovascular	Stroke

Figure 2-2. Categories of post-surgical complications.

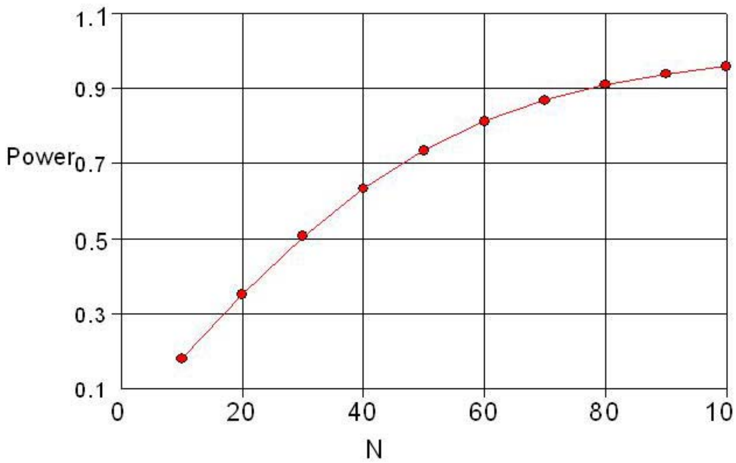

Figure 2-3. Power Versus Sample Size With Alpha = .05 and Slope = .32

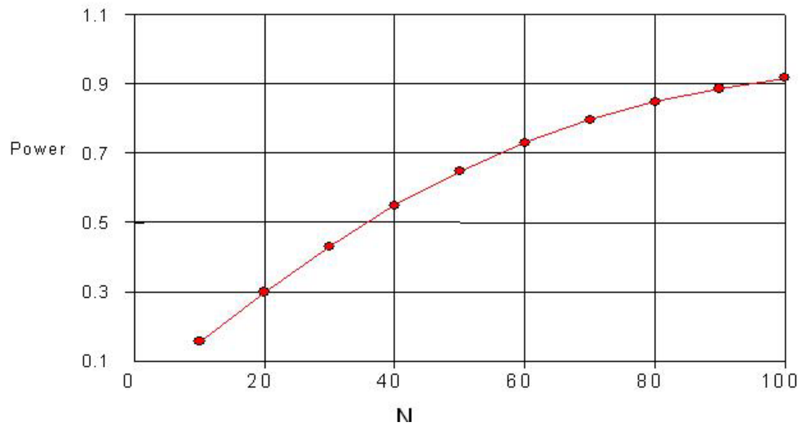

Figure 2-4. Power Versus Sample Size With Alpha = .05 and Slope = .35

CHAPTER 3
RESULTS

Preliminary Analyses

Biological Variables

Raw cortisol values were log transformed prior to calculating diurnal slope as per the methodology of Sephton et al. (2000)[1]. A mean diurnal cortisol slope was created using all cortisol data points for each participant. Mean WBC count during the acute post-surgical hospitalization period was calculated by computing an average WBC count for each hospitalization day blood complete blood cell analysis was performed and then averaging the daily WBC count values.

Outcome Variables

Descriptive analyses examined the normality of the distributions of the main outcome variables. Outliers (defined as greater than three standard deviations from the mean) were eliminated from analyses. The normal distributions of WBC count and post-surgical ambulation data were confirmed. Length of post-surgical hospitalization data were log-transformed to permit the use of parametric analyses. Post-surgical complication data were square root-transformed to permit the use of parametric analyses.

Control Variables

Pearson bivariate correlations were performed to assess for potential relations among a priori continuous biobehavioral control variables and the main variables of interest (Table 3-1).

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[1] Given that the methodology with regard to the log transformation of cortisol during the process of slope calculation is poorly described in the literature, a random sample of analyses were rerun using diurnal cortisol slope which was calculated from the raw cortisol concentrations. A constant of "1" was added to each slope calculation and slopes were then log transformed. The use of slopes calculated in this alternative manner failed to produce different results than those reported based on cortisol slopes calculated from log-transformed cortisol values.

Spearman's correlations were performed to assess for potential relations among a priori ordinal biobehavioral control variables (e.g. FIGO stage) and the main variables of interest. Independent samples t-tests were performed to assess for relations among a priori categorical biobehavioral control variables and the main variables of interest (Tables 3-2 and 3-3). Independent samples t-tests also examined potential differences between participants who collected saliva samples to determine cortisol levels and those who did not (Table 3-4). There were no significant differences in main outcome variables between those participants with cortisol data and those without cortisol data; however, participants who collected cortisol samples had a marginally shorter length of hospitalization than participants who did not (p = .06).

Relations Among Length of Hospitalization and Control Variables

Age was significantly related to length of hospitalization (r = .27, p < .05), such that older women had a longer length of hospitalization. Length of surgery (in minutes) was also significantly related to length of hospitalization (r = .35, p < .01), such that greater length of surgery was associated with longer post-surgical hospitalization. Consequently, age and length of surgery were controlled for in subsequent analyses examining length of hospitalization. No other a priori control variables were related to length of hospitalization.

Relations Among Post-surgical Complications and Control Variables

Medical comorbidity was significantly related to post-surgical complications (r = .24, p < .05), such that women with greater pre-surgical medical comorbidity experienced more severe post-surgical complications. Thus, medical comorbidity was controlled for in subsequent analyses examining post-surgical complications. No other a priori control variables were related to post-surgical complications.

Relations Among Post-Surgical Ambulation and Control Variables

There were no significant relationships between a priori control variables and post-surgical ambulation.

Relations Among WBC Count and Control Variables

There were no significant relationships between a priori control variables and post-surgical WBC count.

Relations Among Stress and Control Variables

Age was significantly related to both impact of negative life events ($r = -.26$, $p < .05$) and number of negative life events ($r = -.29$, $p < .05$), such that younger women reported more negative life events and greater impact of negative life events during the past six months.

Relations Among Emotional Support and Control Variables

Pre-surgical BMI was significantly related to emotional support ($r = -.36$, $p < .01$), such that women with lower BMI perceived greater emotional support from primary support person prior to surgery. Mean post-surgical pain during hospitalization was also significantly related to emotional support ($r = -.25$, $p < .05$), such that women who perceived greater emotional support from primary support person pre-surgically reported lower mean post-surgical pain during hospitalization.

Relations Among Diurnal Cortisol Slope and Control Variables

There were no significant relationships between a priori control variables and diurnal cortisol slope.

Descriptive Results

Participants ($N = 75$) were a mean of 60.71 years old ($SD = 9.65$) at study entry. They had a mean BMI of 35.86 ($SD = 11.22$). Thirteen participants (17.3%) had a BMI within the normal range (18.5 – 24.9), 14 participants (18.7%) had a BMI within the overweight range (25.0 -29.9), and 48 participants (64%) had a BMI within the obese range (>30.0). Participants had a mean medical comorbidity index score of 2.65 (*SD* = 1.40). At study entry, 2.7% of participants were taking corticosteroid medications. The mean length of surgery was 177.14 minutes (*SD* = 55.75) and 14.7% of participants experienced intra-operative complications. Participants reported a mean pain rating of 2.45 (*SD* = 1.52) on a scale from zero to ten during the post-surgical hospitalization period. Medical records revealed that common post-surgical analgesics included Morphine PCA, Tylox, Motrin 600, Percocet, and Dilaudid; however, not all participants received all of these medications and the present study did not collect data on analgesic doses for each participant. Pathology revealed that 48 participants (64.0%) had Stage I endometrial cancer, 11 (14.7%) had Stage II endometrial cancer, and 10 (13.3%) had Stage III endometrial cancer. Six participants (8%) were identified as having benign or pre-cancerous endometrial disease. According to pathology reports, 62 participants (84.9%) had a histology type of endometrioid adenocarcinoma, three participants (4.1%) had a histology type of complex endometrial hyperplasia with atypia, three participants (4.1%) had a histology type of papillary serous carcinoma, one participant (1.4%) had a histology type of complex endometrial hyperplasia without atypia, one participant (1.4%) had a histology type of clear cell carcinoma of the endometrium, one1 participant (1.4%) had a histology type of mixed clear cell and endometrial adenocarcinoma, and one participant (1.4%) had a histology type of endocervical adenocarcinoma, endometrioid type.

Participants reported experiencing a mean of 3.45 (*SD* = 2.87) negative life events during the six months prior to surgery and a mean impact of negative life events of 9.66 (*SD* = 11.35). The five most common negative life events during the past six months included major illness related to cancer (64.4% of participants), worsening financial situation (24.3%), major illness other than cancer (18.9%), worked long hours (18.1%), and change in closeness to a family member (13.5%). Participants reported perceiving a mean emotional support from primary support person of 16.57 (*SD* = 3.56). The mean diurnal slope was -.04 (*SD* = .02). Figure 3-1 displays examples of a selection of study participants' diurnal cortisol slopes.

Participants were hospitalized a mean of 4.38 (*SD* = 1.98) days following surgery. Forty-six percent of women experienced post-surgical complications during the post-surgical hospitalization period. Participants experienced a mean of .98 (*SD* = 1.46) post-surgical complications during hospitalization and their mean post-surgical complication severity rating was 1.12 (*SD* = 1.82). Common post-surgical complications included fever (12.2% of participants), blood transfusion (10.8%), atelectasis (9.5%), low hematocrit (9.5%), pleural effusion (6.8%), urinary tract infection (5.4%), low oxygen saturation (5.4%), arrhythmias (4.1%), and, aspiration (4.1%). Participants first ambulated a mean of 1.28 (*SD* = .88) days post-surgery. Their mean WBC count during post-surgical hospitalization was 10.60×10^9 cells/L (*SD* = 2.60×10^9 cells/L). Differential complete blood cell count data revealed that the mean neutrophil percentage was 77.50% (*SD* = 8.61%) and the mean lymphocyte percentage was 15.39% (*SD* = 7.72%). 49.3% of participants had mean WBC counts that fell within the normal range ($5.0\text{-}10.0 \times 10^9$ cells/L) and 50.7% of participants had leukocytosis ($>10.0 \times 10^9$ cells/L). No participants had mean WBC counts indicating leukopenia ($< 5.0 \times 10^9$ cells/L).

Relations Among Stress, Cortisol, and Surgical Outcome

Length of Hospitalization

Based on results of preliminary analyses, age and length of surgery were entered as control variables in block one for all analyses examining length of hospitalization (in log days). These control variables accounted for 21.3% of the variance explained in length of hospitalization. Significant effects for length of surgery ($p < .01$) indicated that women who underwent longer surgeries had longer post-surgical hospital stays. Age emerged as a marginally significant predictor of post-surgical length of hospitalization, such that there was a trend toward older women experiencing longer post-surgical hospital stays ($p = .08$). The addition of impact of negative life events in block two, and the addition of pre-surgical diurnal cortisol slope in block three did not significantly increase the variance explained in length of post-surgical hospitalization (p's > .50). The main effect analysis for the model is summarized in Table 3-5. In the full model, only length of surgery emerged as significant predictor of length of hospitalization, with a trend toward age as a predictor of length of hospitalization. Due to the lack of significant relations among impact of negative life events, pre-surgical diurnal cortisol slope, and length of hospitalization, test for mediation was not performed.

Post-Surgical Complication Severity

Based on results of preliminary analyses, medical comorbidity score was entered as a control variable in block one, impact of negative life events was entered in block two, and pre-surgical diurnal cortisol slope was entered in block three. However, none of these variables accounted for significant variance in post-surgical complication severity (p's > .10). Table 3-6 summarizes the main effects model. Due to the lack of significant relations among impact of negative life events, pre-surgical diurnal cortisol slope, and post-surgical complication severity, test for mediation was not performed.

Post-Surgical Ambulation

A main effects model was created by entering impact of negative life events in the first block and pre-surgical diurnal cortisol slope in the second block of a hierarchical linear regression. Neither impact of life events nor pre-surgical diurnal cortisol slope significantly accounted for the variance explained in post-surgical time to ambulation (p's > .10). Table 3-7 summarizes the main effects model. Due to the lack of significant relations among impact of negative life events, pre-surgical diurnal cortisol slope, and post-surgical time to ambulation, test for mediation was not performed.

WBC Count

A main effects model was created by entering the impact of negative life events in the first block and pre-surgical diurnal cortisol slope in the second block of a hierarchical linear regression. Neither impact of negative life events nor pre-surgical diurnal cortisol slope significantly accounted for the variance explained in WBC count (p's > .50). Table 3-8 summarizes the main effects model. Due to the lack of significant relations among impact of negative life events, pre-surgical diurnal cortisol slope, and post-surgical WBC count, test for mediation was not performed.

Relations Among Emotional Support, Cortisol, and Surgical Outcome

Length of Hospitalization

Age and length of surgery were entered as control variables in block one, emotional support from primary support person was entered in block two, and pre-surgical diurnal cortisol slope was entered into block three. The addition of emotional support from primary support person and pre-surgical diurnal cortisol slope did not significantly account for the variance explained in length of post-surgical hospitalization above and beyond the control variables (p's > .10). Please refer to table 3-9 for the main effect analysis for the model. Due to the lack of significant relations among pre-surgical emotional support from primary support person, pre-surgical diurnal cortisol slope, and length of hospitalization, test for mediation was not performed.

Post-Surgical Complication Severity

Medical comorbidity score was entered as a control variable in block one, emotional support from primary support person was entered in block two, and pre-surgical diurnal cortisol slope was entered in block three. None of these variables accounted for significant variance in post-surgical complication severity (p's > .10). Table 3-10 summarizes the main effects model. Due to the lack of significant relations among emotional support from primary support person, pre-surgical diurnal cortisol slope, and post-surgical complication severity, test for mediation was not performed.

Post-Surgical Ambulation

A main effects model was created by entering emotional support from primary support person in the first block and pre-surgical diurnal cortisol slope in the second block of a hierarchical linear regression equation. Neither emotional support from primary support person nor pre-surgical diurnal cortisol slope significantly accounted for the variance explained in post-surgical time to ambulation (p's > .10). Table 3-11 summarizes the main effects model. Due to the lack of significant relations among pre-surgical emotional support from primary support person, pre-surgical diurnal cortisol slope, and time to post-surgical ambulation, test for mediation was not performed.

WBC Count

A main effects model was created by entering emotional support from primary support person in the first block and pre-surgical diurnal cortisol slope in the second block of a hierarchical linear regression equation. Emotional support from primary support person emerged as a significant predictor of post-surgical WBC count, such that women with greater pre-surgical emotional support from primary support person had less elevated post-surgical WBC counts ($p < .05$). The addition of pre-surgical diurnal cortisol slope in block two of the model did not result in a significant increase in variance explained in post-surgical WBC count ($p > .90$). The main effect analysis for the model is summarized in Table 3-12. Although a significant relationship emerged between pre-surgical emotional support from primary support person and post-surgical

WBC count, pre-surgical diurnal cortisol slope and post-surgical WBC count were not significantly related; thus, test for mediation was not performed.

Given that the relationship between emotional support from primary support person and post-surgical WBC count was not in the hypothesized direction, a logistic regression equation examined emotional support from primary support person and pre-surgical diurnal cortisol slope as predictors of WBC count clinical categories, ranging from 0.0-10.0x10^9 cells/L and greater than 10.0 x10^9 cells/L (leukocytosis). The entry of emotional support from primary support person in block one and pre-surgical diurnal cortisol slope in block two did not significantly account for the variance explained in presence of pre-surgical leukocytosis (p's > .10). Table 3-13 summarizes the main effects model.

Additionally, emotional support from primary support person and pre-surgical diurnal cortisol slope were examined as predictors of differential blood cell count. Neither emotional support from primary support person nor pre-surgical diurnal cortisol slope significantly accounted for variance explained in either neutrophil percentage or lymphocyte percentage (p's > .60). Table 3-14 summarizes the main effects model for neutrophil percentage and Table 3-15 summarizes the main effects model for lymphocyte percentage.

Finally, a main effects model was created in which emotional support from primary support person was entered into block one and pre-surgical diurnal cortisol slope was entered into block two to examine mean WBC count during the first four days post-surgery (given that the mean hospitalization length was 4.58 days). Emotional support received from primary support person accounted for a marginally significant 5.3% increase in variance explained in WBC count during the first 4 days post-surgery (p = .08); however, pre-surgical diurnal cortisol slope did not account for a significant amount of variance in WBC count in the first 4 days post-surgery above and beyond this. The direction of the relationship between emotional support from primary support person and WBC count suggested that greater emotional support from primary support person was marginally associated with less elevated WBC count during the first 4 days post-surgery. Table 3-16 summarizes the main effects model.

Exploratory Analyses

Rationale for Exploratory Analyses

Given the fact that impact of negative life events and diurnal cortisol rhythm failed to emerge as predictors of the criteria of interest, exploratory analyses were pursued to assess whether an additional measure of life stress and additional indices of cortisol production were associated with outcomes. Specifically, perceived life stress as measured by the PSS over the past month was examined as an additional measure of life stress, while AUC-G, AUC-I, mean daily cortisol, and mean morning cortisol were examined as additional measures of cortisol production. Furthermore, total emotional support was examined as an additional measure of emotional support.

Several factors contributed to the decision to include perceived stress, additional cortisol indices, and total emotional support in exploratory analyses of the main outcome variables. First, impact of negative events was not significantly related to any of the outcome variables, nor was it significantly related to cortisol. The lack of a relationship with cortisol is inconsistent with a robust literature linking measures of stress to cortisol production (e.g., Seedat, et al. 2003). Hence, it is possible that the lack of relationship between impact of negative events and cortisol may possibly be attributable to the timeframe covered by the instrument used to measure impact of negative events, the LES. The LES assesses the incidence and impact of negative life events over the previous six months. As such, it is more of a measure of chronic stress than acute, pre-surgical stress. Consequently, it was determined that the measurement of acute, pre-surgical stress may be more likely to demonstrate a relationship with pre-surgical cortisol. The PSS measures perceived stress during the past month, which may better reflect the degree of stress experience by participants undergoing diagnosis and treatment for endometrial cancer. Similarly, it is possible that diurnal cortisol slope may not fully capture the possibility of abnormal cortisol production during the immediate pre-surgical period. Whereas diurnal cortisol slope is a measure of the pattern of cortisol production over course of a day, other cortisol indices may be more reflective of HPA reactivity. For example, the early morning peak in cortisol is considered to be representative of HPA axis reactivity to waking, whereas AUC-G reflects basal HPA activity and AUC-I reflects post-basal HPA reactivity (Vedhara et al., 2006). Thus, given that the present study examines the acute peri-operative period, it is possible that the cancer diagnosis and surgery are more representative of acute stressors than chronic, and therefore it is possible that cortisol measures reflective of HPA reactivity may provide more useful information above and beyond diurnal cortisol slope.

Finally, operationalizing emotional support as emotional support received only from a primary support person (spouse, or in the absence of spouse, adult female friend) may have excluded potentially valuable emotional support received from secondary sources. The relational cultural theory posits that women commonly identify themselves through their relation to others (Jordan et al., 1991). This may be of particular importance during a time in which they may be undergoing acute stress, such as undergoing cancer diagnosis/treatment, or may be in need of tangible assistance or reassurance from others. Thus, it was determined that examining perceived emotional support from all potential sources (e.g., female friends, healthcare providers, other family members) may provide a more comprehensive measure of emotional support than emotional support from primary support person.

Preliminary Analyses

AUC-G and AUC-I for each day of collection were averaged to create a mean AUC-G and AUC-I for each participant. The daily mean cortisol and daily morning cortisol values for each day of collection were also averaged to create a mean daily cortisol value and a mean morning cortisol value for each participant. Pearson bivariate correlations were performed to assess for potential relations among a priori continuous biobehavioral control variables and the exploratory variables of interest (Table 3-17). Spearman's correlations were performed to assess for potential relations among a priori ordinal biobehavioral control variables (e.g. FIGO stage) and the exploratory variables of interest. Independent samples t-tests were performed to assess for relations among a priori categorical biobehavioral control variables and the exploratory variables of interest. Age was marginally related to AUC-I ($r = .23$, $p = .08$), such that older age was associated with greater pre-surgical AUC-I. Length of surgery was significantly related to pre-surgical AUC-I ($r = -.29$, $p < .05$), such that lower pre-surgical AUC-I was associated with longer surgery. Mean post-surgical pain during hospitalization was marginally related to AUC-I ($r = -.25$, $p = .07$), such that lower pre-surgical AUC-I was associated with greater mean post-surgical pain during hospitalization. There was a significant difference in AUC-I between participants who experienced an intra-operative complication ($M = 1.06$, $SD = 1.14$) and those who did not ($M = .99$, $SD = .53$), $t = -.28$, $p < .05$. FIGO stage was significantly related to both AUC-G ($r = -.27$, $p < .05$) and AUC-I ($r = -.26$, $p < .05$), such that less advanced tumor stage was associated with greater AUC-G and AUC-I. Women taking corticosteroid medications did not differ significantly from those not taking corticosteroids in AUC-G ($t(57) = .93$, $p = .39$), AUC-I ($t(57) = .29$, $p = .34$), mean daily cortisol ($t(59) =.75$, $p = .32$), or mean morning cortisol ($t(57) = .77$, $p = .70$). Participants had a mean AUC-G of 1.82 nmol/l ($SD = .98$) and a mean AUC-I of 1.01 nmol/l ($SD = .65$). They had a mean daily cortisol of .15 nmol/l ($SD = .09$).

Participants had a mean morning cortisol of .27 nmol/l (*SD* = .19). It should be noted that AUC-G, AUC-I, mean daily cortisol, and mean morning cortisol were all computed from raw cortisol values.

Age was marginally related to perceived stress ($r = -.21$, $p = .08$), such that younger participants reported marginally greater perceived stress. Greater perceived stress was also marginally associated with greater post-surgical pain ($r = .22$, $p = .08$). Significant relations also emerged between perceived stress and BMI ($r = .31$, $p < .01$), such that women with greater BMI reported more perceived stress. Greater BMI was also significantly associated with lower total emotional support ($r = -.29$, $p < .05$). Women taking corticosteroid medications did not differ significantly from those not taking corticosteroids in terms of perceived stress ($t(68) = -.54$, $p = .59$) or total emotional support ($t(63) = .14$, $p = .42$). Participants who experienced intra-operative complications did not differ from those who experienced no intra-operative complications in perceived stress ($t(68) = -.70$, $p = .49$) or in total emotional support ($t(62) = 1.46$, $p = .15$). Participants reported a mean perceived stress score of 22.14 (*SD* = 8.81) and mean perceived total emotional support of 67.86 (*SD* = 18.03).

To begin with, relations among impact of negative life events, perceived stress, emotional support from primary support person, total emotional support, diurnal cortisol slope, the 4 additional indices of cortisol production, and the criteria of interest were assessed by calculating Pearson bivariate correlations. These data are presented in Table 3-18. Then, a series of regression equations were constructed to examine whether these additional predictors were associated with the criteria interest, as described below.

Length of Hospitalization, Stress, and Cortisol

Impact of negative life events/perceived stress and the additional indices of cortisol production (i.e., AUC-G, AUC-I, mean daily cortisol, mean morning cortisol) were examined as predictors of length of hospitalization with a series of hierarchical regression analyses. Eight individual equations were constructed. In the first set of equations, age and length of surgery were entered as control variables into Block 1, impact of negative life events was entered into Block 2, and the four additional indices of cortisol production were entered individually into Block 3, resulting in a total of 4 regression equations. In the second set of equations, perceived life stress was substituted for impact of negative life events in Block 2, resulting in 4 additional regression equations.

As presented earlier, impact of negative life events did not emerge as a predictor of length of hospitalization after controlling for age and length of surgery (See Table 3-5). However, none of the 4 additional indices of cortisol production accounted for significant variance in length of hospitalization above and beyond age/length of surgery and impact of negative life events. Perceived stress also failed to emerge as a predictor of length of hospitalization after controlling for age and length of surgery; furthermore, the four additional indices of cortisol production failed to predict length of hospitalization above and beyond age/length of surgery and perceived stress.

Although neither perceived stress nor mean morning cortisol emerged as predictors of length of hospitalization, a significant relationship in the expected direction emerged between perceived stress and mean morning cortisol ($r = .28$, $p < .05$). Specifically, greater perceived stress was associated with more elevated mean morning cortisol (Table 3-18).

Post-surgical Complication Severity, Stress, and Cortisol

Impact of negative life events/perceived stress and the additional indices of cortisol production (i.e., AUC-G, AUC-I, mean daily cortisol, mean morning cortisol) were examined as predictors of post-surgical complication severity with a series of hierarchical regression analyses. The analyses were identical to those described above for length of hospitalization; however, post-surgical complication severity was substituted as the outcome variable and medical comorbidity score was substituted for the control variable.

As reported in the analyses for the specific aims, impact of negative life events did not emerge as a predictor of post-surgical complication severity after controlling for medical comorbidity score (See Table 3-6). None of the four additional indices of cortisol production accounted for significant variance in post-surgical complication severity above and beyond medical comorbidity score and impact of negative life events. Perceived stress did not emerge as a significant predictor of post-surgical complication severity after controlling for medical comorbidity score. The four additional indices of cortisol production also failed to predict post-surgical complications above and beyond medical comorbidity score and perceived stress.

Time to Ambulation, Stress, and Cortisol

Impact of negative life events/perceived stress and the additional indices of cortisol production (i.e., AUC-G, AUC-I, mean daily cortisol, mean morning cortisol) were examined as predictors of time to post-surgical ambulation with a series of hierarchical regression analyses. The analyses were identical to those described above for other outcome variables, with ambulation substituted for the outcome variable. No control variables were entered into the regression

As reported in the analyses for the specific aims, impact of negative life events did not emerge as a predictor of post-surgical time to ambulation (See Table 3-7). None of the four additional indices of cortisol production accounted for significant variance in time to post-surgical ambulation above and beyond impact of negative life events. Perceived stress did not emerge as a significant predictor of time to post-surgical ambulation and the four additional indices of cortisol production failed to predict time to post-surgical ambulation above and beyond perceived stress.

WBC Count, Stress, and Cortisol

Impact of negative life events/perceived stress and the additional indices of cortisol production (i.e., AUC-G, AUC-I, mean daily cortisol, mean morning cortisol) were examined as predictors of post-surgical WBC count with a series of hierarchical regression analyses. The analyses were identical to those described above for other outcome variables, with WBC count substituted as the outcome variable. No control variables were entered.

As reported in the analyses for the primary specific aims, impact of negative life events did not emerge as a predictor of post-surgical WBC count (See Table 3-8). However, when impact of negative events was controlled for, AUC-G (but not AUC-I) accounted for significant incremental variance in post-surgical WBC count ($p < .05$). Specifically, greater AUC-G was significantly associated with more elevated post-surgical WBC count (see Table 3-19 for main effects model). Additionally, mean daily cortisol and mean morning cortisol emerged as significant predictors of post-surgical WBC count when impact of life events was controlled for ($p < .05$). Greater mean daily and morning cortisol were associated with more elevated WBC counts (both *p's* < .05). Tables 3-19 through 3-21 summarize these results. Identical results emerged when perceived stress was substituted for impact of negative life events (Tables 3-22 through 3-24).

Length of Hospitalization, Emotional Support, and Cortisol

Emotional support from primary support person/total emotional support and the additional indices of cortisol production (i.e., AUC-G, AUC-I, mean daily cortisol, mean morning cortisol) were examined as predictors of length of hospitalization with a series of hierarchical regression analyses. As previously described in the exploratory analyses examining stress, cortisol and outcome variables, 8 individual equations were constructed. Emotional support from primary support person/total emotional support were substituted as the Block 1 predictors and length of hospitalization was substituted for the outcome variable.

As presented earlier, emotional support from primary support person did not emerge as a predictor of length of hospitalization after controlling for age and length of surgery (See Table 3-9). None of the four additional indices of cortisol production accounted for significant variance in length of hospitalization when either emotional support from primary support person or total emotional support were covaried. Total emotional support also failed to emerge as a predictor of length of hospitalization after controlling for age and length of surgery.

Post-surgical Complication Severity, Emotional Support, and Cortisol

Emotional support from primary support person/total emotional support and the additional indices of cortisol production (i.e., AUC-G, AUC-I, mean daily cortisol, mean morning cortisol) were examined as predictors of post-surgical complication severity with a series of hierarchical regression analyses. The analyses were identical to those described in the previous section, with post-surgical complication severity substituted as the outcome variable and medical comorbidity score substituted as the control variable.

Consistent with previous analyses of the specific aims, emotional support from primary support person did not emerge as a predictor of post-surgical complication severity after controlling for medical comorbidity score (See Table 3-10). None of the four additional indices of cortisol production accounted for significant variance in post-surgical complication severity when controlling for medical comorbidity score, and either emotional support from primary support person or total emotional support. Total emotional support failed to emerge as a predictor of post-surgical complications after controlling for medical comorbidity score.

Time to Ambulation, Emotional Support, and Cortisol

Emotional support from primary support person/total emotional support and the additional indices of cortisol production (i.e., AUC-G, AUC-I, mean daily cortisol, mean morning cortisol) were examined as predictors of post-surgical time to ambulation with a series of hierarchical regression analyses. Analyses were identical to those described in previous sections, with time to ambulation substituted as the outcome variable. No variables were covaried.

As reported earlier, emotional support from primary support person did not emerge as a predictor of time to post-surgical ambulation (See Table 3-11). None of the four additional indices of cortisol production accounted for significant variance in time to post-surgical ambulation when medical comorbidity score and either emotional support from primary support person or total emotional support were covaried. Total emotional support also failed to emerge as a predictor of time to post-surgical ambulation.

WBC Count, Emotional Support, and Cortisol

Emotional support from primary support person/total emotional support and the additional indices of cortisol production (i.e., AUC-G, AUC-I, mean daily cortisol, mean morning cortisol) were examined as predictors of post-surgical WBC count with a series of hierarchical regression analyses. The analyses were identical to those described in earlier sections, with WBC count substituted as the outcome variable. No variables were covaried.

As reported in the analyses for the specific aims, emotional support from primary support person emerged as a predictor of post-surgical WBC count ($p < .05$). such that greater emotional support was associated with a less elevated WBC count. Moreover, when emotional support from primary support person was controlled for, AUC-G, mean daily cortisol, and mean morning cortisol emerged as significant predictors of WBC count above and beyond the effect of emotional support from primary support person (p's $< .05$). Greater AUC-G, mean daily cortisol, and mean morning cortisol were all associated with greater WBC count. Tables 3-25 through 3-27 summarize the full models. AUC-I did not emerge as a significant predictor of post-surgical WBC count above and beyond emotional support from primary support person. Due to the lack of a significant relationship between emotional support and indices of cortisol production (r = .00, p> .90), test for mediation was not performed. Total emotional support marginally explained the variance in post-surgical WBC count (p = .09); however, AUC-G, AUC-I, mean daily cortisol, and mean morning cortisol all emerged as significant predictors of post-surgical WBC count when total emotional support was controlled for (p's < .05). Greater AUC-G, AUC-I, mean daily cortisol, and mean morning cortisol were associated with more elevated WBC count. Tables 3-28 through 3-31 summarize the main effect models.

Post-Surgical Pain

Given the finding that emerged in preliminary analyses revealing a significant relationship between greater pre-surgical emotional support from primary support person and lower mean post-surgical pain ratings, as well as previous studies which have examined post-surgical pain as an index of post-surgical recovery, a series of exploratory analyses examined potential psychoneuroimmunologic relations to post-surgical pain. Participants' pain ratings (on a scale from 0 to 10) were abstracted from medical records and all pain ratings during the post-surgical hospitalization were averaged to create a mean pain rating. Correlations examined potential relations between the a priori continuous control variables and mean post-surgical pain. There was a significant relationship between age and mean post-surgical pain (r = -.30, p <.05), such that younger women reported more elevated mean post-surgical pain. Mean pain ratings did not differ significantly between women taking corticosteroid medications pre-surgically (M = 2.78, SD = .72) and those not taking corticosteroid medications pre-surgically (M = 2.43, SD = 1.52), t (69) = -.32, p = .75. Mean pain ratings also did not differ significantly between women who experienced an intra-operative complication (*M* = 2.34, *SD* = 2.24) and those who did not (*M* = 2.43, *SD* = 1.33), *t* (69) = .19, *p* = .85. There were no significant differences in mean pain between women who collected cortisol samples (*M* = 2.45, *SD* = 1.46) and those who did not (*M* = 2.38, *SD* = 1.71), *t* (70) = -.16, *p* = .88. Age was controlled for in all analyses examining post-surgical pain.

Stress, Emotional Support, Cortisol, and Post-surgical Pain

Neither of the pre-surgical indices of stress (impact of negative life events, perceived stress) was significantly associated with post-surgical pain ratings above and beyond the effects of age. However, emotional support from primary support person (but not total emotional support received) emerged as a marginally significant predictor of post-surgical pain ratings above and beyond the effects of age (Table 3-32).

Diurnal cortisol slope emerged as a marginally significant predictor of post-surgical pain ratings above and beyond the effects of age and life stress ($p = .08$), as well as above and beyond the effects of age and interpersonal coping, ($p = .08$). In both instances, more positive (abnormal) diurnal cortisol slopes were marginally associated with greater post-surgical pain ratings (see Tables 3-33 and 3-32). In addition, AUC-I emerged as a marginally significant predictor of post-surgical pain ratings above and beyond the effects of age and impact of life events ($p = .07$) (Table 3-34), as well as above and beyond the effects of age and emotional support from primary support person ($p = .09$) (Table 3-35). In contrast, AUC-I was a significant predictor of post-surgical pain ratings above and beyond the effects of age and perceived stress ($p < .05$) (Table 3-36). The direction of all three of these relationships indicated that greater AUC-I was associated with lower post-surgical pain ratings. AUC-G was a marginally significant predictor of post-surgical pain ratings above and beyond the effects of age and perceived stress only (p = .09) (Table 3-37); once again, the direction of this relationship indicated that greater AUC-G was marginally associated with lower post-surgical pain ratings. Neither mean daily or mean morning cortisol were associated with post-surgical pain ratings above and beyond age and life stress or above and beyond age and interpersonal coping.

Moderation Analyses

Moderation analyses were performed to examine the possibility that perceived emotional support from primary support person moderated the relationship between impact of negative events and surgical outcome. Perceived emotional support from primary support person did not emerge as a significant moderator of the relationship between impact of negative events and the four indices of surgical recovery (e.g., length of hospitalization, severity of post-surgical complications, time to post-surgical ambulation, post-surgical WBC count). Tables 3-38 through 3-41 display the full effects models.

Table 3-1. Correlations between a priori biobehavioral control variables (columns) and main predictors and criteria of interest (rows)

	Age (Years)	BMI (kg/m^2)	Comorbidity (Severity-weighted sum)	Mean Pain (VAS scale)	Length of Surgery (Minutes)	FIGO Stage
Criteria						
Length of hospitalization (days[a])	.27* $N = 73$	.08 $N = 73$	.16 $N = 72$	-.08 $N = 63$	.35** $N = 61$	.14 $N = 73$
Post-surgical complications (severity-weighted sum[b])	.11 $N = 73$	-.08 $N = 73$	.24* $N = 72$	.-.01 $N = 63$	.02 $N = 61$	.16 $N = 73$
Post-surgical ambulation (days)	.11 $N = 43$	.19 $N = 43$	-.16 $N = 42$	-.21 $N = 42$	.15 $N = 40$	-.09 $N = 43$
Post-surgical WBC (10^9 cells/liter [L])	.10 $N = 74$	.16 $N = 74$	-.15 $N = 73$	.11 $N = 64$	.19 $N = 62$	-.14 $N = 74$
Predictors						
Impact Negative Life Events (Weighted sum)	-.29* $N = 71$	-.02 $N = 71$	.05 $N = 70$	.19 $N = 61$	.03 $N = 59$	.05 $N = 71$
Emotional Support	.17 $N = 75$	-.36** $N = 75$	.05 $N = 74$	-.35** $N = 65$	.01 $N = 63$	.12 $N = 75$
Mean cortisol slope (Unstandardized beta)	.15 $N = 61$	.18 $N = 61$	-.14 $N = 60$	.21 $N = 55$	.03 $N = 53$	-.05 $N =61$

* = $p < .05$, ** = $p < .01$, *** = $p < .001$. [a] log transformed. [b] square root transformed.

Table 3-2. Relationship between intra-operative complications (columns) and criteria of interest (rows)

	Complications During Surgery			
	Yes	No	*t* (df)	*p*
Length of hospitalization (Days[a])	*M* = .69 *SD* = .21	*M* = .59 *SD* = .16	-1.81 (70)	.07
Post-surgical complications (severity-weighted sum[b])	*M* = .66 *SD* = 1.01	*M* = .67 *SD* = .81	.014 (70)	.99
Time to Ambulation (Days)	*M* = 1.78 *SD* = 1.10	*M* = 1.15 *SD* = .80	-1.93 (40)	.06
WBC (10^9 cells/L)	*M* = 10.83 *SD* = 2.39	*M* = 10.56 *SD* = 2.65	-.31(72)	.76

[a] log transformed. [b] square root transformed.

Table 3-3. Relationship between use of corticosteroid medication (columns) and criteria of interest (rows)

	Use of corticosteroid medication			
	No	Yes	*t* (df)	*p*
Length of hospitalization (Days[a])	*M* = .60 *SD* = .17	*M* = .60 *SD* = .00	.003 (70)	1.0
Post-surgical complications (severity-weighted sum[b])	*M* = .67 *SD* = .85	*M* = .50 *SD* = .71	.29 (70)	.76
Time to Ambulation (Days)	*M* = 1.30 *SD* = .88	*M*= .5 *SD* = .71	1.26 (40)	.22
WBC (10^9 cells/L)	*M* = 10.63 *SD* = 2.62	*M* = 9.97 *SD* = 3.59	.36 (71)	.72

[a] log transformed. [b] square root transformed.

Table 3-4. Relationship between cortisol collection (columns) and outcome variables (rows)

	Cortisol Samples Collected			
	No	Yes	*t* (df)	*p*
Length of hospitalization (Days[a])	*M* = .69 *SD* = .20	*M* = .59 *SD* = .16	1.91 (70)	.06
Post-surgical complications (severity-weighted sum[b])	*M* = .54 *SD* = .77	*M* = .69 *SD* = .85	-.59 (70)	.56
Time to Ambulation (Days)	*M* = 1.50 *SD* = 1.07	*M*= 1.23 *SD* = .84	.78 (41)	.44
WBC ($10.0x10^3$ mm^3)	*M* = 11.13 *SD* = 2.77	*M* = 10.44 *SD* = 2.57	.86 (71)	.39

[a] log transformed. [b] square root transformed.

Table 3-5. Regression analysis examining length of hospitalization (in log days): Effect of impact of negative events and diurnal cortisol slope

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Biobehavioral Control Variables:	.21		.21	6.22***
	Length of surgery		.46***		
	Age		.24*		
2	Impact of Negative life events	.22	.09	.01	.40
3	Pre-surgical diurnal cortisol slope	.22	.05	.00	.13

N = 49, Significance of model, $F(4,44) = 3.14$, $p < .05$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-6. Regression analysis examining post-surgical complication severity (in square-root transformed sum of severity ratings): Effect of impact of negative events and diurnal cortisol slope

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Biobehavioral Control Variables: Medical comorbidity	.04	.20	.04	2.32
2	Impact of Negative life events	.05	-.12	.01	.76
3	Pre-surgical diurnal cortisol slope	.05	-.01	.00	.01

N = 57, Significance of model, $F(3,53) = 1.00$, $p = .40$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-7. Regression analysis examining post-surgical ambulation (in days): Effect of impact of negative events and diurnal cortisol slope

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Impact of Negative life events	.05	-.23	.05	1.75
2	Pre-surgical diurnal cortisol slope	.09	.20	.04	1.27

N = 33, Significance of model, $F(2,30) = 1.52$, $p = .24$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-8. Regression analysis examining post-surgical WBC count: Effect of impact of negative events and diurnal cortisol slope

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Impact of Negative life events	.01	-.08	.01	.33
2	Pre-surgical diurnal cortisol slope	.01	-.01	.00	.01

$N = 57$, Significance of model, $F(2,54) = .16$, $p = .85$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-9. Regression analysis examining length of hospitalization (in log days): Effect of emotional support (primary support person) and diurnal cortisol slope

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Biobehavioral Control Variables:	.22		.22	7.00***
	Length of surgery		.46***		
	Age		.26**		
2	Emotional support (Primary support person)	.25	.17	.03	1.83
3	Pre-surgical diurnal cortisol slope	.25	.06	.00	.23

N = 52, Significance of model, $F(4,47) = 4.01$, $p = .07$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-10. Regression analysis examining post-surgical complication severity (in square-root transformed sum of severity ratings): Effect of emotional support (primary support person) and diurnal cortisol slope

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Biobehavioral Control Variables: Medical comorbidity	.05	.22	.05	2.77
2	Emotional Support (Primary Support Person)	.05	.05	.00	.14
3	Pre-surgical diurnal cortisol slope	.05	-.01	.00	.01

N = 59, Significance of model, $F(3,55) = .94$, $p = .43$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-11. Regression analysis examining post-surgical ambulation (in days): Effect of emotional support (primary support person) and diurnal cortisol slope

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Emotional Support (Primary support person)	.02	.15	.02	.80
2	Pre-surgical diurnal cortisol slope	.08	.23	.06	1.95

N = 36, Significance of model, $F(2,33) = 1.38$, $p = .27$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-12. Regression analysis examining post-surgical WBC count: Effect of emotional support (primary support person) and diurnal cortisol slope

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Emotional Support (Primary support person)	.07	-.27**	.07	4.37**
2	Pre-surgical diurnal cortisol slope	.07	.00	.00	.00

N = 60, Significance of model, $F(2,57) = 2.16$, $p = .13$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-13. Logistic regression analysis examining post-surgical WBC count (normal versus leukocytosis): Effect of emotional support (primary support person) and diurnal cortisol slope

Step #	Variables	Wald Statistic	95%CI	*P Value*
1	Emotional Support (Primary Support Person)	2.19	.77 - .1.04	.14
2	Pre-surgical diurnal cortisol slope	.07	.00 -.00	.79

N = 59, Significance of model, *F*(2,56) = .88, *p* = .42. * *p* < .10. ** *p* < .05. *** *p* < .01.

Table 3-14. Regression analysis examining post-surgical neutrophil percentage: Effect of emotional support (primary support Person) and diurnal cortisol slope

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Emotional Support (Primary Support Person)	.00	-.05	.00	.04
2	Pre-surgical diurnal cortisol slope	.01	.10	.01	.16

$N = 20$, Significance of model, $F(2,17) = .10$, $p = .90$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-15. Regression analysis examining post-surgical lymphocyte percentage: Effect of emotional support (primary support person) and diurnal cortisol slope

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Emotional Support (Primary Support Person)	.00	-.01	.00	.00
2	Pre-surgical diurnal cortisol slope	.01	-.09	.01	.13

N = 20, Significance of model, $F(2,17) = .06$, $p = .94$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-16. Regression analysis examining post-surgical WBC count in first four days post-surgery: Effect of emotional support (primary support person) and diurnal cortisol slope

Step #	Variables	R^2	ß	Δ R^2	*F* of Δ R^2
1	Emotional Support (Primary Support Person)	.05	-.23^	.05	3.17^
2	Pre-surgical diurnal cortisol slope	.05	-.01	.00	.01

N = 59, Significance of model, $F(2,56) = 1.57$, $p = .22$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-17. Correlations between a priori biobehavioral control variables (columns) and exploratory predictors (rows)

	Age (Years)	BMI (kg/m^2)	Comorbidity (Severity-weighted sum)	Mean Pain (VAS scale)	Length of Surgery (Minutes)	FIGO Stage
Predictors						
Perceived Stress	-.21* *N* = 71	.31*** *N* = 71	.06 *N* = 70	.22* *N* = 62	.20 *N* =60	-.12 *N* = 70
Total Emotional Support	-.02 *N* = 65	-.29** *N* = 65	.03 *N* = 65	-.09 *N* = 57	-.31** *N* = 55	-.07 *N* = 64
AUC-G (nmol/l)	.15 *N* = 59	-.05 *N* = 59	.01 *N* = 59	-.23 *N* = 53	-.20 *N* = 59	-.27** *N* = 59
AUC-I (nmol/l)	.23* *N* = 59	-.04 *N* = 59	-.07 *N* = 59	-.26* *N* = 53	-.29** *N* = 51	-.26** *N* = 59
Mean daily cortisol (nmol/l)	.18 *N* = 62	-.06 *N* = 62	.07 *N* = 61	-.18 *N* = 55	-.12 *N* = 53	-.20 *N* = 62
Mean morning cortisol (nmol/l)	.04 *N* = 61	-.01 *N* = 61	-.04 *N* = 61	-.08 *N* = 52	-.04 *N* = 52	-.04 *N* = 59

* $p < .10$. ** $p < .05$. *** $p < .01$. [a] log transformed. [b] square root transformed.

Table 3-18. Correlations among alternative measures of stress, emotional support, cortisol and criteria

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1 Length of Hospitalization (Days)	--	.49*** N=72	.51*** N=71	.39** N=42	.13 N=72	.07 N=60	.11 N=58	.11 N=58	.11 N=61	.10 N=58	-.01 N=69	.01 N=70	.15 N=73	-.09 N=63
2 Post-surgical complications severity	.49*** N=72	--	.99*** N=72	.34** N=41	.01 N=72	-.04 N= 60	.00 N=58	.00 N=58	.07 N=61	.05 N=58	-.10 N=70	.15 N=69	.01 N=73	-.04 N=63
3 Number of post-surgical complications	.51*** N=71	.99*** N=72	--	.36** N=40	.01 N=71	-.04 N= 59	.00 N=58	.00 N=58	.07 N=61	.06 N=58	-.10 N=69	.18 N=68	.01 N=72	-.05 N=63
4 Post-surgical ambulation (Days)	.39** N=42	.34** N=41	.36** N=40	--	-.01 N=42	.24 N= 36	.28 N=35	.28 N=35	.23 N=36	.18 N=35	-.18 N=39	.18 N=41	.15 N=43	.20 N=38
5 Post-surgical WBC count	.13 N=72	.01 N=72	.01 N=71	-.01 N=42	--	-.01 N= 60	.31** N=58	.20 N=58	.33** N=61	.31** N=58	-.13 N=70	.05 N=70	-.15 N=74	-.18 N=64
6 Diurnal cortisol slope	.07 N= 60	-.04 N= 60	-.04 N=59	.24 N=36	-.01 N= 60	--	-.13 N= 59	.13 N=59	-.16 N=61	-.37*** N=58	-.01 N=58	.03 N=60	.01 N=61	-.08 N=54
7 AUC-G	.11 N=58	.00 N=58	.00 N=58	.28 N=35	.31** N=58	-.13 N = 39	--	.84*** N=59	.96*** N=59	.75*** N=47	-.03 N=56	.11 N=58	.00 N=59	.29** N=53
8 AUC-I	.11 N=58	.00 N=58	.00 N=58	.28 N=35	.20 N=58	.13 N= 59	.84*** N=58	--	.70*** N=59	.28** N=57	-.01 N=56	.02 N=58	.05 N=59	.29** N=53
9 Mean daily cortisol	.11 N=61	.07 N=61	.07 N=60	.23 N=36	.33** N=61	-.16 N= 61	.96*** N=59	.70*** N=59	--	.85*** N=59	-.10 N=59	.22* N=61	-.02 N=62	.20 N=54
10 Mean morning cortisol	.10 N=58	.05 N=58	.06 N=58	.18 N=35	.31** N=58	-.37*** N= 58	.75*** N=57	.28** N=57	.85*** N=59	--	-.03 N=56	.28** N=58	-.08 N=59	.22 N=52
11 Impact of negative events	-.01 N=69	-.10 N=70	-.10 N=69	-.18 N=39	-.13 N=70	-.01 N=58	-.03 N=56	-.01 N=56	-.10 N=59	-.03 N=56	--	.30** N=68	-.14 N=71	.07 N=61
12 Perceived stress	.01 N=70	.15 N=69	.18 N=68	.18 N=41	.05 N=70	.03 N= 60	.00 N=59	.05 N=59	.22* N=61	.28** N=58	.30** N=68	--	-.45*** N=71	-.08 N=61
13 Emotional Support (primary support person)	.15 N=73	.01 N=73	.01 N=72	.15 N=43	-.15 N=74	.01 N= 61	.00 N=59	.05 N =59	-.02 N=62	-.08 N=59	-.14 N=71	-.45*** N=71	--	.23* N=65
14 Emotional support (total)	-.09 N=63	-.04 N=63	-.05 N=63	.20 N=38	-.18 N=64	-.08 N= 54	.29** N=53	.29** N=53	.20 N=54	.22 N=52	.07 N=61	-.08 N=61	.23* N=65	--

* $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-19. Regression analysis examining post-surgical WBC count: Effect of impact of negative events and AUC-G

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Impact of negative life events	.01	-.07	.01	.26
2	AUC-G	.10	.31**	.10	5.48**

N = 55, Significance of model, $F(2,53) = 2.88$, $p = .07$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-20. Regression analysis examining post-surgical WBC count : Effect of impact of negative events and mean daily cortisol

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Impact of negative life events	.01	.08	.01	.39
2	Mean daily cortisol	.12	.33***	.11	6.71***

N = 58, Significance of model, $F(2,55) = 3.56$, $p < .05$. * $p < .10$ ** $p < .05$. *** $p < .01$.

Table 3-21. Regression analysis examining post-surgical WBC count: Effect of impact of negative events and mean morning cortisol

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Impact of negative life events	.00	.01	.00	.00
2	Mean morning cortisol	.11	.33**	.11	6.32**

N = 55, Significance of model, $F(2,52) = 3.16$, $p = .05$.* $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-22. Regression analysis examining post-surgical WBC count: Effect of perceived stress and AUC-G

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Perceived Stress	.01	.10	.01	.59
2	AUC-G	.10	.31**	.09	5.60**

N = 57, Significance of model, $F(2,54) = 3.12$, $p = .05$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-23. Regression analysis examining post-surgical WBC count: Effect of perceived stress and mean daily cortisol

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Perceived stress	.02	.13	.02	.91
2	Mean daily cortisol	.12	.33***	.10	6.52***

N = 60, Significance of model, $F(2,59) = 3.76$, $p < .05$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-24. Regression analysis examining post-surgical WBC count: Effect of perceived stress and mean morning cortisol

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Perceived stress	.01	.12	.01	.80
2	Mean morning cortisol	.11	.32**	.09	5.56**

N = 57, Significance of model, $F(2,54) = 3.21$, $p < .05$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-25. Regression analysis examining post-surgical WBC count: Effect of emotional support (primary support person) and AUC-G

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Emotional support (Primary Support Person)	.07	-.26**	.07	4.10**
2	AUC-G	.16	.31**	.10	6.28**

N = 58, Significance of model, $F(2,55) = 5.37$, $p < .01$. *$p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-26. Regression analysis examining post-surgical WBC count: Effect of emotional support (primary support person) and mean daily cortisol

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Emotional support (Primary Support Person)	.07	-.26**	.07	4.31**
2	Mean daily cortisol	.17	.32***	.10	7.31***

N = 61, Significance of model, $F(2,58) = 6.04$, $p < .01$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-27. Regression analysis examining post-surgical WBC count: Effect of emotional support (primary support person) and mean morning cortisol

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Emotional support (Primary Support Person)	.05	-.23*	.05	3.04*
2	Mean morning cortisol	.14	.29**	.08	5.27**

N = 58, Significance of model, $F(2,55) = 4.27$, $p < .05$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-28. Regression analysis examining post-surgical WBC count: Effect of total emotional support and AUC-G

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Total emotional support	.06	-.24*	.06	3.01*
2	AUC-G	.25	.46***	.19	12.23***

$N = 52$, Significance of model, $F(2,49) = 7.96$, $p < .01$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-29. Regression analysis examining post-surgical WBC count: Effect of total emotional support and AUC-I

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Total emotional support	.06	-.24*	.06	3.01*
2	AUC-I	.17	.35**	.11	6.45**

N = 52, Significance of model, $F(2,49) = 4.89$, $p < .05$.* $p < .10$ ** $p < .05$, *** $p < .01$.

Table 3-30. Regression analysis examining post-surgical WBC count: Effect of total emotional support and mean daily cortisol

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Total emotional support	.06	-.24*	.06	3.12*
2	Mean daily cortisol	.23	.43***	.17	11.17***

N = 53, Significance of model, $F(2,50) = 7.46$, $p < .01$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-31. Regression analysis examining post-surgical WBC count: Effect of total emotional support and mean morning cortisol

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Total emotional support	.05	-.23	.05	2.74
2	Mean morning cortisol	.18	.37***	.13	7.70***

N = 51, Significance of model, $F(2,48) = 4.41$, $p < .01$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-32. Regression analysis examining effect of emotional support (primary support person) and diurnal cortisol slope on post-surgical pain ratings

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Age	.03	-.17	.03	1.48
2	Emotional Support (Primary Support Person)	.09	-.24*	.06	3.32*
3	Diurnal cortisol slope	.14	.23*	.05	3.16*

$N = 55$, Significance of model, $F(3,51) = 2.75$, $p = .05$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-33. Regression analysis examining effect of impact of negative events and diurnal cortisol slope on post-surgical pain ratings

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Age	.03	-.16	.03	1.31
2	Impact of negative events	.05	.15	.02	1.05
3	Diurnal cortisol slope	.11	.25*	.06	3.26*

N = 52, Significance of model, $F(3,48) = 1.91$, $p = .14$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-34. Regression analysis examining effect of impact of negative events and AUC-I on post-surgical pain ratings

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Age	.02	-.15	.02	1.17
2	Impact of negative events	.05	.16	.02	1.07
3	AUC-I	.11	-.26*	.07	3.40*

$N = 50$, Significance of model, $F(3,46) = 1.92$, $p = .14$.* $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-35. Regression analysis examining effect of emotional support (primary support person) and AUC-I on post-surgical pain ratings

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Age	.03	-.16	.03	1.33
2	Emotional Support (Primary Support Person)	.08	-.24*	.06	3.05*
3	AUC-I	.13	-.24*	.05	2.91*

N = 53, Significance of model, $F(3,49) = 2.50$, $p = .07$.* $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-36. Regression analysis examining effect of perceived stress and AUC-I on post-surgical pain ratings

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Age	.01	-.12	.01	.70
2	Perceived Stress	.04	.15	.02	1.06
3	AUC-I	.12	-.31**	.08	4.57**

N = 52, Significance of model, *F*(3,48) = 2.15, *p* = .11. *p* < .10. ** *p* < .05. *** *p* < .01.

Table 3-37. Regression analysis examining effect of perceived stress and AUC-G on post-surgical pain ratings

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Age	.01	-.12	.01	.70
2	Perceived stress	.04	.15	.03	1.07
3	AUC-G	.09	-.25*	.05	3.03*

N = 52, Significance of model, $F(3,48) = 1.62$, $p = .2$. * $p < .10$. ** $p < .05$. *** .$p < .01$.

Table 3-38. Regression analysis examining the relationship between post-surgical length of hospitalization (in log days) and impact of negative events: Effect of emotional support (primary support person) as a moderator

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Age	.23	.33**	.23	7.90***
	Length of Surgery		.42***		
2	Impact of Negative Events	.23	1.35	.00	.24
3	Perceived Emotional Support (Primary Support Person)	.27	.40	.04	2.83*
4	Impact of Negative Events x Perceived Emotional Support Interaction	.30	-1.27	03	1.88

N = 53, Significance of model, *F*(3,49) = 2.50, *p* = .07. * *p* < .10. ** *p* < .05. *** *p* < .01.

Table 3-39. Regression analysis examining the relationship between severity of post-surgical complications (in square-root transformed sum of severity ratings) and impact of negative events: Effect of emotional support (primary support person) as a moderator

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Medical Comorbidity Score	.05	.22*	.05	3.61*
2	Impact of Negative Events	.06	.61	.01	.82
3	Perceived Emotional Support (Primary Support Person)	.06	.15	.00	.05
4	Impact of Negative Events x Perceived Emotional Support Interaction	.07	-.71	.01	.59

$N = 53$, Significance of model, $F(3,49) = 2.50$, $p = .07$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-40. Regression analysis examining the relationship between time to post-surgical ambulation (in days) and impact of negative events: Effect of emotional support (primary support person) as a moderator

Step #	Variables	R^2	ß	ΔR^2	F of ΔR^2
1	Impact of Negative Events	.03	-.61	.03	1.21
2	Perceived Emotional Support (Primary Support Person)	.03	-.09	.00	.04
3	Impact of Negative Events x Perceived Emotional Support Interaction	.03	.41	.00	.05

N = 53, Significance of model, $F(3,49) = 2.50$, $p = .07$. * $p < .10$. ** $p < .05$. *** $p < .01$.

Table 3-41. Regression analysis examining the relationship between post-surgical WBC count and impact of negative events: Effect of emotional support (primary support person) as a moderator

Step #	Variables	R^2	ß	ΔR^2	*F* of ΔR^2
1	Impact of Negative Events	.02	-.88	.02	1.17
2	Perceived Emotional Support (Primary Support Person)	.05	-.32	.03	2.65
3	Impact of Negative Events x Perceived Emotional Support Interaction	.06	.73	.01	.64

N = 53, Significance of model, $F(3,49) = 2.50$, $p = .07$. * $p < .10$. ** $p < .05$. *** $p < .01$.

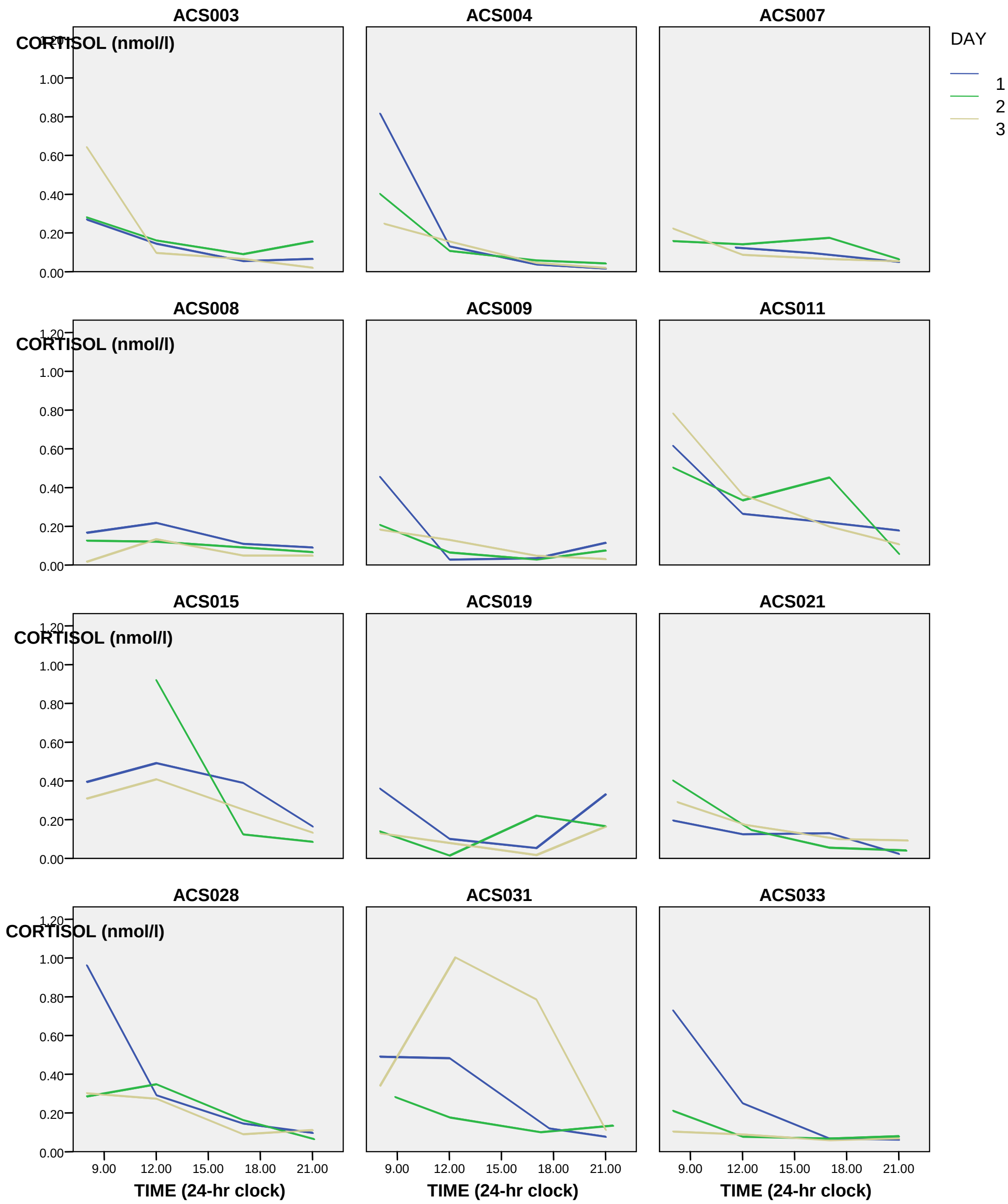

Figure 3-1. Examples of graphical representations of diurnal cortisol slopes from study participants

CHAPTER 4
DISCUSSION

Discussion of Results

The current study is the first to examine psychoeneuroimmunologic predictors of post-surgical recovery among women with endometrial cancer, a group of women who may be at greater risk for a more complicated surgical recovery. The primary hypothesis of this study was that women who reported greater pre-surgical psychosocial stress would have a more complicated post-surgical recovery (as evidenced by longer length of post-surgical hospitalization, greater severity of post-surgical complications, longer time to post-surgical ambulation, and less elevated WBC count), and that the relationship between pre-surgical psychosocial stress and a more complicated post-surgical recovery would be mediated by more abnormal diurnal cortisol slopes. Similarly, it was expected that women who reported greater pre-surgical adaptive interpersonal coping (as evidenced by greater perceived emotional support from primary support person) would have a less complicated post-surgical recovery, and the relationship between pre-surgical adaptive interpersonal coping and a less complicated post-surgical recovery would be mediated by a less abnormal diurnal cortisol slope. Finally, it was hypothesized that among women with high pre-surgical psychosocial stress, those who report less use of pre-surgical adaptive interpersonal coping strategies will have a more complicated post-surgical recovery. Although the findings did not fully support the hypotheses, the present study yielded a number of important findings that extend the literature examining predictors of surgical recovery.

Psychosocial Stress and Surgical Recovery

Previous data suggest that elevated pre-surgical psychosocial distress is associated with less favorable surgical recovery (e.g., Katz et al., 2005, Kain et al., 2000, Cohen et al., 2005, Broadbent et al., 2003). The present study explored the potential relationship between two types of psychosocial distress, life event stress and perceived stress, and four indices of surgical recovery: length of post-surgical hospitalization, severity of post-surgical complications, time to post-surgical ambulation, and post-surgical WBC count. In the present study, no significant relations emerged between measures of psychosocial stress and indices of post-surgical recovery. This may reflect a true lack of relationship between psychosocial stress and surgical recovery; however, although the explanation for this lack of relations among pre-surgical psychosocial stress and surgical outcome remains unclear, several plausible explanations exist. First, it is possible that the measures of stress used in the present study did not capture the potential stress associated specifically with cancer diagnosis and surgery. Previous research examining the effects of stress on surgical outcome has found relations between surgical outcome and psychosocial distress when measuring constructs more related to pre-surgical distress or anxiety (e.g., Kain et al., 2000; Cohen et al., 2005; Broadbent et al., 2003), as opposed to life events or perceived stress. It is possible that acute distress related to surgery may be more strongly related to surgical outcome than measures of life events or perceived stress in the months preceding surgery. Indeed, it is possible that greater life event stress during the preceding months might result in a blunted response to acute stress, such that individuals might experience less pronounced stress in response to the acute pre-surgical period. However, it should be noted that the present study offers no empirical data to support this hypothesis. Second, the absence of a relationship between psychosocial stress and surgical outcome may also be attributable to the possibility that the present population is unique in terms of its experience and/or reporting of negative life events. It might be that women in the present study tended to perceive the negative life events that they experienced as minimally stressful and consequently, examining these variables in relation to surgical outcome results in no significant relationship. Stawski, Sliwinski, Almeida, and Smyth (2008) found that, compared to younger individuals, older individuals reported decreased exposure to daily stressors, but older individuals (men and women) did not report different emotional reactivity to daily stressors. Although research indicates that women report greater mean stressful life events when compared to men (Bieliauskas, Counte, & Glandon, 1995; Turner & Avison, 2003), there is a paucity of research examining the perceived impact of stressful life events among populations similar to the women in the present study (e.g., older, rural women). Similarly, given that the women in the present study experienced high rates of comorbid medical conditions, it is possible that their experience with previous medical conditions and treatment resulted in less perceived distress related to their diagnosis of endometrial cancer and subsequent surgical treatment. For example, Wells et al. (2006) found that women with both endometrial cancer and diabetes evidenced fewer negative coping behaviors, more positive affect, and less anxiety than their counterparts diagnosed with endometrial cancer who were not diabetic, suggesting that women with diabetes who develop endometrial cancer may be buffered from the stress related to the diagnosis of endometrial cancer through previously developed adaptive health-related coping strategies. Furthermore, Yang, Thornton, Shapiro, and Andersen (2008) found that women experiencing a recurrence of breast cancer demonstrated notable resilience, with lower anxiety reported among women with recurrent cancer, compared to women coping with an initial cancer diagnosis. Thus, the possibility that the level of psychosocial stress experienced by the sample in the present study was too minimal to affect surgical response must be considered.

Psychosocial Stress and Cortisol

The literature is replete with evidence for the relationship between psychosocial stress and dysregulated cortisol production. The relationship between psychosocial stress and dysregulated cortisol was thought to be of particular salience to the potential relationship between psychosocial functioning and surgical outcome, given that neuroendocrine functioning has been hypothesized to modulate the effects of psychosocial functioning on surgical recovery (Ben Eliyahu, 2004). Consequently, it was expected that greater pre-surgical stress would be associated with more dysregulated cortisol indices. Interestingly, among women in the present study, psychosocial stress was not significantly related to any index of cortisol production. Several potential explanations may account for the absence of a relationship between psychosocial stress and cortisol in the present study. First, it is possible that the lack of relationship between stress and cortisol in this study is due to the way in which stress was measured. Although stress was examined both through the impact of negative life events and perceived stress, it is possible that neither measure of stress accurately captured participants' psychosocial stress at the time of surgery. The LES examined the occurrence and impact negative life events during the previous six months and the PSS examined perceived stress during the past month. Neither measure specifically assessed the situation-specific psychosocial stress that participants may experience during the acute pre-surgical period. Consequently, these measures of stress are likely more reflective of chronic or cumulative stress as opposed to the situation-specific stress of cancer diagnosis and surgery. As such, they may not be associated with the acute cortisol response to stress that may be evident in the pre-surgical period. Although diurnal slope is an index of chronicity of HPA response, it remains unclear whether cortisol response to acute stress may alter the diurnal cortisol production in different ways than the chronic stress response. For example, research has found evidence that among individuals with chronic illness, dysregulated inflammatory response may result in a blunted cortisol response to acute stressors (Nijm, Kristenson, Olsson, & Jonasson, 2007). Second, as discussed above, it is possible that the level of psychosocial stress perceived by women in the present study was too minimal to significantly affect cortisol production. However, the perceived stress reported by women in the present study (*M* = 22.14, *SD* = 8.81) did not significantly differ from the perceived stress reported by a sample of 17 metastatic breast cancer patients (*M* = 21.5, *SD* = 2.8) in a study by Abercrombie et al. (2004) ($t = .30$, $p > .05$). However, it should also be noted that perceived stress was unrelated to diurnal cortisol slope in the Abercrombie et al. (2004) study.

Interpersonal Coping and Surgical Recovery

Previous research has identified coping as a predictor of post-surgical outcome (e.g., Cohen et al., 2005; Contrada et al., 2004; Krohne et al., 2005; Kopp et al., 2003; Manyande et al., 1995). Interpersonal coping has emerged as a particularly important predictor of health outcomes and post-surgical recovery (Krohne et al., 2005; Kopp et al., 2003; Manyande et al., 1995). Thus, the present study explored potential relations among pre-surgical perceived emotional support from primary support person and indices of post-surgical recovery. In the present study, no relationships emerged between pre-surgical perceived emotional support from primary support person and length of hospitalization, severity of post-surgical complications, or time to post-surgical ambulation. Despite the absence of relationship between perceived emotional support from primary support person and the above-mentioned indices of post-surgical recovery, perhaps the most robust relationship that emerged in the present study was between pre-surgical interpersonal coping and post-surgical WBC count. Women who reported greater perceived emotional support pre-surgically had less elevated WBC counts post-surgically. The direction of this relationship was not consistent with the initial hypothesis that women with greater perceived emotional support would experience more elevated WBC count post-surgically. The initial hypothesis was based on the typical systemic immune response to surgery marked by leukocytosis, which is considered to be an adaptive physiologic response that favors survival (Salo, 1992). Consequently, it was expected that women with more adaptive interpersonal coping (e.g., greater perceived emotional support from primary support person) would have more elevated WBC counts post-surgically. Given that WBC count is clinically viewed categorically with either low WBC count (leukopenia) or high WBC count (leukocytosis) considered pathologic, several post-hoc exploratory analyses were performed in an effort to elucidate the nature of the relationship between emotional support and WBC count. When WBC count was examined categorically (normal WBC count versus leukocytosis), no significant relationships emerged with emotional support from primary support person. Additionally, because the adaptive increase in WBC count may be more likely to emerge in the acute post-surgical time period when the immune system experiences greater activation, exploratory analysis examined relations between emotional support and mean WBC count during the first four days following surgery (given that the average length of stay was 4.58 days). A marginally significant relationship emerged between emotional support from primary support person and post-surgical WBC count during the first four days post-surgery; however, greater pre-surgical emotional support from primary support person continued to predict less elevated WBC count. Given that the typical systemic immune response to surgery also involves an increase in the percentage of neurophils (neutrophilia) and a decrease in the percentage of lymphocytes (lymphocytopenia) (Salo, 1992), exploratory post-hoc analyses examined the relationship between emotional support from primary support person and neutrophil and lymphocyte percentages; however, no significant relationship emerged between emotional support from primary support person and these indicators of systemic immune status. It should be noted that only a small portion of the sample had complete blood cell differentials with neutrophil and lymphocyte percentages documented in their medical records, resulting in a very small sample size that likely lacked sufficient power to detect a significant relationship. Finally, it is noteworthy that even in the instances in which emotional support from primary support person was significantly related to WBC count, it explained a small amount of the overall variance in WBC count.

Although post-hoc exploratory analyses did not clarify the relationship between greater emotional support and less elevated WBC count, a review of the physiologic role of WBC count in surgical recovery yields a plausible rationale for the unexpected direction of this relationship. Although the total WBC count constitutes a gross measure of the systemic immune and inflammatory changes that may result from surgical tissue injury, there are several factors that increase the complexity in its interpretation in relation to surgical outcome. For example, the relationship between leukocytosis and surgical outcome tends to be complex and nonlinear (Coller, 2005; Gurm et al., 2003). To fully address the complexities associated with interpreting the role of WBC count in surgical outcome, it is necessary to review the physiologic response to tissue injury. The physiologic response to tissue injury is proposed to consist of three stages: hypodynamic ebb phase (shock), hyperdynamic flow phase, and recuperation phase (Smith & Giannoudis, 1998). The hypodymamic ebb phase is characterized by an attempt to limit the blood loss and to maintain perfusion to the vital organs. The hyperdynamic flow phase is characterized by increased blood flow to eliminate waste products and to facilitate the migration of nutrients to the site of injury for repair. The recuperation phase, which can last for months, is characterized by attempts to return the human body to its pre-injury level. WBC count plays a critical role in the inflammatory response to tissue injury. This inflammatory response involves a series of adaptive steps, including increase in blood flow to site of trauma, increased capillary permeability, and leukocyte migration out of circulatory system into surrounding tissue (Clancy 1998). Although this response may be initiated within minutes of tissue injury, it can persist for weeks (Clancy, 1998). During the inflammatory response to tissue injury, leukocytes serve to remove debris and restore normal tissue structure and function, as well as to fight infection (Clancy, 1998). The activation of the inflammatory response is followed by the release of cytokines and the migration of leukocytes into inflamed tissues (Giannoudis, Dinopoulos, Chalidis, & Hall, 2006). Leukocytes are comprised of a number of cell subsets, including neutrophils, lymphocytes, mast cells, eosinophils, basophils, and monocytes. Neutrophils typically arrive first at the site of injury and engage in phagocytosis of bacteria in an effort to stave off infection (Clancy, 1998). The mobilization of leukocytes to the site of the injury to engage in tissue repair is facilitated by a state of hyperglycemia that results from a concentration gradient in which there is a 'downhill' flow of glucose across the extracellular matrix to the areas of damage where leukocytes amass (Kohl & Deutschman, 2006). This response of leukocytes to the site of injury is also modulated by the production and secretion of catecholamines, antidiuretic hormone, cortisol, insulin,glucagon, growth hormone and cytokines (Kohl & Deutschman, 2006). The adaptive response of leukocyte migration from the systemic circulatory system into the tissues surrounding the injury raises concerns about the interpretability of WBC count derived from peripheral blood draw. Specifically, WBC count based on peripheral blood draw may not reflect an increase of leukocytes at the site of tissue injury and thus, may not reflect the hypothesized elevations in WBC count. Moreover, it could be argued that the lack of elevation observed in WBC count from peripheral blood draw may actually reflect the migration of blood cells from the systemic circulatory system and into the site of injured tissue. The potential difference in WBC count systemically versus at the site of tissue injury complicates the interpretation of research examining WBC count in the context of surgery. It also serves as a potential explanation for the association between greater pre-surgical perceived emotional support and less elevated WBC count. Because the methodology of the present study did not allow for an examination of WBC count at the site of tissue injury (where the elevation in WBC count would be expected to occur), the initial hypothesis that interpersonal coping would be associated with more elevated WBC count did not account for potential different WBC count response as measured by peripheral blood draw, which would be a measure of WBC count in the systemic circulatory system.

Moreover, although elevated WBC count is expected as part of the adaptive physiologic response to surgical tissue trauma, recent research examining WBC count and cardiac surgical outcome also suggests that elevated post-surgical WBC count may confer deleterious effects to indices of surgical recovery. For example, Lamm et al. (2006) found that a more pronounced increase in post-surgical WBC count was an independent predictor of the development of postoperative atrial fibrillation among individuals undergoing elective cardiac surgery. Additionally, Abdelhadi, Gurm, Van Wagoner, and Chung (2004) reported that elevated WBC count independently predicted post-surgical atrial fibrillation in individuals undergoing coronary bypass or cardiac valve surgery. Leukocytosis has also been established as a significant predictor of post-surgical renal insufficiency among individuals undergoing coronary artery bypass graft surgery (Brown et al., 2007). The findings on the relationship between elevated WBC count and complicated surgical recovery among individuals undergoing cardiac surgery suggest that perhaps elevated WBC count and failure to achieve leukocytosis may each be associated with individual indices of poor surgical recovery unique to that disease state and surgery. Given the deleterious effects of leukocytosis observed in the cardiac surgery literature, the relationship between greater pre-surgical perceived emotional support and less elevated WBC count appears to be reflective of a potentially more adaptive WBC count response than was specified in the initial hypothesis.

In addition, it is possible that the predictive nature of WBC count on surgical outcome may be more related to a change in WBC count from pre- to post-surgery. For example, Amar, Goenka, Zhang, Park, and Thaler (2006) found that the increase in WBC count from pre-surgical to post-surgical day one, along with age, significantly predicted post-surgical atrial fibrillation among individuals who underwent general thoracic surgery. Specifically, a two-fold increase in WBC from pre-surgery to post-surgical day one resulted in a 3.3-fold increase in the odds of developing atrial fibrillation (Amar et al., 2006). In the present study, baseline pre-surgical WBC count was unknown for the majority of participants. Consequently, it is possible that mean WBC counts observed post-surgically, although not clinically elevated, did demonstrate an elevation relative to WBC count pre-surgically. This would indicate a within-person increase in WBC count that is not detectable when solely examining post-surgical WBC count. As such, the finding that greater perceived emotional support is associated with less elevated WBC count does not take into account a change from pre-surgical to post-surgical WBC count, which would be more reflective of the specific immune response to surgical tissue trauma.

Based on evidence of the existence of a J-shaped relationship between WBC count and mortality following percutaneous coronary intervention (Gurm et al., 2003), it has recently been suggested that overall WBC count may be limited in its predictive ability (Gibson et al., 2007). Consequently, a subset of research has examined the predictive ability of leukocyte subsets on surgical outcome. Among individuals undergoing coronary artery bypass surgery (CABG), an elevated neutrophil count and a depressed lymphocyte count (the normal response to surgery) were both associated with a worse surgical outcome (Gibson et al., 2007). Specifically, elevated neutrophil count was associated with an increased risk of death, and lower preoperative lymphocyte count was a predictor of mortality (Gibson et al., 2007). Gibson et al. (2007) also found that an elevated neutropohil/lymphocyte (N/L) ratio was associated with a poorer survival after CABG, and that this finding was independent of other recognized risk factors. Moreover, elevated N/L ratio independently predicted cardiovascular mortality in the subgroup of patients with a *normal* WBC count undergoing CABG (Gibson et al., 2007). Once again, these findings about the potentially damaging effects of elevated neutrophil counts and depressed lymphocyte counts following surgery are somewhat inconsistent with that which would be expected, based upon the fact that neutrophilia is an expected and adaptive response to tissue injury. Additionally, it is noteworthy that the N/L ratio was predictive of mortality, even among individuals with normal WBC counts. These findings suggest that overall WBC count may have limited predictive ability. Thus, although the relationship between interpersonal coping and WBC count was in the opposite direction than that expected in the initial hypothesis, it is possible that the overall WBC count may not be clinically meaningful when considered in the absence of N/L ratio. In the present study, analyses examining interpersonal coping, neutrophil percentage, and lymphocyte percentage yielded no significant relationships. However, the percentage nature of these data, and the limited availability of neutrophil/lymphocyte data limited the ability to adequately explore these WBC subsets, which according to previous research, may constitute more clinically meaningful predictors of surgical outcome than overall WBC count on its own.

The quality of overall WBC count's predictive ability of surgical outcome is further questioned by results from research examining the utility of leukodepletion on surgical outcome.

The possibility that less elevated WBC count may be an adaptive response to surgical tissue injury receives indirect support from research examining leukodepletion procedures during cardiac surgery. Due to the observed detrimental effects of leukocyte activation on end-organ injury, it has been proposed that leukocyte removal with special filters may diminish the deleterious effects of leukocyte activation during coronary artery bypass machine procedures (Alexiou et al., 2006). Although leukocyte filters do not appear to significantly decrease overall WBC counts, there is evidence that filters act to preferentially reduce activated leukocytes, resulting in improvements in post-surgical pulmonary function and attenuation of reperfusion injury at the cellular level (Warren et al., 2007). Thus, it is possible that examining the subset of leukocytes that are activated may yield more meaningful predictive ability than overall WBC count. However, it should be noted that these findings have been found among individuals whose surgery does not involve organ removal, whereas the individuals in the present study undergo surgery which removes the diseased organ. Once again, this highlights the complex nature of interpreting the relationship between greater perceived emotional support and less elevated WBC count. Thus, although the methodology of the present study did not allow for the collection of data on activated leukocytes, this information may help to elucidate the robust relationship that emerged between interpersonal coping and less elevated WBC count.

It is also possible that medications administered either pre- or post-surgically may have resulted in a limited the range of response in WBC counts post-surgically. For example, results from the LIPID study revealed that WBC count predicted cardiovascular mortality in patients with ischemic disease randomized to placebo, but not in those receiving pravastatin (Stewart et al., 2005), suggesting that statin medications may modulate the effects of WBC count on surgical outcome. Because data for the present study did not include information about statin medications during the acute peri-operative period, it is possible that unmeasured statin use may impact WBC count response to surgery. However, it should be noted that there were no significant differences in WBC count between women who took corticosteroid medications pre-surgically and those who did not. The unexpected direction of the relationship between interpersonal coping and WBC count may also be related to the potential effects of comorbid medical conditions on WBC count response to surgery. Specifically, comorbid conditions, such as chronic obstructive pulmonary disease, renal failure, coronary artery disease and diabetes interact with the inflammatory response and may impact an individual's ability to mount an appropriate stress response. (Kohl & Deutschmann, 2006). Given that the women in the present study are commonly affected by comorbid medical conditions, it is possible that these conditions may have affected the WBC count response to surgery in this population; however, it should be noted that medical comorbidy score was not significantly associated with post-surgical WBC count. In addition to comorbid medical conditions, reproductive hormones may affect immune response to tissue trauma. Specifically, female reproductive hormones have been found to exhibit immunoprotective properties after trauma and severe blood loss (Angele & Chaudry, 2005). Given that most of the participants in the present study were post-menopausal and all underwent a surgical procedure involving the removal of female reproductive organs, it is unlikely that changes in female reproductive hormones would explain affect WBC count in this sample. Finally, genetic variation has been proposed to account for individual differences in the immune response and development of complications following tissue trauma. Research has identified a genetic polymorphism of the neutrophil receptor for immunoglobulin G (CD16) which may be associated with differences in neutrophil phagocytosis (Salmon, Edberg, Brogle, 1992). Thus, it is possible that genetic variation may be a possible factor contributing to the relationship between pre-surgical perceived emotional support and less elevated post-surgical WBC count in the present study.

In addition to the complex nature of WBC count in the surgical context, it is possible that the unexpected direction of the relationship between interpersonal coping and post-surgical WBC count may stem from unmeasured psychosocial factors between the time emotional support was assessed and the measurement of post-surgical WBC count. For example, it is possible that women who perceived greater emotional support from primary support person prior to surgery and hospitalization, experienced a change in their perception of emotional support at the time of surgery or during the acute post-surgical period. Indeed, due to environmental and physical restrictions during the acute post-surgical period, it is possible that women had less access to their primary support person. According to the “tend-and-befriend” theory of stress response, women are more likely to respond to stress by social affiliation (Taylor et al., 2000). Consequently, perception of isolation or decreased affiliation with primary support person during the period of time immediately following surgery may confer deleterious effects for women who previously relied heavily on emotional support from their primary support person. Although the methodology of the present study did not include a measure of perceived emotional support from primary support person during hospitalization, the possibility that a change in emotional support from primary support person from pre- to immediately post-surgery resulted in exploratory analyses examining total perceived emotional support. This measure of interpersonal coping allowed for the inclusion of perceived emotional support from a wider range of potential sources, including female friends, healthcare providers, and other family members. However, total emotional support emerged as only a marginally significant predictor of post-surgical WBC count. Although the inclusion of total emotional support may have captured perceived support from a wider range of sources than emotional support from primary support person, it is not sensitive to potential changes in support or affiliation that may be inherent in the post-surgical hospitalization experience. Future research is necessary to clarify these relations through the investigation of interpersonal coping during the acute post-surgical hospitalization period.

Previous research has identified cortisol as a potential neuroendocrine modulator of the relationship between psychosocial functioning and immune functioning. The findings of the present study revealed a significant relationship between pre-surgical cortisol and post-surgical WBC count; however, like the findings with emotional support and WBC count, the direction of the relationship between cortisol and WBC count was opposite of that originally hypothesized. Specifically, findings revealed that greater pre-surgical cortisol indices (e.g., AUG-G, AUC-I, mean daily cortisol, mean morning cortisol) were associated with more elevated WBC count post-surgically. This is contrary to what would be expected, given the immunosuppressive effects of dysregulated cortisol. The present study was unable to empirically examine potential mechanisms that may account for the unexpected relationship between greater pre-surgical cortisol and more elevated WBC counts. However, it is possible that this relationship emerged due to the timing and nature in which cortisol was measured in the present study. The short duration of measurement (three days) and the fact that cortisol was measured immediately prior to surgery may suggest that it captured the cortisol response to a more acute stressor, namely impending surgery. The literature is replete with evidence that dysregulation of cortisol confer deleterious effects to immune functioning (see Antoni et al., 2006 for a review). In the psycho-oncology literature, researchers have approached cortisol in several ways. Sephton and colleagues (2000) found that flatter diurnal cortisol slopes were predictive of shorter survival times among women with metastatic breast cancer; however, marital distress was the only psychosocial variable associated with diurnal cortisol slope. Abercrombie and colleagues (2004) examined cortisol among women with metastatic breast cancer and healthy controls, finding that no psychosocial variables were associated with flattened cortisol slopes. Additionally, Turner-Cobb et al. (2000) examined relations among cortisol production and social support in women with metastatic breast cancer. Although diurnal cortisol slope was not significantly associated with social support, although greater mean cortisol was associated with less social support (Turner-Cobb et al., 2000). Giese-Davis et al. (2004) found that highly anxious women with metastatic breast cancer displayed more flattened diurnal cortisol slopes. Vedhara and colleagues (2006) examined psychosocial predictors of various indices of diurnal cortisol (e.g., diurnal slope, AUC-G, AUC-I, morning peak) among women with breast cancer and healthy controls, and found that only neuroticism emerged as a significant predictor of morning peak cortisol. No other psychosocial constructs emerged as significant predictors of any other cortisol indices (Vedhara et al., 2006). Thus, the research thus far has been variable in its examination of indices of diurnal cortisol production and psychosocial factors. The majority of research thus far has been conducted among women with metastatic breast cancer, a population noted to have unusually high rates of diurnal cortisol dysregulation. Additionally, none of the aforementioned studies examined women recently diagnosed with cancer, or those preparing for oncologic surgery. Consequently, the results of this literature may not easily translate to the present study.

Additionally, research examining the effects of chronic distress and cortisol in non-oncology populations has identified blunted cortisol production in response to long-term distress (Ahrens et al., 2008; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996). Under normal conditions, a negative feedback loop causes an inhibition of stress-elicited HPA activation when an individual no longer perceives a stressor as stressful. This results when increases in circulating glucocorticoids act on the hypothalamus to inhibit further secretion of CRF and, subsequently, the secretion of ACTH from the pituitary gland. However, chronically high levels of perceived stress may override this negative feedback loop, resulting in dysregulation of circulating cortisol and dysregulation in the overall cortisol stress response (McEwen, 1998). It is plausible that coping with ongoing life stressors resulted in a blunted cortisol response in which lower levels of cortisol can not necessarily be interpreted as adaptive; however, if this were the case, one might expect a stronger relationship between chronic life event stress (e.g., as was measured by the LES) and cortisol, which was not the case in the present study. Moreover, the methodology of the present study did not allow for experimental examination of cortisol response to a stressor; consequently, the findings yield no empirical evidence that participants in the present study demonstrated a blunted cortisol stress response.

Although this pattern leading to blunted cortisol production may be a plausible explanation for the lack of relationship between measures of stress and cortisol indices, it does not explain why elevated cortisol levels were associated with more elevated WBC counts. As discussed above, it is likely that complexities in the WBC count surgical response raise questions about what constitutes the adaptive WBC count response to surgery. However, greater indices of cortisol were associated not only with a potentially adaptive systemic immune response post-surgically (i.e., greater elevations in WBC count), but were also associated with lower pain ratings post-surgically. The robust nature of these findings suggests the possibility that, contrary to hypothesis, elevated pre-surgical cortisol confers benefits for post-surgical recovery. Although elevated cortisol is typically discussed as a maladaptive response to chronic stress, research also indicates that in response to an acute, short-term stressor, increased cortisol can be an adaptive response. Hans Selye (1936) originally described the adaptive response to stress in his General

Adaptation Syndrome theory. More recent interpretations of this theory posit that when faced with a stressor, physiologic mediators of stress, such as glucocorticoids, are released and promote adaptation to the stressor (McEwen, 2005). Consequently, the results of the present study may be interpreted as an adaptive, short-term increase in cortisol related to a potentially adaptive post-surgical systemic immune response. Although this post-hoc hypothesis cannot be examined directly by the present study, the possibility that cortisol levels among participants were more reflective of acute stress response, as opposed to chronic dysregulation, may explain the unexpected nature of the relationship between greater cortisol and more elevated WBC count.

Additionally, given evidence that the surgical immune response is characterized by both hyperinflammation and immunosuppression, and that the local immune response differs from the systemic response in the context of surgery, it is possible that the effects of cortisol on post-surgical immune response may differ depending on whether one examines local versus systemic immune response. Given that the present study did not examine the local immune response, it is not possible to determine whether cortisol confers unique effects systemically, as opposed to locally. It should also be noted that decline in the estrogen secretion at menopause is associated with increased HPA axis activity (Van Cauter, Leproult, & Kupfer, 1996). Given that post-menopausal status is a significant risk factor for endometrial cancer, as well as the advanced age of the sample in the present study, the effects of female reproductive hormones on cortisol production cannot be ruled out. Finally, research examining cortisol among women with metastatic breast cancer has identified high rates of dysregulated diurnal cortisol production. Indeed, research indicates that among women with metastatic breast cancer, approximately 70% display dysregulated diurnal cortisol slopes, characterized by flattened slopes, high levels of cortisol, or erratic fluctuations (Touitou, Bogdan, Levi, Benavides, & Auzeby, 1996). Given that both breast and endometrial cancers are endocrine-mediated, it is possible that disease processes related to cancer account for dysregulation in cortisol and its unexpected relations with surgical outcomes and psychosocial predictors.

It is noteworthy that no significant relations emerged between indices of cortisol and interpersonal coping. Previous research has identified relationships between social support and cortisol among women with cancer (e.g.,Turner-Cobb et al., 2000), although as Vedhara et al. (2006) point out, there is a growing scarcity in the reliability of relationships between indices of cortisol and psychosocial factors in the literature. This may reflect a genuine lack of a relationship between cortisol indices and aspects of psychosocial functioning, or may reflect methodologic challenges in this line of research. The lack of significant relationship between psychosocial functioning and cortisol among participants in the present study raises several questions. First, it may be that underlying disease process related to endometrial cancer affects cortisol level to a greater degree than do psychosocial factors. Indeed, endometrial cancer is an endocrine mediated cancer and although relations between psychosocial functioning and cortisol have emerged in research examining other endocrine mediated cancers (e.g., Turner-Cobb et al., 2000), very little research has examined psychoneuroendocrine relations specifically in women with endometrial cancer. Therefore, disease impact on neuroendocrine functioning and its response to psychological factors is largely unknown in this population. Second, it is possible that other comorbid conditions such as diabetes or obesity, which are known to impact cortisol (Tomlinson, Finney, Hughes, & Stewart, 2008), may influence cortisol levels to a greater degree than psychosocial factors. Although the comorbidity index, which includes diabetes, was not significantly associated with measures of cortisol, the present study did not examine the degree to which participants' diabetes was well-controlled, which may serve as a better predictor of cortisol production than simply the diagnosis of diabetes. BMI was also not significantly related to indices of cortisol; however, more specific measures, such as abdominal adiposity, may be better predictors of cortisol production. Although the relationship between disease process, comorbid conditions, and obesity were not directly examined in the present study, they cannot be ruled out as potential explanations for the lack of relationship between psychosocial factors and cortisol.

Furthermore, the present study found no evidence that interpersonal coping moderates the potential relationship between psychological stress and indices of post-surgical recovery.

The findings of the present study were also somewhat surprising, given the lack of significant relations between psychosocial and endocrine predictors and three of the four main outcome variables: length of hospitalization, post-surgical complications, and time to ambulation. These variables were selected in an effort to examine surgical outcome from a diverse and clinically meaningful perspective. Several previous studies have identified significant relationships between psychosocial predictors and length of hospitalization. For example, Krohne et al (2005) found that individuals receiving more emotional support were hospitalized approximately 1.5 fewer days post maxillofacial surgery than those individuals receiving less emotional support. Moreover, Contrada et al. (2004) found that individuals with stronger religious beliefs had significantly shorter hospitalization periods following CABG. In the present study, only a priori biobehavioral control variables significantly predicted post-surgical length of hospitalization. Thus, in the present study, a stronger relationship emerged between medical variables, such as length of surgery, and post-surgical hospitalization than the relationship between psychosocial/endocrine variables and length of hospitalization. Additionally, given the multifactorial nature of post-surgical hospitalization, it is possible that non-measured factors other than the a priori biobehavioral control variables contributed to post-surgical hospitalization. Given the high costs associated with inpatient hospitalizations, it is possible that economic factors such as health insurance played a role in the length of hospitalization post-surgery. Additionally, given the potential susceptibility to infection and illness in the hospital, it may be that healthcare providers took a more proactive approach to early discharge. Finally, although previous research has identified significant psychosocial predictors of post-surgical length of hospitalization, it should be noted that those studies examined surgical populations that are potentially quite disparate from participants in the present study. Krohne et al. (2005) investigated individuals undergoing maxillofacial surgery and Contrada et al. (2004) investigated individuals undergoing CABG. Both of these procedures likely involve different levels of tissue trauma and sizes of incision sites. Thus, it is possible that among women undergoing an invasive procedure such as TAH-BSO, the effect of psychosocial factors on length of hospitalization is minimal when compared to clinical medical factors.

Contrary to the present study, previous studies have identified significant relationships between psychosocial predictors and post-surgical complications. For example, in a population of individuals undergoing CABG surgery, Contrada et al. (2004) reported that individuals with stronger religious beliefs had fewer post-surgical complications. Moreover, in a general surgery population, Kopp et al. (2003) found that life satisfaction and social support predicted surgical recovery without complications. The present study did not yield evidence of a relationship between psychosocial and endocrine predictors and post-surgical complications. Moreover, the present study examined not only incidence of post-surgical complications, but also severity-weighted incidence of complications as rated by a board-certified gynecologic oncologist. It was expected that examining severity of post-surgical complications would yield more clinically relevant results than past studies that have only examined incidence of post-surgical complications. It should be noted that post-hoc analyses revealed a significant relationship between severity of post-surgical complications and post-surgical length of hospitalization (r = .49, p < .001), such that women with more severe complications had longer length of hospitalization. Due to the correlational, cross-sectional nature of this data, it is not possible to determine causality from this finding. However, in research examining psychosocial predictors of post-surgical complications, Contrada et al. (2004) found that post-surgical complications mediated the relationship between psychosocial predictor and length of hospitalization. However, in the present study, post-surgical complications and length of hospitalization were treated as independent outcomes of post-surgical outcome, given the inability to establish causal direction between the two variables. It should also be noted that, unlike the findings related to length of hospitalization, no biobehavioral control variables emerged as significant independent predictors of post-surgical complications. Several factors may account for the lack of support for relations between psychosocial and endocrine functioning and severity of post-surgical complications. First, data about post-surgical complications was abstracted from participants' official discharge notes, which summarize the events of their entire hospitalization. Through the course of the study, raters observed a wide range of variation in the level of detail or content of information in the discharge notes, suggesting that the validity of the data is dependent upon the healthcare providers' documentation of complications in the discharge notes. Thus, it is possible that minor complications that would be part of the participants' paper inpatient medical chart may not have been uniformly documented in their electronic discharge summaries. Although the methods of the present study limit further investigation of this possibility, anecdotal evidence from raters of post-surgical complications suggests that this is a plausible concern. Second, the present study was limited to the examination of complications that arose during post-surgical hospitalization. As such, analyses were not able to examine incidence or severity of complications that may have arisen later in post-surgical recovery after hospitalization. It is likely that certain types of post-surgical complications (e.g., wound complications) may not be identified until participants present to the outpatient gynecologic oncology clinic for removal of surgical staples. Thus, the data in the present study fails to capture the full spectrum of potential post-surgical complications that participants may have experienced during their recovery, which may account for the lack of significant findings between psychosocial functioning and post-surgical complications.

Psychosocial and endocrine variables also did not emerge as significant predictors of time to post-surgical ambulation in this study. Time to post-surgical ambulation was included as an outcome variable in this study both because it represents a more functional outcome of surgery, as well as an outcome that may be more related to behavioral factors, such as adherence to medical recommendations. Similar to observed inconsistencies in the documentation of post-surgical complications, day of post-surgical ambulation was infrequently clearly documented in participants' medical records, leading to a sizeable amount of missing data. Additionally, review of participants' medical records revealed that the recommendation that hospital staff encourage ambulation shortly after the participant's return from the recovery room was a standard entry in the acute post-surgical physicians' orders. Thus, it is possible that time to post-surgical ambulation emerged more as a proxy measure of compliance with medical recommendations than a functional index of post-surgical recovery. Nevertheless, it is likely that the small number of participants with complete post-surgical ambulation data limited the power to detect meaningful relationships with this outcome variable.

Overall, only post-surgical WBC count was significantly related to psychosocial functioning and cortisol. It is noteworthy that, whereas length of hospitalization, post-surgical complications, and time to ambulation may be considered more indirect indices of the potential effect of stress, coping, and cortisol dysregulation on surgical outcome, given the previously established relationship between psychosocial, endocrine factors, and immune functioning, WBC count appears to be a more directly related outcome measure of psychoneuroimmunologic predictors.

Psychoneuroimmunologic Predictors of Post-Surgical Pain

In addition to the findings related to the designated outcome variables discussed above, exploratory post-hoc analyses yielded interesting findings related to psychosocial and endocrine predictors of post-surgical pain. Specifically, preliminary analysis identified a significant relationship between greater pre-surgical perceived emotional support and lower post-surgical pain ratings. When perceived stress and cortisol were examined as predictors in a model with post-surgical pain as the outcome variable, AUC-I emerged as a significant independent predictor of post-surgical pain, such that greater pre-surgical AUC-I was associated with lower post-surgical pain ratings. Similarly, in a model examining emotional support and cortisol as predictors of post-surgical pain, AUC-I emerged as a marginally significant predictor of post-surgical pain, with a trend toward lower AUC-I being related to greater post-surgical pain. Emotional support from primary support person also emerged as a marginally significant predictor of post-surgical pain, with a trend toward a relationship between lower pre-surgical perceived emotional support and greater post-surgical pain. These findings are consistent with previous research examining psychosocial predictors of post-surgical pain. Kain et al. (2000) also found support for the relationship between pre-surgical psychosocial factors and post-surgical pain, with greater pre-surgical anxiety related to greater post-operative pain among women undergoing abdominal hysterectomy. Moreover, Cohen et al. (2005) examined both pre-operative distress and coping as predictors of post-operative pain and morphine consumption. The findings revealed that greater pre-operative distress predicted greater post-operative pain and morphine consumption; however, this relationship was no longer significant when pre-operative coping was controlled for (Cohen et al., 2005). Cohen et al (2005) also found that the use of more passive coping strategies was associated with elevated pain and morphine consumption post-operatively (Cohen et al., 2005).

The lack of support for a relationship between pre-surgical stress and post-surgical pain may be attributable to the measurement of stress in the current study, as discussed earlier. It is possible that measures of stress such as "distress," as was used by Cohen et al., as opposed to life stress or perceived stress, are more closely related to the experience or report of post-surgical pain. However, the present study extends the findings of Cohen et al. (2005) and Kain et al. (2000) via the finding that greater pre-surgical AUC-I was a significant predictor of less post-surgical pain. It should be noted that due to the exploratory nature of this analysis the present study was not able to examine analgesic consumption during the period of time in which participants were rating their pain levels. As such, the possibility exists that participants who perceived greater pre-surgical emotional support were also more likely to request pain medications when needed, resulting in better managed pain and lower pain ratings. Nevertheless, these exploratory findings provide converging evidence to support the relationship between coping and post-surgical pain.

Implications of Findings

The present study is among the first to examine psychoneuroimmunologic predictors of clinical surgical outcome in the context of oncologic surgery. As such, the findings of the present study extend the literature on predictors of post-surgical recovery, which has generally been carried out in the context of general surgery populations. Although the present study yielded some unexpected findings, it presents important implications for future research. First, the findings of the present study revealed that among participants in this sample, more elevated pre-surgical cortisol indices predicted post-surgical systemic immune response and lower post-surgical pain ratings. Thus, future research may clarify these relationships through the inclusion of repeated measures of cortisol indices, as opposed to solely measuring cortisol immediately prior to surgery. Such research may elucidate whether the relationship between more elevated pre-surgical cortisol indices and improved surgical outcome is reflective of a blunted cortisol response to stress, or simply reflective of an adaptive physiologic response to an acute stressor (e.g., surgery). Future research may also consider employing behavioral stress paradigms to directly and empirically examine the cortisol stress response in this population.

Second, the finding that greater pre-surgical perceived emotional support (both from primary support person as well as multiple sources) was predictive of less elevated WBC counts, highlights the importance of examining interpersonal coping during the immediate post-surgical (e.g., hospitalization) period. Future research incorporating measures of psychosocial functioning and interpersonal coping while recovering in the hospital may provide important insight into the relationship between psychosocial functioning and surgical recovery. Such research may also yield important clinical implications for potential psychosocial interventions for individuals hospitalized during post-surgical recovery.

Third, the present study focused on psychoneuroimmunologic predictors of post-surgical recovery restricted to the acute post-surgical hospitalization period. As such, longer-term aspects of both physical and functional recovery were not included in the analyses of the present study. Future research in this area should consider investigation of longer-term post-surgical recovery in this population, particularly given the often lengthy recovery from TAH-BSO. A longer follow-up period would also provide the opportunity to examine aspects of psychosocial functioning once women have been discharged from the hospital and may elucidate the potential psychosocial changes as women progress from diagnosis, to preparation for surgery, to hospitalization, and to longer term recovery and adaptation to cancer.

Finally, the present study attempted to look at multiple clinically meaningful indices of post-surgical recovery. However, recovery from invasive surgery presents many more challenges than those captured in the outcome variables in the present study. Specifically, given their high rate of comorbid conditions, such as obesity and diabetes, as well as the experience of significant surgical incision and tissue removal, women with endometrial cancer are at greater risk for wound healing complications. The psychoneuroimmunologic literature is replete with evidence that psychosocial factors such as distress may impede healthy wound healing. Consequently, future research may wish to examine psychoeneuroimmunologic aspects of wound healing in this population. Such research would extend laboratory research on PNI factors in wound healing and may yield important clinical implications in a population at risk for wound complications.

Study Limitations

Despite the important implications discussed above, the results of the present study should be interpreted with caution, given a number of important limitations. First, although the prospective nature of this design suggests temporal directionality in relations between pre-surgical and post-surgical variables, the correlational nature of the research precludes interpreting causality. In particular, the present study did not assess or control for numerous psychological and medical variables that may account for relations that emerged in the findings of the present study. Future research is necessary to clarify the complex and likely multifactorial nature of the relationships observed in the present study.

Second, the measurement of the variables of interest presents another potential limitation for the present study. As discussed earlier, it is possible that the selection of impact of negative events during the past six months and perceived stress during the past month, did not specifically capture stress participants experienced related to their cancer diagnosis and upcoming surgery. As such, whereas the measures of stress were likely more reflective of long-term or more chronic stress, the mediating (indices of cortisol) variables, as well as the outcome variables may be more susceptible to the effects of acute stress, distress, or anxiety during the peri-operative period. Additionally, as discussed above, the lack of information about stress or interpersonal coping during the acute post-surgical hospitalization period presents a significant limitation in the interpretation of the observed findings. As such, it remains unclear whether psychosocial functioning immediately following surgery may have had a greater impact on surgical recovery than psychosocial functioning during the pre-surgical period. The utilization of overall WBC count from peripheral blood draw constitutes another significant limitation of the present study. Examination of immune response at the site of tissue injury (as opposed to systemically), as well as inclusion of data related to activation of leukocytes and leukocyte subsets may yield more interpretable and clinically meaningful findings. Moreover, the present study is also limited by its restricted focus on surgical recovery during post-surgical hospitalization. Although the post-surgical hospitalization period represents a critical point in the peri-operative period, recovery from TAH-BSO frequently extends well beyond the time of discharge and there may be unique challenges to surgical recovery that arise after women return to their homes. Consequently, future research is needed to examine the entire spectrum of the peri-operative period in order to clarify the psychoneuroimmunologic relations and their association with clinical indices of both short-term and long-term post-surgical recovery.

Third, the lack of information about participants' compliance with the saliva collection protocol presents another salient limitation, particularly given the unexpected relationships that emerged between more elevated indices of cortisol and improved post-surgical recovery. Participants were asked to collect four samples each day, for three consecutive days. This sample collection schedule may have been burdensome to participants, particularly those at an advanced age, due to the need for participants to carry their collection supplies with them throughout the day. Compliance with saliva sampling is essential to the accurate measurement and interpretation of cortisol (Kudielka, Broderick, & Kirschbaum, 2003). In fact, diurnal cortisol slope can demonstrate a 100% change within 30 minutes (Kirschbaum & Hellhammer, 1994). In an effort to ensure more accurate cortisol data, participants were instructed to label salivettes with the actual time the sample was collected, even if it deviated from the collection times specified in the protocol. Indices of cortisol were computed based on the time participants indicated their samples were collected, as opposed to the designated collection times. However, the methodology of this study provided no means to assess whether samples were actually collected when participants reported. Although it is generally assumed that participants would record the actual time of sample collection, it is possible that demand characteristics may have led some participants to report collecting their samples at the designated time, even if they did not do so. Future research should consider the use of compliance monitoring devices to ensure more reliable diurnal cortisol data.

It should also be noted that the present study's saliva collection protocol may raise limitations when interpreting the findings. The current study used four saliva samples per day (8AM, 12PM, 5PM, 9PM) to plot the diurnal cortisol slope and calculate AUC-G, AUC-I, mean daily cortisol and mean morning cortisol. 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), many studies examining diurnal cortisol among non-oncologic populations have collected more than four daily samples (Kirschbaum & Hellhammer, 1994; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). Specifically, some researchers have raised concern that a small number of potentially unreliable samples could bias the estimation of diurnal slope (Stone et al., 2001). Consequently, it should be noted that the four samples collected in the current study may not have provided adequate or reliable data from which to calculate indices of diurnal cortisol. Moreover, some research has focused on the participants' actual time of waking, as opposed to a designated morning collection time, for the first saliva collection of the day. It is possible that using individual participants' actual time of waking may produce a more accurate approximation of their diurnal cortisol slope, including the peak at waking. As such, the present's study's designation of 8:00 AM as the first saliva collection time may result in less accurate determination of indices of diurnal cortisol.

Fourth, a considerable limitation of the present study involves missing data across variables, resulting in smaller than desired sample size in a number of analyses. For example, it was not possible to obtain cortisol samples from a substantial portion of participants in the present study, as a result of participants declining to collect samples, non-compliance with collection, insufficient quantity of saliva for assay, and timing of recruitment. This missing cortisol data resulted in smaller than projected sample sizes and likely inadequate power to detect significant results. Similarly, inconsistencies in documentation in participants' medical records resulted in substantially more missing data for time to post-surgical ambulation than the other main outcome variables. Again, the sample size in analyzes involving post-surgical ambulation likely lacked the power to detect significant relations with predictor variables. In addition, inconsistencies in the content and level of detail of documentation of post-surgical complications raises some questions about the accuracy of the post-surgical complication data included in the present study. Although these types of problems are inherent to conducting clinical research in an applied medical setting (as opposed to laboratory), future research should consider employing methods to ensure more rigorous and consistent documentation of variables of interest and should over-estimate sample size calculation in a conservative attempt to circumvent often inevitable problems due to missing data.

Fifth, the multiple comparisons and analyses performed in the present study present a notable limitation, given the potential for increased likelihood of Type I error. Type I error involves rejecting the null hypothesis when it is actually true, leading to falsely positive results. Although the number of analyses performed in the present study may introduce Type I error, given that very few analyses yielded significant findings, it is unlikely that the Type I error would have impacted the pattern of results in the present study.

A final limitation involves the clinical relevance of examining psychoneuroimmunologic predictors of post-surgical recovery. It has been argued that the identification of new psychosocial predictors of medical outcome carries little weight within the field of medicine unless these predictors are independent of already established (e.g., medical/biologic) predictors (Freedland, 2004). In other words, it could be argued that the findings of the present study have little real-world significance if they do not predict surgical outcome above and beyond other well-established predictors. Although the findings of the present study are not likely to significantly influence gynecologic surgery practice, they provide important information about risk factors for complicated surgical recovery among women with endometrial cancer. Moreover, they highlight risk factors that, unlike certain medical/surgical factors, may be amenable to modification via psychosocial intervention.

Conclusions

The present study is among the first studies to examine psychoneuroimmunologic predictors of post-surgical recovery. Moreover, it extends previous findings about relationships between psychosocial factors and surgical outcome in the general surgery population by examining these relationships in the unique context of oncologic surgery. The present study also extends the previous literature by examining these potential relationships specifically in a population of women who are thought to be at greater risk for more complicated post-surgical recovery.

The findings suggest significant relationships between interpersonal coping and indices of post-surgical recovery, including post-surgical systemic immune response and post-surgical pain ratings. The present study also found relations among pre-surgical indices of cortisol production and post-surgical systemic immune response and post-surgical pain ratings. Contrary to initial hypothesis, greater pre-surgical emotional support was associated with less elevated post-surgical WBC count and more elevated pre-surgical indices of cortisol were associated with more elevated post-surgical WBC count. The findings suggest a trend toward a relationship between greater pre-surgical perceived emotional support from primary support person and lower post-surgical pain ratings. The present study also found that more elevated pre-surgical indices of cortisol were associated with lower post-surgical pain ratings. Contrary to hypothesis, psychosocial stress was not related to any index of post-surgical outcome, nor was it related to any index of cortisol production. Post-surgical WBC count and post-surgical pain ratings were the only indices of post-surgical recovery that were significantly related to psychoneuroimmunologic predictors, above and beyond the effects of biobehavioral control variables. The present study highlights both the importance of and methodologic challenges related to conducting psychoneuroimmunologic research in the applied medical setting. It provides preliminary data for future research to examine psychoneuroimmunologic relations during the peri-operative period among women with endometrial cancer.

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BIOGRAPHICAL SKETCH

Sally Elizabeth Jensen was born in 1978, in Waupun, Wisconsin. She remained in Wisconsin until her graduation from Waupun High School in 1996. She then enrolled in the University of Minnesota in Minneapolis. In 2000, she graduated summa cum laude from the University of Minnesota, where she received a Bachelor of Arts degree in psychology and spanish. In 2000, she was inducted as a member of the Phi Beta Kappa honor society. Ms. Jensen was then employed for three years as a Community Program Specialist in the University of Minnesota, Division of Epidemiology, where she 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.

In 2003, Ms. Jensen enrolled in the doctoral program in the Department of Clinical and Health Psychology at the University of Florida in Gainesville, Florida. Under the mentorship of Deidre Pereira, Ph.D., Ms. Jensen worked as a graduate research assistant conducting research at the interface of psycho-oncology, psychoneuroimmunology, and women's health. In 2005, she received the American Psychosomatic Society Young Scholar Award and was awarded a Citation Poster for her project titled, "Cognitive Behavioral Stress Management (CBSM) Effects on Social Support and Positive Affect among HIV+ Women at Risk for Cervical Cancer." In 2006, Ms. Jensen received the University of Florida College of Public Health and Health Professions Outstanding Research Award for her project entitled, "Maladaptive Interpersonal Coping Predicts Poorer Surgical Recovery Among Women with Endometrial Cancer." She received the Clinical Health Psychology Research Award from the Department of Clinical and Health Psychology at the University of Florida in 2007. In June 2007, Ms. Jensen began her one-year pre-doctoral internship at the Vanderbilt-VA Internship Consortium in Nashville, Tennessee. After completing her pre-doctoral internship, Ms. Jensen began a postdoctoral fellowship in psychosocial oncology at NorthShore University HealthSystem (Kellogg Cancer Care Center and the Center on Outcomes, Research and Education) in Evanston, Illinois.